



The Proportion of SARS-CoV-2 Infections That Are Asymptomatic

FREE

A Systematic Review

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Abstract

Background:

Asymptomatic infection seems to be a notable feature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen that causes coronavirus disease 2019 (COVID-19), but the prevalence is uncertain.

Purpose:

To estimate the proportion of persons infected with SARS-CoV-2 who never develop symptoms.

Data Sources:

Searches of Google News, Google Scholar, medRxiv, and PubMed using the keywords *antibodies*, *asymptomatic*, *coronavirus*, *COVID-19*, *PCR*, *seroprevalence*, and *SARS-CoV-2*.

Study Selection:

Observational, descriptive studies and reports of mass screening for SARS-CoV-2 that were either cross-sectional or longitudinal in design; were published through 17 November 2020; and involved SARS-CoV-2 nucleic acid or antibody testing of a target population, regardless of current symptomatic status, over a defined period.

Data Extraction:

The authors collaboratively extracted data on the study design, type of testing performed, number of participants, criteria for determining symptomatic status, testing results, and setting.

Data Synthesis:

Sixty-one eligible studies and reports were identified, of which 43 used polymerase chain reaction (PCR) testing of nasopharyngeal swabs to detect current SARS-CoV-2 infection and 18 used antibody testing to detect current or prior infection. In the 14 studies with longitudinal data that reported information on the evolution of symptomatic status, nearly three quarters of persons who tested positive but had no symptoms at the time of testing remained asymptomatic. The highest-quality evidence comes from nationwide, representative serosurveys of England ($n = 365\,104$) and Spain ($n = 61\,075$), which suggest that at least one third of SARS-CoV-2 infections are asymptomatic.

Limitation:

For PCR-based studies, data are limited to distinguish presymptomatic from asymptomatic infection. Heterogeneity precluded formal quantitative syntheses.

Conclusion:

Available data suggest that at least one third of SARS-CoV-2 infections are asymptomatic. Longitudinal studies suggest that nearly three quarters of persons who receive a positive PCR test result but have no symptoms at the time of testing will remain asymptomatic. Control strategies for COVID-19 should be altered, taking into account the prevalence and transmission risk of asymptomatic SARS-CoV-2 infection.

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The asymptomatic fraction of infection is the proportion of infected persons who never develop, perceive, and report symptoms (1). Among common pathogens, the asymptomatic fraction varies widely. For example, an asymptomatic carrier state has not been documented for measles virus infection (2), whereas a significant proportion of persons with cytomegalovirus or poliovirus infection have no symptoms and are unaware of infection (3, 4). The asymptomatic fraction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection seems to be sizable (5). The range of severity of illness associated with SARS-CoV-2 infection is noteworthy because it spans asymptomatic infection; mild

illness; and severe, life-threatening illness.

Perhaps because of this broad spectrum of presentation, the topic of asymptomatic SARS-CoV-2 infection has generated some controversy (6). Imprecise use of the term “asymptomatic” is partly to blame. “Asymptomatic” should be reserved for persons who never develop symptoms, whereas “presymptomatic” is a better description of those who have no symptoms when they receive a positive test result but who eventually develop symptoms. We know for certain who is asymptomatic only in retrospect. On the basis of our current knowledge of the natural history of coronavirus disease 2019 (COVID-19), after a person is infected with SARS-CoV-2, we must wait approximately 14 days to determine whether symptoms have developed (7). Infection without symptoms, whether presymptomatic or asymptomatic, is important because infected persons can transmit the virus to others even if they have no symptoms (8, 9).

In June 2020, we published a review of the limited data then available on the prevalence of asymptomatic SARS-CoV-2 infection (5). Since then, considerable new data have become available. The present review summarizes currently available data that might allow us to estimate the proportion of persons infected with SARS-CoV-2 who are asymptomatic.

