CORRESPONDENCE

Prevalence of Asymptomatic SARS-CoV-2 Infection

TO THE EDITOR: Oran and Topol's narrative review (1) is commendably useful for being one of the first attempts to estimate the *proportion* of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) carriers who are asymptomatic. However, their conclusion that therefore "asymptomatic SARS-CoV-2 infection . . . is a significant factor in the rapid progression of [coronavirus disease 2019 (COVID-19)]" seems to be utterly unsubstantiated. This is surprising considering *Annals*' normally rigorous peer-review standards.

Oran and Topol's assertion in the abstract that "asymptomatic persons . . . can transmit the virus" is supported by only 2 data. They claim that the authors of an Italian study "confirmed that several new cases of SARS-CoV-2 infection . . . had been caused by exposure to asymptomatic persons." However, the cited (non–peer-reviewed) article merely mentions that 2 or at most 3 of 8 persons studied "*may* [emphasis added] have become infected from an asymptomatic carrier" (2). For example, the authors of this study state, "Subject 5 reported meeting an asymptomatic infected individual before the lockdown." Of note, the same study reported, "No infections were detected in . . . 234 tested children [younger than 11 years], despite . . . living in [the] same household as infected people." This finding is consistent with other evidence that children are much less likely to become infected and, when infected, are typically asymptomatic (as opposed to presymptomatic) carriers (3, 4).

The only other evidence cited by Oran and Topol to support the role of asymptomatic transmission comes from just 1 of the other 16 cohort studies they reviewed. They include the following statement from that study: "More than half of [infected nursing facility] residents . . . were asymptomatic at the time of testing and most likely contributed to transmission" (5). In fact, the cited study explains that "7 days after their positive test, 24 of 27 asymptomatic residents (89%) had onset of symptoms and were recategorized as pre-symptomatic." Oran and Topol seem to have confused the same issue of asymptomatic versus presymptomatic transmission that they attempt to clarify at the beginning of their own review when they state, "To be clear, the asymptomatic individual . . . will never develop symptoms."

I ask that the Editors retract this review or at least request that the authors modify their perhaps unintentional but clearly misleading conclusion about the contagiousness of asymptomatic SARS-CoV-2 carriers. Any objective expert or careful reader surely would wonder whether the review's conclusion, which warns about "the high risk for silent spread by asymptomatic persons" and suggests that therefore "[m]edical practice and public health measures should be modified to address this challenge," is in fact substantiated by the "data" cited by the authors (that is, that 2 or 3 persons in Italy who reported having had contact with asymptomatic carriers *may* thus have become infected). This review and in particular its dubiously substantiated conclusion have been widely cited—including in many reports asserting that "up to 45% of all Covid-19 infections are from asymptomatic persons" (4)—and therefore urgently require correction.

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Disclosures: The author has disclosed no conflicts of interest. The form can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1282.

doi:10.7326/L20-1282

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TO THE EDITOR: We read Oran and Topol's narrative review with interest (1). There is a clear need to better understand the contribution of persons with asymptomatic SARS-CoV-2 infection (that is, those with no symptoms throughout their infection) in driving the current pandemic. However, we believe that there are caveats that are pertinent when interpreting the findings of this review, including the lack of a clear definition of "asymptomatic infection" and selective inclusion of cross-sectional studies.

First, a narrative review containing a dearth of poor-quality evidence resulting in an overestimate of asymptomatic infections is problematic and may misinform policy response. Of the 16 studies included in this review, 4 defined symptoms of COVID-19 as fever and respiratory symptoms, 3 did not clearly define symptoms, and 6 were media articles that provided no information about symptoms. Respiratory symptoms or fever do not cover the spectrum of COVID-19 presentations, and many persons with nonspecific or mild symptoms are misclassified as being asymptomatic.

Second, cross-sectional studies cannot determine who will remain asymptomatic throughout their infection (2). For example, a study of 359 COVID-19 cases in Guangzhou, China, found that 71 persons (86%) later developed symptoms (3). Nine of the 16 studies that Oran and Topol include are cross-sectional in design, but Oran and Topol describe them as cohorts. As such, whether some patients might have developed symptoms later is unclear. Only 1 study included other symptoms (such as malaise, rhinorrhea, and those involving the throat) and followed patients, with 89% developing symptoms later (4).

