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Prevalence of Asymptomatic SARS-CoV-2 Infection

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A Narrative Review

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Eligible for CME Point-of-Care

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly throughout the world since the first cases of coronavirus disease 2019 (COVID-19) were observed in December 2019 in Wuhan, China. It has been suspected that infected persons who remain asymptomatic play a significant role in the ongoing pandemic, but their relative number and effect hav uncertain. The authors sought to review and synthesize the available evidence on asymptomatic SARS-CoV-2 infection. Asymptomatic persons seem to account for approximately 40% to 45% of SARS-CoV-2 infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days. Asymptomatic infection may be associated with subclinical lung abnormalities, as detected by computed tomography. Because of the high risk for silent spread by asymptomatic persons, it is imperative that

testing programs include those without symptoms. To supplement conventional diagnostic testing, which is constrained by capacity, cost, and its one-off nature, innovative tactics for public health surveillance, such as crowdsourcing digital wearable data and monitoring sewage sludge, might be helpful.

Key SummaryPoints

The likelihood that approximately 40% to 45% of those infected with SARS-CoV-2 will remain asymptomatic suggests that the virus might have greater potential than previously estimated to spread silently and deeply through human populations.

Asymptomatic persons can transmit SARS-CoV-2 to others for an extended period, perhaps longer than 14 days.

The absence of COVID-19 symptoms in persons infected with SARS-CoV-2 might not necessarily imply an absence of harm. More research is needed to determine the significance of subclinical lung changes visible on computed tomography scans.

The focus of testing programs for SARS-CoV-2 should be substantially broadened to include persons who do not have symptoms of COVID-19.

In the early months of the coronavirus disease 2019 (COVID-19) pandemic, an iconic image has been the “proned” patient in intensive care, gasping for breath, in imminent need of artificial ventilation. This is the deadly face of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which as of

26 May 2020 had claimed more than 348 000 lives worldwide (1). But it is not the only face, because SARS-CoV-2 now seems to have a dual nature: tragically lethal in some persons and surprisingly benign in others.

Since February 2020 (2, 3), there have been reports of persons who were infected with SARS-CoV-2 but did not develop symptoms of COVID-19. In some cases (4, 5), the viral load of such asymptomatic persons has been equal to that of symptomatic persons, suggesting similar potential for viral transmission. The prevalence of asymptomatic SARS-CoV-2 infection, however, has remained uncertain. We sought to review and synthesize the available evidence on testing for SARS-CoV-2 infection, carried out by real-time reverse transcriptase polymerase chain reaction using nasopharyngeal swabs in all studies that specified the method of testing.

Most data from the 16 cohorts in this narrative review are not the output of large, carefully designed studies with randomly selected, representative samples. They do not generally purport to depict anything more than certain circumscribed cohorts at specific moments in time. We have not attempted to pool them for the purposes of statistical analysis. When viewed as a collection, though—as a kind of mosaic or patchwork—these data may yield potentially valuable insights into SARS-CoV-2 incidence and the highly variable effect of infection.

The difficulty of distinguishing asymptomatic persons from those who are merely presymptomatic is a stumbling block. To be clear, the asymptomatic individual is infected with SARS-CoV-2 but will never develop symptoms of COVID-19. In contrast, the presymptomatic individual is similarly infected

but eventually will develop symptoms. The simple solution to this conundrum is longitudinal testing—that is, repeated observations of the individual over time. Unfortunately, only 5 of our cohorts include longitudinal data. We must therefore acknowledge the possibility that some of the proportions of asymptomatic persons are lower than reported.

Methods

From 19 April through 26 May 2020, using the keywords *COVID-19*, *SARS-CoV-2*, *symptoms*, and *asymptomatic*, we periodically searched the published medical literature using the PubMed service maintained by the U.S. National Library of Medicine of the National Institutes of Health. We also searched for unpublished manuscripts using the bioRxiv and medRxiv services operated by Cold Spring Harbor Laboratory. In addition, we searched for news reports using Google and monitored relevant information shared on Twitter.