Methods

Data Sources, Search Terms, and Study Selection

Using the keywords *antibodies*, *asymptomatic*, *coronavirus*, *COVID-19*, *PCR*, *seroprevalence*, and *SARS-CoV-2*, we periodically searched Google News, Google Scholar, medRxiv, and PubMed for observational, descriptive studies and reports of mass screening for SARS-CoV-2 that were either cross-sectional or longitudinal in design; were published through 17 November 2020; and involved SARS-CoV-2 nucleic acid or antibody testing of a target population, regardless of current symptomatic status, over a defined period.

Data Extraction and Quality Assessment

We recorded the total number of persons tested, the number that tested positive, the number of positive cases without symptoms, the criteria for determining symptomatic status, whether the data were cross-sectional or longitudinal in nature, whether random selection techniques were used to achieve a representative sample of a target population, and whether the testing involved polymerase chain reaction (PCR) analysis of a nasopharyngeal swab or serologic analysis of antibodies in a blood sample. For longitudinal studies that provided information on the evolution of symptomatic status, we recorded the proportion of persons who tested positive but had no symptoms at the time of testing and who then remained asymptomatic during a follow-up period. In addition, we flagged studies that required clarification of ambiguous details.

Studies or reports that are based on PCR results and include only cross-sectional data do not make it possible to distinguish between

presymptomatic and asymptomatic SARS-CoV-2 infection because symptomatic status is observed on only 1 occasion, which may occur before the development of symptoms, if any. In contrast, we can distinguish between presymptomatic and asymptomatic infection with either antibody-based studies, in which an interview or questionnaire gathers information about symptoms reported at the time a blood sample is taken and during a prior period, or PCR-based studies that include longitudinal data.

In assessing quality, we put the greatest emphasis on random selection of participants to achieve a representative sample of a regional or national population, a large number of study participants ($n > 10\,000$), and study designs that make it possible to distinguish between presymptomatic and asymptomatic infection. Evaluated in this manner, the highest-quality evidence comes from large-scale, national studies with representative samples that include data from either antibody or longitudinal PCR testing. In Tables 1 and 2, we show in boldface the details that increase a study's likelihood of providing higher-quality evidence.

Table 1. Nucleic Acid PCR Testing

| Study or Report | Tested, n ^a | Longitudinal Data ^b | Random Sampling ^c | SARS-CoV-2-Positive, n (%) | Positive, but No Symptoms, n (%) |
|--|------------------------|--------------------------------|------------------------------|----------------------------|----------------------------------|
| England residents 1 (10-12) | 932 072 | No | Yes | 3029 (0.3) | 1425 (47.0) |
| Belgium long-term care facility residents and staff (13) | 280 427 | No | No | 6343 (3.0) | 6244 (74.8) |
| England residents 2 (14) | 36 061 | No | Yes | 115 (0.3) | 88 (76.5) |
| U.S. skilled-nursing facility residents (15) [†] | 22 368 | Yes | No | 5403 (24.2) | 2194 (40.6) |
| Iceland residents (16) | 13 080 | No | Yes | 100 (0.8) | 43 (43.0) |
| Vo', Italy, residents (17) | 5155 | Yes | No | 102 (2.0) | 34 (42.5) |
| U.S. Navy aircraft carrier crew (18) | 4779 | Yes | No | 1271 (26.6) | 572 (45.0) |
| Arkansas, North Carolina, Ohio, and Virginia inmates (19) | 4693 | No | No | 3277 (69.8) | 3146 (96.0) |
| San Francisco, California, residents (20) | 3871 | Yes | No | 83 (2.1) | 23 (27.7) |
| Arkansas poultry employees (21) | 3748 | No | No | 481 (12.8) | 455 (94.6) |
| Diamond Princess cruise ship passengers and crew (22) | 3618 | Yes | No | 712 (19.7) | 311 (43.7) |
| Indiana residents (23) ^{†‡} | 3605 | No | Yes | 47 (1.7) | 18 (44.2) |
| South London, England, nursing home residents and staff (24) | 2455 | No | No | 160 (6.5) | 115 (71.9) |
| U.S. Marine recruits (25) | 1801 | Yes | No | 51 (2.8) | 46 (90.2) |
| Charles de Gaulle aircraft carrier crew (26) | 1568 | Yes | No | 1001 (63.8) | 130 (13.0) |
| Marseille, France, long-term care facility residents (27) | 1691 | Yes | No | 226 (13.4) | 46 (23.0) |
| King County, Washington, homeless shelter residents and staff (28) | 1434 | No | No | 29 (2.0) | 21 (72.4) |
| Germany oncology clinic patients (29) | 1206 | No | No | 40 (3.1) | 37 (92.5) |
| Pasadena, California, long-term care facilities residents and staff (30) | 938 | No | No | 631 (67.3) | 257 (40.7) |
| Rutgers University students and employees (31) | 829 | No | No | 41 (4.9) | 27 (65.9) |
| Greek citizens evacuated from the United Kingdom, Spain, and | 783 | Yes | No | 40 (5.1) | 35 (87.5) |