Third, none of the studies cited included contact tracing; therefore, we cannot comment on asymptomatic transmission based on included studies. In contrast to Oran and Topol's conclusions, recent studies assessing longitudinal characteristics of viral load and transmission have found that truly asymptomatic patients have significantly lower viral loads than those who develop symptoms and transmit infection to fewer secondary cases (5).

Finally, a systematic review addressed the same question using a robust methodology, excluded several of the studies that Oran and Topol included, and concluded that 15% to 20% of persons infected with SARS-CoV-2 remain asymptomatic (3). There remains an immediate need to fill knowledge gaps on COVID-19; however, efforts must coalesce to conduct systematic reviews using robust and transparent methods to avoid

selective reporting and provide a balanced synthesis of evidence. Academic groups should join forces to coordinate efforts, share the burden to deliver timely and robust systematic reviews, avoid duplication, and improve quality.

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Acknowledgment: The authors thank the CORRE Network (International COVID-19 Rapid Evidence Reviews Group).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1283.

doi:10.7326/L20-1283

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TO THE EDITOR: The existence of a substantial but unclear number of asymptomatic patients with SARS-CoV-2 worldwide has raised concerns among global public health authorities. Oran and Topol's narrative review (1) concluded that asymptomatic patients might account for approximately 40% to 45% of SARS-CoV-2 infections on the basis of results from 16 cohort studies from different sources. Unfortunately, their review did not include any studies from China.

In China, the detection of asymptomatic infection is a core task for combating the spread of COVID-19. Studies in China that have been peer-reviewed and officially published show that asymptomatic infection occurred in no more than 20% of cases (specifically, between 6% and 15.8%). This proportion is much lower than the 40% to 45% reported in Oran and Topol's review.

These studies in China were based on different populations, including hospitalized contacts of patients with COVID-19 (34 of 279 [12.2%] persons in Wuhan City in Hubei province [2]), all infected persons tracked throughout a city (25 of 391 [6%] persons in Shenzhen City in Guangdong province [3]), and asymptomatic infections in childhood cases across China (94 of 731 [12.9%] persons [4]) and in Wuhan city (27 of 171 [15.8%] persons [5]). Because of the differences in the study setting and included populations of all the studies (including the 16 cohorts in Oran and Topol's narrative review), the inferred proportion of asymptomatic SARS-CoV-2 infection—whether 20% or 40%—may not be accurate. The true proportion needs to be determined by more carefully designed studies in the future. Nevertheless, in the context of the current research, we believe that Oran and Topol's review should supplement the information we provide here in order to give readers a more objective understanding of the proportion of asymptomatic infections.

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1281.

doi:10.7326/L20-1281

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TO THE EDITOR: Oran and Topol (1) reviewed 16 studies that provide data on asymptomatic persons who tested positive for SARS-CoV-2 infection by real-time reverse transcriptase polymerase chain reaction (RT-PCR) assays. On the basis of 3 representative studies, they concluded that 40% to 45% of infected

persons are asymptomatic. From this, they made several policy recommendations. However, their calculations did not take into account the tests' sensitivity or specificity.

We found 20 studies that reported false-negative rates of 0% to 52% (that is, sensitivities of 48% to 100%) using RT-PCR assays for SARS-CoV-2 (2). Though these tests typically have 100% analytical specificity, their clinical specificity–which includes false-positive results due to contamination and other human error–is lower. In a review of 37 large external quality assessments of PCR assays of RNA viruses between 2004 and 2019, false-positive rates ranged from less than 0.6% to 8.1%; a total of 7 external quality assessments of RT-PCR assays for SARS-CoV-2 yielded false-positive rates of less than 0.4% to 0.9%; and 3 studies of RT-PCR assays for SARS-CoV-2 used in clinical settings reported false-positive rates of 0.5% to 3.0% (2). These data show that false-positive rates vary with circumstances and that a low rate in 1 institution, state, or country does not mean that the rate is low everywhere.

The 3 representative studies cited by Oran and Topol had positivity rates of 0.8% to 2.0%. With a false-negative rate of 0% to 52%, false positive-rates of 0.3% to 0.9% would yield enough false-positive results to account for all the asymptomatic infected persons reported. In other words, these persons may not actually have been infected.