Cohorts

Iceland

In the largest cohort in our set (6), researchers in Iceland used the following 2 methods to screen the general population for SARS-CoV-2 infection: an open invitation for interested parties to register online then provide biosamples at a Reykjavik location, and a text message sent to "randomly chosen Icelanders between the ages 20 and 70 years" inviting them to participate in the same manner as the first group (Table)<(7–19)>. In all,

13 080 persons volunteered for the screening, 100 (0.8%) of whom tested positive for SARS-CoV-2. All who tested positive were aged 10 years or older. None of the 848 children younger than 10 years in the sample tested positive. Among those with positive results, 43 (43%) had no symptoms of COVID-19 at the time of testing. As the researchers note, though, "symptoms almost certainly developed later in some of them" (6).

Table. Summary of SARS-CoV-2 Testing Studies

Table. Summary of SARS-CoV-2 Testing Studies

Cohort	Tested, *n*	SARS-CoV-2 Positive, *n* (%)	Positive but Asymptomatic, *n* (%)	Notes*
Iceland residents (6)	13 080	100 (0.8)	43 (43.0)	R
Vo', Italy, residents (7)	5155	102 (2.0)	43 (42.2)	R, L
Diamond Princess cruise ship passengers and crew (8)	3711	712 (19.2)	331 (46.5)	–
Boston homeless shelter occupants (9)	408	147 (36.0)	129 (87.8)	–
New York City obstetric patients (11)	214	33 (15.4)	29 (87.9)	L
U.S.S. *Theodore Roosevelt* aircraft carrier crew (12)	4954	856 (17.3)	~500 (58.4)	E
Japanese citizens evacuated from Wuhan, China (2)	565	13 (2.3)	4 (30.8)	L
Greek citizens evacuated from the United Kingdom, Spain, and Turkey (14)†	783	40 (5.1)	35 (87.5)	L
Charles de Gaulle aircraft carrier crew (13)	1760	1046 (59.4)	~500 (47.8)	E
Los Angeles homeless shelter occupants (10)	178	43 (24.2)	27 (62.8)	–
King County, Washington, nursing facility residents (15)	76	48 (63.2)	3 (6.3)	L
Arkansas, North Carolina, Ohio, and Virginia inmates (16)	4693	3277 (69.8)	3146 (96.0)	–
New Jersey university and hospital employees (17)	829	41 (4.9)	27 (65.9)	–
Indiana residents (18)	4611	78 (1.7)	35 (44.8)	R
Argentine cruise ship passengers and crew (19)	217	128 (59.0)	104 (81.3)	–
San Francisco residents (29)	4160	74 (1.8)	39 (52.7)	–

E = estimated from incomplete source data; L = longitudinal data collected; R = representative sample.
* A dash indicates that the study did not have a representative sample, collected no longitudinal data, and did not require estimation of missing data.
† Clarified via e-mail communication with coauthor.

Vo', Italy

At the beginning and end of a 14-day lockdown imposed by authorities in the northern Italian town of Vo' (7), researchers collected nasopharyngeal from 2812 residents during the first sampling effort and 2343 during the second; this represented 85.9% and 71.5%, respectively, of the entire population. In the first group, 30 (41.1%) of 73 persons who tested positive for SARS-CoV-2 had no symptoms. In the second, 13 (44.8%) of 29 who tested positive were asymptomatic. According to the researchers, in the roughly 2-week period between the sampling efforts, none of the asymptomatic persons developed any symptoms of COVID-19. In addition, through contact

tracing, they confirmed that several new cases of SARS-CoV-2 infection that appeared during the second sampling had been caused by exposure to asymptomatic persons. In Vo' during the 14-day period studied, young children seemed to play no role in the transmission of SARS-CoV-2: "No infections were detected in either survey in 234 tested children ranging from 0 to 10 years, despite some of them living in the same household as infected people" (7).