| | | | | | |
|--|-----|-----|----|------------|------------|
| Boston, Massachusetts, obstetric patients (33) | 757 | No | No | 20 (2.6) | 9 (45.0) |
| Córdoba, Colombia, residents (34) | 686 | No | No | 35 (5.1) | 18 (51.4) |
| New York City obstetric patients 1 (35) | 675 | No | No | 70 (10.4) | 55 (78.6) |
| Santiago, Chile, obstetric patients (36) | 586 | No | No | 37 (6.3) | 16 (43.2) |
| Japanese citizens evacuated from Wuhan, China (37) | 564 | Yes | No | 11 (2.0) | 3 (27.3) |
| London nursing home residents and staff (38) | 518 | Yes | No | 158 (30.5) | 72 (45.6) |
| Indian citizens evacuated from Iran (39) | 474 | Yes | No | 48 (10.1) | 44 (91.7) |
| Maryland long-term care facility residents (40) | 426 | Yes | No | 177 (41.5) | 154 (87.0) |
| South India retinal surgery patients (41) | 413 | No | No | 9 (2.2) | 9 (100.0) |
| Boston homeless shelter occupants (42) | 408 | No | No | 147 (36.0) | 129 (87.8) |
| Seafood plant employees (43)§ | 376 | No | No | 124 (33.0) | 118 (95.0) |
| Genoa, Italy, obstetric patients (44) | 333 | No | No | 7 (2.1) | 6 (85.7) |
| London maternity hospital staff (45) | 266 | Yes | No | 47 (17.7) | 16 (34.0) |
| Argentine cruise ship passengers and crew (46) | 217 | No | No | 128 (59.0) | 104 (81.3) |
| New York City obstetric patients 2 (47) | 214 | Yes | No | 33 (15.4) | 29 (87.9) |
| Bogotá, Colombia, airport employees (48) | 212 | Yes | No | 35 (16.5) | 24 (68.6) |
| Porto, Portugal, obstetric patients (49) | 184 | No | No | 11 (6.0) | 9 (81.8) |
| Los Angeles, California, homeless shelter occupants (50) | 178 | No | No | 43 (24.2) | 27 (62.8) |
| Illinois skilled-nursing facility residents (51) | 126 | Yes | No | 33 (26.2) | 13 (39.4) |
| Boston grocery store employees (52) | 104 | No | No | 21 (20.2) | 16 (76.2) |
| Los Angeles skilled-nursing facility residents (53) | 99 | Yes | No | 19 (19.2) | 6 (31.6) |
| King County nursing facility residents (54) | 76 | Yes | No | 48 (63.2) | 3 (6.3) |

PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Boldface indicates details that increase the likelihood of higher-quality evidence.

† Data clarified via personal communication with coauthor.

‡ Percentages reflect weighting by the study's authors to estimate statewide prevalence.

§ Estimated from incomplete source data.