They also may not have been asymptomatic. Oran and Topol note that asymptomatic persons–that is, those who are infected but never develop symptoms–must be distinguished from presymptomatic ones. Doing so requires checking for symptoms over the period of time in which symptoms could potentially appear: the maximum reported incubation period starting from the person's date of infection (if known) or the first positive result on PCR testing. Oran and Topol acknowledge that longitudinal observations were made in only 5 of the 16 studies they reviewed. However, in 4 of those 5 studies, the actual or median observation periods were 2 days (obstetric patients), 7 days (nursing home residents), 0 to approximately 14 days (persons in Italy), and approximately 14 days (Greek evacuees). In contrast, the maximum incubation period for COVID-19 is reported as more than 14 days (3). In the 3 representative studies specifically, there was no effort made to determine symptoms over time (Iceland and Indiana) or the effort was insufficient (Italy).

We do not contend that there are no asymptomatic carriers of SARS-CoV-2. Rather, we suggest that the data reviewed do not support the review's conclusion that a large proportion of infected persons are asymptomatic.

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1284.

doi:10.7326/L20-1284

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TO THE EDITOR: Oran and Topol's narrative review (1) catalogs the existing evidence on the prevalence of asymptomatic SARS-CoV-2 infection and thus provides a useful resource for clinicians and policymakers. However, they draw several provocative conclusions that are not supported by the data.

The authors accurately report that after 2 weeks of quarantine, some sailors on the U.S.S. *Theodore Roosevelt* continued to test positive for SARS-CoV-2. In their discussion, the authors state that "the experience aboard the U.S.S. *Theodore Roosevelt* suggests that they might be able to transmit the virus for longer than 14 days." However, results of the RT-PCR assays that are commonly used to diagnose COVID-19 can remain positive for weeks after the onset of symptoms. This does not imply that such patients remain infectious; instead, data suggest that it would be unusual to detect infectious viral particles more than 10 days after illness onset where symptoms have resolved (2). The authors' key summary point stating that "asymptomatic persons can transmit SARS-CoV-2 to others for an extended period, perhaps longer than 14 days" does not follow from the U.S.S. *Theodore Roosevelt* experience and thus seems misleading.

The authors cite data from Vo', Italy, in support of the idea that asymptomatic persons can transmit SARS-CoV-2. That such asymptomatic transmission can take place is widely accepted; however, the extent to which this is so and the contribution that this phenomenon makes to the spread of the pandemic remain uncertain. In 1 analysis from Singapore, presymptomatic transmission was implicated in only 6.4% of cases (3). In any case, Oran and Topol's review adds no new information to this discussion. The statement in their concluding paragraph that "the early data that we have assembled on the prevalence of asymptomatic SARS-CoV-2 infection suggest that this is a significant factor in the rapid progression of the COVID-19 pandemic" likewise seems exaggerated and premature.

Much about SARS-CoV-2 remains unknown. The narrative review by Oran and Topol will serve as a helpful reference. However, scientists can help to balance a public environment already saturated with disinformation and media hype by modeling accurate reporting, prudence, and restraint.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1279.

doi:10.7326/L20-1279

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TO THE EDITOR: I read Oran and Topol's narrative review with interest (1). The world is facing a problem that is very rare to date. Since COVID-19 was first diagnosed in December 2019, a total of 8 860 331 persons have been infected worldwide and 465 740 persons have died as of 22 June 2020 (2). Many issues related to this disease have yet to be clarified. Oran and Topol analyzed 16 studies on patients with positive results for SARS-CoV-2 infection by RT-PCR testing and suggest that this disease may be asymptomatic in 40% of 45% of infected persons (1).

Although the evidence level of their included studies is low, we believe that Oran and Topol's review makes a remarkable point that may affect the daily functioning of health institutions and public health professionals in pandemic conditions. However, the sensitivity of RT-PCR testing may be low because of such factors as suboptimal clinical sampling, variability in viral load, and sensitivity of the manufacturer test kit (3). The false-negative rate for SARS-CoV-2 was reported to be between 2% and 29% (3). In a study of 205 patients, the sensitivity of RT-PCR testing was 93% for bronchoalveolar lavage, 72% for sputum, 63% for nasal swabs, and 32% for throat specimens (4).