Diamond Princess

On 3 February 2020, the *Diamond Princess* cruise ship returned to Yokohama, Japan, for quarantine (8), having transferred an ill passenger to shore in Hong Kong on 25 January who later tested positive for SARS-CoV-2. As of 16 March, 712 (19.2%) of 3711 passengers and crew had tested positive. At the time of testing, 331 (46.5%) of those with positive results were asymptomatic. Although the latter infected persons reported no symptoms, some actually had subclinical changes in their lungs. When computed tomography scans for 76 of these persons were examined, 54% showed lung opacities (20).

An independent statistical modeling analysis (21) based on data available as of 21 February claimed to estimate—with "a Bayesian framework using Hamiltonian Monte Carlo algorithm"—the proportion of asymptomatic persons on the *Diamond Princess*; it arrived at a figure of 17.9%. Considering, though, that data for asymptomatic persons were available only for 15 through 20 February and that the actual proportions of asymptomatic

persons among those tested on these dates were 56.7%, 54.3%, 70.7%, 73.9%, 86.1%, and 46.2%, this estimate seems puzzling. In a separate news account (22), one of the coauthors of this analysis was reported to have estimated that "40% of the general population might be able to be infected [with SARS-CoV-2] without showing any signs."

Boston Homeless Shelter

After a cluster of 15 COVID-19 cases was identified over 5 days at a large homeless shelter in Boston, Massachusetts, the infected persons were removed from the shelter, and all occupants were subsequently tested over a 2-day period (9). Among 408 occupants, 147 (36.0%) tested positive for SARS-CoV-2, of whom 129 (87.8%) were asymptomatic (23). The researchers concluded that "front-door symptom screening in homeless shelter settings will likely miss a substantial number of COVID-19 cases in this high-risk population" (9).

Los Angeles Homeless Shelter

On 28 March, an initial case of COVID-19 was diagnosed with a positive test result at a homeless shelter in downtown Los Angeles, California (10). After a cluster of symptomatic persons was identified early in the week of 20 April, the shelter was closed to new occupants and testing was started for current occupants. As of 22 April, 43 (24.2%) of 178 completed tests were positive for SARS-CoV-2 and 27 (63.8%) of the persons who tested positive were asymptomatic.

New York City Obstetric Patients

Between 22 March and 4 April 2020, women who delivered infants at 2 New York City hospitals were tested for SARS-CoV-2 (11). Among 214 patients, 33 (15.4%) tested positive, 29 (87.9%) of whom were asymptomatic. The researchers note that "fever developed in 3 (10%) before postpartum discharge (median length of stay, 2 days)" (11). Two of those patients, though, were presumed to have endomyometritis, for which they were treated with antibiotics.

U.S.S. *Theodore Roosevelt*

The first case of SARS-CoV-2 infection aboard the American aircraft carrier U.S.S. *Theodore Roosevelt* was diagnosed on 22 March 2020 (24). As of 24 April, 4954 crew members had been tested for the virus; 856 (17.3%) tested positive (12). According to a news report, about 60% of those with positive results were asymptomatic (25). After an extended period of isolation, many of these asymptomatic persons continued to test positive for SARS-CoV-2. An internal U.S. Navy document stated, "Results of out-testing portions of [*Theodore Roosevelt*] crew following 14 days of quarantine leads us to reevaluate our assessment of how the virus can remain active in an asymptomatic host" (26).

Charles de Gaulle Aircraft Carrier

On 8 April 2020, crew members aboard the French naval vessel *Charles de Gaulle* first began showing symptoms of COVID-19, 24 days after last having had contact with those outside the ship while docked on 15 March (27). On 10 April, 50 crew members received positive test results for SARS-CoV-2. The entire crew of 1760 was subsequently tested. As of 18 April, 1046 (59.4%) had tested positive, and of these, nearly 50% were asymptomatic (13).

Japanese Citizens Evacuated From Wuhan, China

As of 6 February 2020, a total of 565 Japanese citizens had been repatriated from Wuhan, China, on charter flights. Thirteen (2.3%) tested positive for SARS-CoV-2, of whom 4 (30.8%) were asymptomatic. As of 6 March, none of the latter persons had developed COVID-19 symptoms (2).