Table 2. Antibody Testing

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| Study or Report | Tested, n* | Random Sampling* | SARS-CoV-2-Positive, n (%) | Asymptomatic, n (%) |
|---|------------|------------------|----------------------------|---------------------|
| England residents (55) | 365 104 | Yes | 17 576 (4.8) | 5694 (32.4) |
| Spain residents (56) | 61 075 | Yes | 3053 (5.0) | 1008 (33.0) |
| Detroit, Michigan, hospital staff (57) | 20 614 | No | 1818 (8.8) | 798 (43.9) |
| Wuhan, China, hospital staff (58) | 8553 | No | 424 (5.0) | 148 (34.9) |
| Bavaria, Germany, children aged 1–18 y (59) | 4859 | Yes | 47 (1.0) | 22 (46.8) |
| Louisiana residents (60) | 4778 | Yes | 311 (6.5) | 147 (47.3) |
| Munich, Germany, hospital staff (61) | 4554 | No | 108 (2.4) | 28 (25.9) |
| Cairo, Egypt, hospital staff (62) | 4040 | No | 170 (4.2) | 116 (68.2) |
| Health care personnel at 13 U.S. medical centers (63) | 3248 | No | 194 (6.0) | 56 (28.9) |
| Maranhão, Brazil, residents (64) | 3156 | Yes | 1167 (37.0) | 320 (27.4) |
| Ischgl, Austria, residents (65) | 1473 | No | 622 (42.2) | 529 (85.0) |
| Wuhan dialysis patients (66) | 1027 | No | 99 (9.6) | 50 (50.5) |
| Buenos Aires, Argentina, residents (67) | 873 | No | 486 (53.4) | 396 (85.0) |
| Connecticut residents (68) | 567 | Yes | 23 (4.1) | 5 (21.7) |
| Sweden nursing home staff (69) | 459 | No | 86 (18.7) | 40 (46.5) |
| London, England, dialysis patients (70) | 358 | No | 129 (36.2) | 52 (40.3) |
| Nashville, Tennessee, hospital staff (71) | 249 | No | 19 (7.6) | 8 (42.1) |
| London maternity unit staff (72) | 200 | No | 29 (14.5) | 10 (34.5) |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Boldface indicates details that increase the likelihood of higher-quality evidence.

Data Synthesis and Analysis

We synthesized evidence qualitatively by evaluating study design, including whether data were collected longitudinally; testing methods; number of participants; and setting. We compared the range and consistency of estimates of the proportion of persons who tested positive but had no symptoms at the time of testing.

Role of the Funding Source

The National Institutes of Health played no role in the design, conduct, or analysis of this review or in the decision to submit the manuscript for publication.

Results

We identified 61 studies or reports that met eligibility criteria. [Table 1](#) summarizes data from the 43 that used PCR testing, and [Table 2](#) summarizes data from the 18 that used antibody testing. The heterogeneity of the studies—in particular, disparate settings and populations—precluded quantitative summaries using meta-analysis. We summarize the evidence in terms of the number of studies and the range, median, and interquartile range (IQR) for persons who tested positive but had no symptoms at the time of PCR testing or who reported having had no symptoms before or at the time of antibody testing. Thirty of the studies included a list of specific symptoms, independent of signs, used to determine symptomatic status ([10–14](#), [17](#), [18](#), [22–28](#), [35](#), [36](#), [38](#), [42](#), [49](#), [51](#), [55–57](#), [60–62](#), [64](#)). Many of the remaining studies used some variation of the catch-all phrase “symptoms compatible with COVID-19.”

Nucleic Acid PCR Testing

Among the 43 studies using PCR testing ([10–41–42–54](#)), the proportion of persons who tested positive but had no symptoms at the time of testing

ranged from 6.3% to 100%, with a median of 65.9% (IQR, 42.8% to 87.0%).

Nineteen of the PCR-based studies collected data on symptoms longitudinally after testing, making it possible to distinguish between presymptomatic and asymptomatic infection (15, 17, 18, 20, 22, 25, 26, 27, 32, 37–40, 45, 47, 48, 51, 53, 54). The follow-up period in these studies ranged from 2 to 70 days, with a median of 14 days (IQR, 14.0 to 15.8 days). The proportion of persons who tested positive and remained asymptomatic ranged from 6.3% to 91.7%, with a median of 42.5% (IQR, 29.6% to 77.8%).