The sensitivity is uncertain for asymptomatic persons. Woloshin and colleagues (5) state that determining the test sensitivity in this population is an urgent priority. They also state that, even in a highly sensitive test, negative results cannot exclude infection if the probability of pretesting is high (5). We believe that the rate of asymptomatic persons in society may be higher because of the lack of a gold standard for the diagnosis of COVID-19.

Despite the World Health Organization report that caused confusion about the contagiousness of asymptomatic COVID-19 cases, we believe the number of asymptomatic cases in the community may be higher than expected. We further contend that public health policies for controlling infection should be developed accordingly.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1280.

doi:10.7326/L20-1280

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IN RESPONSE: In our view, Dr. Halperin does not fairly characterize the evidence of asymptomatic transmission presented by Lavezzo and colleagues (1) concerning their research in Vo', Italy. Lavezzo and colleagues state, "The presence of a significant number of asymptomatic SARS-CoV-2 infections raises questions about their ability to transmit the virus. To address this issue, we conducted an extensive contact tracing analysis of the 8 new infections." After describing the various contacts of the infected persons, Lavezzo and colleagues conclude, "These results suggest that asymptomatic infections may play a key role in the transmission of SARS-CoV-2."

The following is the complete sentence from our review cited by Dr. Halperin: "The early data that we have assembled on the prevalence of asymptomatic SARS-CoV-2 infection suggest that this is a significant factor in the rapid progression of the COVID-19 pandemic." From our perspective, it seems that Dr. Halperin has inferred a far more extreme interpretation than our actual words are meant to convey. We stress that the data are early, not definitive. We describe them as suggestive, not conclusive.

We are puzzled by the critique of Dr. Cevik and associates. In the opening paragraphs of our review, we clearly state that most of the data sets were cross-sectional in nature. In our table, we took care in labeling the minority of data sets that included longitudinal data. We also clearly explained the ambiguity surrounding asymptomatic versus presymptomatic status.

The "systematic review" preprint (2) that Dr. Cevik and associates cite appeared after our article was published. In our opinion, this review fails to adequately address the compelling study that it included from Vo', Italy, which we also included. Not only does this study contain a large representative sample with longitudinal data, but its findings are supported by other data sets that we included. The study was completed over 14 days, and the investigators concluded that the proportion of asymptomatic persons was 42.2%. In addition, none of the participants who was asymptomatic at the beginning of the study had developed symptoms by the end.

None of the sources cited by Drs. Han and Li present data that were collected from representative samples. In contrast, 3 of the studies that we included in our review are the result of representative samples, and 1 of these has the added benefit of longitudinal data from a 14-day period. We were impressed by the narrow range reported in these studies for the proportion of asymptomatic infected persons: between 42.2% and 44.8%. However, in the absence of longitudinal data for 2 of these studies and because of the resulting uncertainty concerning the possible admixture of presymptomatic persons, we suggested that 30% is a conservative estimate.

Drs. Cohen and Kessel are concerned about a potentially high false-positive rate for RT-PCR testing for SARS-CoV-2. Large-scale testing programs in China would seem to be instructive. Between 14 May and 1 June 2020 in Wuhan, public health officials tested 9 899 828 persons, which represented 92.9% of those older than 6 years (3); a total of 300 persons received positive results. In October 2020 in Qingdao, 10.9 million persons were tested (4); of these, 9 persons received positive results.

Even if one were to assume that all of these positive test results were erroneous, that would mean that, as a fraction of total tests performed, 0.003% of the tests in Wuhan and 0.00008% of those in Qingdao were false-positives. This real-world evidence seems to be at odds with the studies cited by Drs. Cohen and Kessel, which are based on considerably smaller data sets. Clearly, more research is needed on this topic.

We assembled the data in our review in April and May 2020, beginning approximately 3 months after the first reports of illness caused by a novel coronavirus. Our review, which was published on 3 June, was our best effort to present and interpret those early data. We believe that it scrupulously adheres to the principles of "accurate reporting, prudence, and restraint" suggested by Dr. Elder.

Like so much else associated with SARS-CoV-2, the finer points of infectiousness and asymptomatic transmission are still, as of this writing in October 2020, hardly settled matters. According to the Centers for Disease Control and Prevention, "Recovery of replication-competent virus between 10 and 20 days after symptom onset has been documented in some persons with severe COVID-19 that, in some cases, was complicated by immunocompromised state" (5). An analysis of the outbreak aboard the *Diamond Princess* cruise ship concluded, "Asymptomatic individuals were the source for 69% (20-85%) of all infections" (6).