Greek Citizens Evacuated From Spain, Turkey, and the United Kingdom

From 20 through 25 March 2020, a total of 783 Greek citizens were repatriated from Spain, Turkey, and the United Kingdom on 7 flights. Forty (5.1%) positive for SARS-CoV-2 (14). At the time of testing, 39 (97.5%) were asymptomatic. At follow-up about 2 weeks later, 35 (87.5%) had remained asymptomatic (Lytras T. Personal communication.).

Nursing Facility Residents in King County, Washington

On 1 March 2020, a staff member who had worked at a 116-bed skilled-nursing facility in King County, Washington, on 26 and 28 February tested positive for SARS-CoV-2 (15). On 13 March, 76 (92.6%) of the facility's 82 current residents were tested; 23 (30.3%) tested positive. At the time of testing, 12 (52.2%) of the latter persons were asymptomatic. On 19 and 20 March, 49 residents were retested, including those who had previously received negative results and those who had tested positive but were asymptomatic or had atypical symptoms. In this second round of testing, 24 residents (49.0%) had positive results. Of these, 15 (63.5%) were asymptomatic. After a median of 4 days of follow-up, 24 (88.9%) of the 27 asymptomatic persons developed symptoms of COVID-19.

The researchers note, “More than half of residents with positive test results were asymptomatic at the time of testing and most likely contributed to transmission. Infection-control strategies focused solely on symptomatic residents were not sufficient to prevent transmission after SARS-CoV-2 introduction into this facility” (15).

Inmates in Arkansas, North Carolina, Ohio, and Virgin

Widespread outbreaks of COVID-19 in the correctional facilities of several states have led to large-scale screening programs. According to research by Reuters journalists (16), as of 25 April 2020, SARS-CoV-2 test results that include data on symptom status were available for 4693 inmates in the state prison systems of Arkansas, North Carolina, Ohio, and Virginia. Among

these inmates, 3277 (69.8%) tested positive, of whom 3146 (96%) had no symptoms at the time of testing.

Rutgers University Students and Employees

From 24 March through 7 April 2020, researchers recruited 829 students and employees at Rutgers University and 2 affiliated hospitals for SARS-CoV-2 testing (17); 546 were health care workers. In total, 41 (4.9%) tested positive. Among health care workers, 40 (7.3%) tested positive, compared with 1 (0.4%) of those in other fields. Of all who tested positive, 27 (65.9%) reported no symptoms when they were tested.

Indiana Residents

From 25 April through 1 May 2020, the Indiana State Department of Health and the Indiana University Richard M. Fairbanks School of Public Health tested 4611 residents of Indiana for SARS-CoV-2 (18, 28). "This number includes more than 3,600 people who were randomly selected and an additional 900 volunteers recruited through outreach to the African American and Hispanic communities to more accurately represent state demographics" (28). In total, 78 (1.7%) tested positive; 35 (44.8%) of these persons were asymptomatic.

Argentine Cruise Ship Passengers and Crew

In mid-March 2020, a cruise ship departed Ushuaia, Argentina, for a planned 21-day expedition (19). After the emergence of a febrile passenger on the eighth day of the cruise, the ship's itinerary was altered, and it eventually docked at Montevideo, Uruguay, on the 13th day. All 217 passengers and crew members were tested; 128 (59.0%) tested positive, of whom 104 (81.3%) were asymptomatic.

San Francisco Residents

During 4 days in late April 2020, "4,160 adults and children, including more than half of the residents in the 16 square blocks that make up San Francisco Census Tract 229.01" in the Mission District, were tested (29). Seventy-four (1.8%) tested positive, of whom 39 (52.7%) were asymptomatic.