Of the 19 longitudinal studies, 14 provided information on the evolution of symptomatic status (Table 3) (15, 17, 18, 20, 22, 32, 37–40, 47, 51, 53, 54). Among persons who tested positive but had no symptoms at the time of testing, the proportion who remained asymptomatic during a follow-up period ranged from 11.1% to 100%, with a median of 72.3% (IQR, 56.7% to 89.7%).

Table 3. Evolution of Symptomatic Status

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| Study | Initially Tested Positive Without Symptoms, n | Remained Asymptomatic, n (%) |
|---|---|------------------------------|
| U.S. skilled-nursing facility residents (15) | 3227 | 2194 (68.0) |
| Vo', Italy, residents (17) | 34 | 34 (100.0) |
| U.S. Navy aircraft carrier crew (18) | 978 | 572 (58.5) |
| San Francisco, California, residents (20) | 41 | 23 (56.1) |
| <i>Diamond Princess</i> cruise ship passengers and crew (22) | 410 | 311 (75.9) |
| Greek citizens evacuated from the United Kingdom, Spain, and Turkey (32)* | 39 | 35 (89.7) |
| Japanese citizens evacuated from Wuhan, China (37) | 6 | 3 (50.0) |
| London, England, nursing home residents and staff (38) | 67 | 46 (68.7) |
| Indian citizens evacuated from Iran (39) | 44 | 44 (100.0) |
| Maryland long-term care facility residents (40) | 177 | 154 (87.0) |
| New York City obstetric patients 2 (47) | 29 | 26 (89.7) |
| Illinois skilled-nursing facility residents (51) | 14 | 13 (92.9) |
| Los Angeles, California, skilled-nursing facility residents (53) | 14 | 6 (42.9) |
| King County, Washington, nursing facility residents (54) | 27 | 3 (11.1) |

* Data clarified via personal communication with coauthor.

Of the 43 studies that used PCR testing, 24 collected cross-sectional data and reported only the symptomatic status at the time of testing, so we could not distinguish between presymptomatic and asymptomatic cases (10–14, 16, 19, 21, 23, 24, 28–31, 33–36, 41–44, 46, 49, 50, 52). In these studies, the proportion of persons who tested positive but had no symptoms at the time of testing ranged from 40.7% to 100%, with a median of 75.5% (IQR, 50.3% to 86.2%).

Of the 43 studies that used PCR testing, 4 used random selection of participants to achieve a representative sample of their target population: residents of England (10–12, 14), Iceland (16), or Indiana (23). Proportions of persons who tested positive but had no symptoms at the time of testing ranged from 43.0% to 76.5%, with a median of 45.6% (IQR, 43.6% to 61.8%). None of the PCR testing studies that used random selection of participants collected longitudinal data on symptoms, so we could not distinguish between presymptomatic and asymptomatic cases.

The largest of the representative data sets, and the largest study identified in our search, was from the REACT (Real-time Assessment of Community Transmission) program. REACT has implemented nationwide nucleic acid and antibody testing (discussed later) for SARS-CoV-2 of persons in England aged 5 years and older in multiple phases since May 2020 ([10–12](#)). In [Table 1](#), we have combined the results of 6 phases of nucleic acid testing from REACT, yielding data for 932 072 persons (England residents 1). At the time of testing, 1425 of 3029 persons (47.0%) who tested positive had no symptoms. The study did not collect longitudinal data on symptoms, so we could not distinguish between presymptomatic and asymptomatic cases.

The second largest of the representative studies was also from England; it included 36 061 persons tested between 26 April and 27 June 2020 ([14](#)). The proportion of persons who tested positive was 0.3%, identical to that reported by REACT, but the proportion of persons who tested positive but had no symptoms at the time of testing was 74.8%, much larger than in the REACT study. The study did not collect longitudinal data on symptoms, so we could not distinguish between presymptomatic and asymptomatic cases.