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-3012.

doi:10.7326/L20-1285

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Serodiagnostics for SARS-CoV-2

TO THE EDITOR: In their narrative review, Cheng and colleagues (1) state, "[I]f testing asymptomatic individuals when the true seroprevalence of a population is only 5%, an assay with a specificity of 95% would produce a false-positive rate of 50%." However, their definition of *false-positive rate* is unclear. Is it defined as 1 − specificity (that is, 5%) or, as it is sometimes referred to, as (false positives)/(total positives)? Even if the authors used the latter definition, the sensitivity should be given for this calculation. We calculated a positive predictive value of 50% and negative predictive value of 99.7% with the assumption of sensitivity at 95%. We recommend that the authors review the calculation and definition of these values.

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1395.

doi:10.7326/L20-1395

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IN RESPONSE: We would like to clarify our statement on the importance of accounting for the prevalence of prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the population when interpreting serologic test results. We apologize that we unintentionally omitted the value of test sensitivity necessary for calculation of the example, for which we were using an estimate of 95%. Furthermore, the use of the term "false-positive rate" may have led to confusion, because it is sometimes used to refer to (1 − specificity) (1). However, we were using a common statistical definition of this term, whereby "the *false positive rate* [emphasis added] is the percentage of people who test positive but do not actually have the disease" (2).

Nevertheless, the key concept expressed in this section of our review is that imperfect test specificity can introduce important bias when prior infection prevalence is very low, where the number of false-positive results could equal or even outnumber true-positive results. Drs. Harada Sassa and Harada have also explored this issue in their own work using lateral-flow and enzyme-linked immunosorbent assays on pre–coronavirus disease 2019 sera in Japan, showing the risk of overestimating SARS-CoV-2 seroprevalence when using these tools (3). Investigators should be encouraged to use analytical methods that adjust for imperfect test sensitivity and specificity and disease prevalence when estimating SARS-CoV-2 seroprevalence (4).

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-2854.

doi:10.7326/L20-1396

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Addressing Patient Bias Toward Health Care Workers

TO THE EDITOR: Paul-Emile and colleagues (1) address the lack of policies at many medical centers dealing with patient abuse that is mostly due to racial bias toward clinicians. They offer guidance on how to create effective policies for a problem experienced by more than one half of physicians (primarily those who are Black and Asian). Two other less-studied stressors on physicians related to this topic also require legal protective measures.

Because hospital reimbursements from Medicare are tied to Press Ganey patient satisfaction scores, most physician incentive structures include the need for high scores. In 1 study involving 678 physicians, White physicians had higher satisfaction ratings than other physicians and received a greater number of positive comments (2). DeLoughery and associates state that, because race does not influence physician competence, this biased measure of physician quality should not be used to evaluate physician skill or ability (2). Physicians already exposed to unfair, biased behavior from patients should not be penalized for something they cannot control; most likely, they will not receive high scores from patients who engage in such behavior. The emotional and financial ramifications of biased patient behavior toward minority physicians have yet to be further studied.

Racially biased behavior against physicians originates from not only patients but also hospital staff, particularly nurses. Unfortunately, only a few studies are available on this topic. One study on interactions between nurses and female physicians identified that nurses would be more willing to provide service to male physicians because of traditional power imbalances in the relationship and could be more hostile toward female physicians (3). When race is also involved in this equation, sex-biased discrimination was reported to be very significant (4). In another study, 44% to 71% of physicians of different races reported experiencing racial and ethnic discrimination at work (5).

Despite the presence of cultural diversity and antidiscrimination policies in hospitals, minority physicians can be the target of microaggressions in terms of verbal or nonverbal insults coming from nurses. Friction during interactions may be considered a failure in simple communication skills when these concerns are taken to leaders (who may be White and might never have experienced a similar incident). Physicians may choose to suffer silently not to damage their reputations. Again, the effects of negative interactions in the workplace due to subtle discrimination by hospital staff on minority physicians' well-being, productivity, success at work, and opportunity for promotion in their career remain undefined. Awareness of this issue and protective policies in medical centers are warranted.

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Disclosures: The author has disclosed no conflicts of interest. The form can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L20-1397.

doi:10.7326/L20-1397

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