Discussion

Despite concerns about distinguishing asymptomatic from presymptomatic persons, data from 4 of 5 of the cohorts with longitudinal reporting suggest that a small fraction of asymptomatic persons may eventually develop symptoms. In the Italian and Japanese cohorts, 0% of asymptomatic persons became symptomatic. In the Greek and New York cohorts, 10.3% of asymptomatic persons became symptomatic. In the New York cohort, the figure might be as low as 3.4% because of the presumed diagnosis of endomyometritis in 2 of the 3 women who developed fevers. The observation period in this cohort, however, was extremely brief: a median of 2 days.

The King County cohort—in a skilled-nursing facility—is an outlier. Of 27 initially asymptomatic residents, 24 (88.9%) eventually developed symptoms and were therefore recategorized as having been presymptomatic. These persons were presumably much older and had more comorbid conditions than those in the other 4 longitudinal cohorts. In addition, they resided together in a single facility, which might have allowed for repeated exposures to infected persons. More research is needed to ascertain the effect of age and environmental factors on the natural history of COVID-19.

The Vo' cohort seems to confirm that asymptomatic persons can indeed transmit SARS-CoV-2 to others, and the experience aboard the U.S.S. *Theodore Roosevelt* suggests that they might be able to transmit the virus to others for longer than 14 days. These worrisome findings could explain, in part, the rapid spread of the virus around the globe. Persons who do not feel or look ill are likely to have far more interaction with others than those who have symptoms. If asymptomatic transmission is indeed common, testing only those with symptoms would seem to be folly.

The finding that 54% of the 76 asymptomatic persons on the *Diamond Princess* who were examined by computed tomography appeared to ha significant subclinical abnormalities in their lungs is disturbing. Further research will be required to confirm this potentially important finding, taking into account possible confounding factors, including the age of passengers aboard the *Diamond Princess*. If confirmed, this finding suggests that the absence of symptoms might not necessarily mean the absence of harm. The subclinical nature of the finding raises the possibility that SARS-

CoV-2 infection causes subtle deficits in lung function that might not be immediately apparent.

Does the relatively high proportion (60.5%) of asymptomatic cases on the U.S.S. *Theodore Roosevelt*—whose crew members, presumably, are mostly in their 20s and 30s—suggest that asymptomatic infection is more likely in younger persons? Perhaps, but it must be noted that the proportion of asymptomatic infection (47.8%) on the *Charles de Gaulle* aircraft carrier seems to be only marginally higher than average. A case series from Wuhan, China, from 24 December 2019 to 24 February 2020 included data for "78 patients from 26 cluster cases of exposure to the Hunan seafood market or close contact with other patients with COVID-19" (30). Asymptomatic patients "were younger (median [interquartile range] age, 37 [26-45] years vs 56 [34-63] years; $P < .001$), and had a higher proportion of women (22 [66.7%] women vs 14 [31.%] [*sic*] women; $P = .002$)."

As noted earlier, the data and studies reviewed here are imperfect in many ways. The ideal study of asymptomatic SARS-CoV-2 infection has yet to be done. What might that study look like? Most important, it must includ large, representative sample of the general population, similar to the U serosurvey for which the National Institutes of Health is currently recruiting (31). In contrast to the narrowly defined cohorts here, it will be illuminating to have data that accurately reflect the population at large. In addition, longitudinal data must be collected over a sufficiently long time to distinguish between asymptomatic and presymptomatic cases.

Closed cohorts, such as cruise ships, aircraft carriers, and correctional facilities, offer both advantages and disadvantages. Because the likelihood of viral exposure is so much greater than in other settings, the "treatment" that participants receive may be close to uniform. As a result, we may learn more about the average incidence of asymptomatic infection. But the confined environment—which ensures frequent, overlapping interaction between participants—makes it challenging to accurately trace contacts and elucidate the chain of viral transmission.

On the basis of the 3 cohorts with representative samples—Iceland and Indiana, with data gathered through random selection of participants, and Vo', with data for nearly all residents—the asymptomatic infection rate may be as high as 40% to 45%. A conservative estimate would be 30% or higher to account for the presymptomatic admixture that has thus far not been adequately quantified. In any case, these high rates are not aligned with current testing programs that have predominantly focused on symptomatic cases. Beyond expanding testing to those without symptoms or known exposure, our inability to recognize carriers might make necessary the broad adoption of preventive strategies, such as masks.