In the cross-sectional study of Belgian long-term care facilities ($n = 280\,427$), age did not seem to affect the proportion of persons who tested positive but had no symptoms at the time of testing ([13](#)). The study tested 138 327 staff and 142 100 residents. Median age was 42 years for staff and 85 years for residents; despite this considerable difference, the proportion of those who tested positive without symptoms was 74.0% for staff and 75.3%

for residents. This finding is consonant with the finding of a longitudinal study from Vo', Italy, in which more than 85% of the town's 3275 residents were tested: "Among confirmed SARS-CoV-2 infections, we did not observe significant differences in the frequency of asymptomatic infection between age groups" (17).

Of the 43 studies that used PCR testing, 21 involved high-density living or working environments, such as nursing homes and factories (13, 15, 18, 19, 21, 22, 24–28, 30, 38, 40, 42, 46, 50, 51, 53, 54). The settings with the highest proportion of persons who tested positive without symptoms included prisons (19) and poultry processing plants (21). Yet, the data seem to be insufficient to conclude that setting was a causative factor. In the 21 studies of high-density environments, the proportion of persons who tested positive but had no symptoms at the time of testing ranged from 6.3% to 96.0%, with a median of 62.8% (IQR, 40.6% to 87.0%). In the remaining 22 studies that did not involve such high-density environments, the proportion ranged from 27.3% to 100%, with a median of 67.2% (IQR, 43.5% to 84.7%).

Antibody Testing

In the 18 studies based on antibody testing (Table 2) (55–72), the proportion of persons who tested positive but did not report having had symptoms ranged from 21.7% to 85.0%, with a median of 41.2% (IQR, 32.6% to 48.1%).

Among the 18 antibody testing studies, 6 used random selection of participants to achieve a representative sample of their target population: residents of England (55); Spain (56); Bavaria, Germany (59); Louisiana (60); Maranhão, Brazil (64); or Connecticut (68). In these antibody studies with representative samples, the proportion of persons who tested positive but did not report having had symptoms ranged from 21.7% to 47.3%, with a median of 32.7% (IQR, 28.7% to 43.4%).

The 2 largest studies based on antibody testing were nationwide serosurveys from England (55) and Spain (56), both designed to achieve representative samples of community-dwelling persons. The English data, from the REACT program described earlier, were collected during 3 rounds of testing from June through September 2020 and include 365 104 persons. The Spanish data were collected 27 April to 11 May 2020 and include 61 075 persons. The proportion of persons who tested positive but did not report having had symptoms was 32.4% in England and 33.0% in Spain.

Discussion

Symptom detection relies on the subjective reports of patients (73). For example, anosmia has turned out to be a distinctive symptom of COVID-19 (74), and we depend on patients to perceive and report a diminution, however slight, of their normal olfactory abilities. But such self-reports are influenced by many factors, including variability in the ability to recall symptoms and idiosyncratic awareness of bodily sensations.

Current data suggest that infected persons without symptoms—including both presymptomatic and asymptomatic persons—account for more than 40% of all SARS-CoV-2 transmission (75–77). The proportion of new infections caused by asymptomatic persons alone is uncertain, but when researchers in Wanzhou, China, analyzed epidemiologic data for “183 confirmed COVID-19 cases and their close contacts from five generations of transmission,” they determined that the asymptomatic cases, which made up 32.8% of infected persons, caused 19.3% of infections (78).

The 61 studies and reports that we have collected provide compelling evidence that the asymptomatic fraction of SARS-CoV-2 infection is sizable. These data enable us to make reasonable inferences about the proportion of SARS-CoV-2 infections that are asymptomatic.

Studies designed to achieve representative samples of large populations provide useful data because they may accurately reflect human populations in general. Four of the PCR-based studies are in this category, with target populations of England (10–12, 14), Iceland (16), and Indiana (23). The proportion of persons who tested positive but had no symptoms at the time of testing ranged from 43.0% to 76.5%, with a median of 45.6% (IQR, 43.6% to 61.8%). However, these studies fall short of providing the highest-quality evidence because they collected only cross-sectional data. As a result, we cannot distinguish between presymptomatic and asymptomatic cases.

In 14 longitudinal studies that reported information on the evolution of

symptomatic status, a median of 72.3% of persons who tested positive but had no symptoms at the time of testing remained asymptomatic during a follow-up period (15, 17, 18, 20, 22, 32, 37–40, 47, 51, 53, 54). If a similar proportion remained asymptomatic in the 4 large, representative, PCR-based studies, in which the median was 45.6%, the asymptomatic fraction of SARS-CoV-2 infection would be 33.0%.

Among the data that we have assembled here, the highest-quality evidence comes from the large-scale studies using antibody testing that were designed to achieve representative samples of nationwide populations in England ($n = 365\,104$) (55) and Spain ($n = 61\,075$) (56). It is remarkable that these independently conducted serosurveys yielded nearly identical proportions of asymptomatic SARS-CoV-2 infections: 32.4% in England and 33.0% in Spain.

We may infer that persons who receive positive antibody test results can be classified accurately as asymptomatic because such results are likely to occur only after the onset of symptoms, if any. In a study of 222 hospitalized patients in Wuhan, China, IgM and IgG antibodies to SARS-CoV-2 were first detected 3 and 4 days, respectively, after symptomatic onset of COVID-19 (79). In a study of 109 health care workers and 64 hospitalized patients in Zurich, Switzerland, the severity of illness seemed to affect how quickly SARS-CoV-2 antibodies appeared (80). Patients with severe COVID-19 had detectable SARS-CoV-2 antibody titers after symptom onset, but those with mild cases “remained negative or became positive [for SARS-CoV-2 antibodies] 12 to 14 days after symptom onset” (80). These

data suggest that positive antibody test results are unlikely to occur during the period when it is uncertain whether an infected person is presymptomatic or asymptomatic.

However, serosurveys do have significant limitations for the purpose of estimating the asymptomatic fraction. Not all persons who are believed to have been infected with SARS-CoV-2 later have a positive result for SARS-CoV-2 antibodies (81). The reasons may include a false-positive result on the initial PCR test; a false-negative result on the antibody test; or the absence of detectable antibodies, perhaps because the infection was cleared without requiring adaptive immunity. In addition, the role of mucosal immunity in clearing SARS-CoV-2 infection has not yet been fully elucidated (82), and a nasal wash to detect the IgA antibodies active in mucosal immunity is not part of standard testing practice. Persons who clear SARS-CoV-2 infection through innate or mucosal immunity might be more likely to be asymptomatic but would not be categorized as such in a serosurvey, possibly contributing to an underestimate of the asymptomatic fraction.

Another limitation of serosurveys is the requirement that an interview or questionnaire about symptomatic status accompany the blood sample. The onus is on the study participant to accurately recall symptoms, if any, from weeks or even months earlier. In the midst of a pandemic that has transformed everyday life around the globe, it seems reasonable to hypothesize that awareness of and memory for symptoms possibly related to COVID-19 are heightened. This might result in a greater likelihood of

noticing and reporting symptoms that would otherwise be missed or ignored, thereby leading to a lower estimate of the asymptomatic fraction. For these reasons, we have evaluated serosurveys in the context of other results and found them to be concordant.

When estimates from large-scale, cross-sectional, PCR-based studies with representative samples; longitudinal PCR-based studies; and nationwide serosurveys with representative samples are combined, it seems that the asymptomatic fraction of SARS-CoV-2 infection is at least one third. To confirm this estimate, large-scale longitudinal studies using PCR testing with representative samples of national populations would be useful. As SARS-CoV-2 vaccination campaigns are implemented worldwide, though, the window for such research may be closing.

In light of the data presented here, we believe that COVID-19 control strategies must be altered, taking into account the prevalence and transmission risk of asymptomatic SARS-CoV-2 infection. Frequent, inexpensive, rapid home tests (83) to identify and contain presymptomatic or asymptomatic cases—along with government programs that provide financial assistance and, if necessary, housing to enable infected persons to isolate themselves (84)—may be a viable option. And as the first generation of SARS-CoV-2 vaccines is deployed, more research will be needed to determine their efficacy in preventing asymptomatic infection (85).

Comments

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