The 96% rate of asymptomatic infection among thousands of inmates in 4 state prison systems is remarkable. Without any longitudinal data, we cannot estimate the number of presymptomatic cases. If the missing data prove to be similar to the Italian, Japanese, Greek, and New York cohorts, though, the vast majority of these persons will remain asymptomatic. Why, then, might the asymptomatic infection rate in this setting be so anomalously high?

One plausible factor could be cross-immunity imparted by the betacoronaviruses HCoV-OC43 and HCoV-HKU1, which has been proposed as a mitigating factor in the spread of SARS-CoV-2 (32). According to the U.S. Centers for Disease Control and Prevention, HCoV-HKU1 was active across the United States from late November 2019 through mid-February 2020 (33). In a locked-down congregate setting like a prison, it seems possible that contagious respiratory viruses could spread rapidly, so it would be interesting to do a serosurvey for antibodies to these betacoronaviruses. Still, 96% is very high. It would be prudent to review the source data carefully for errors.

What individual differences might account for why 2 persons of the same age, sex, and health status, for example, have idiosyncratic responses to SARS-CoV-2 infection? Why does one come through with nary a symptom, while the other lies near death in intensive care? At the moment, we simply do not know. If ever there were a need for precision medicine—for deeply and thoroughly understanding the multitudinous "-omics" that shape each of us—this is it. Perhaps there will be not just 1 therapy or vaccine for SARS-CoV-2 but versions that are individualized to maximize their efficacy.

In countries like the United States that have been hardest hit by the SARS-CoV-2 pandemic, it has been apparent for some time that the amount of testing must be significantly and rapidly increased—perhaps by an order of magnitude or more. With this new knowledge that a large proportion of those infected with SARS-CoV-2 have no symptoms, the urgency for more testing becomes even greater.

In a perfect world, perhaps using simple, accurate, inexpensive technology that is still on the drawing board (34), we would test each person every day for SARS-CoV-2. Until that is possible, innovative surveillance tactics might provide useful data for public health officials. Self-monitoring with internet-connected thermometers and smart watches that monitor heart rate, then crowdsourcing the resulting data, has been shown to accurately predict the incidence of influenza-like illness as reported by the California Department of Public Health and the Centers for Disease Control and Prevention (35–37). Similarly, monitoring sewage sludge provided "SARS-CoV-2 RNA concentrations [that] were a seven-day leading indicator ahead of compiled COVID-19 testing data and led local hospital admissions data by three days" (38).

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. Medical practice and public health measures should be modified to address this challenge.

This article was published at Annals.org on 3 June 2020.

Comments

7 Comments

Daniel T. Halperin • Adjunct Full Professor, Gillings School of Global Public Health, University of North Carolina, Chapel Hill • 10 June 2020

A Very Useful, also Highly Problematic Review Article

Comment: This review is commendably useful for estimating the PROPORTION of SARS-CoV-2 carriers who are asymptomatic. However, the additional conclusion that “asymptomatic SARS-CoV-2 infection…is a significant factor in the rapid progression of COVID-19” appears to be utterly unsubstantiated (and surprising, considering this journal’s normally rigorous peer review standards). Regarding the authors’ assertion, in the abstract, that “asymptomatic persons…can transmit the virus,” only two data are presented to support this: 1) Citing an Italian study, they claim (my CAPS for emphasis) that the Italian authors: “CONFIRMED several new cases of SARS-CoV-2 infection had been caused by exposure to asymptomatic persons.” However, the (non-peer-reviewed) online paper cited merely mentions that 2 (or at most 3) of 8 persons studied “MAY have become infected from an asymptomatic carrier.” (E.g., “Subject 5 reported meeting an asymptomatic infected individual before the lockdown…”) Note the same study reported that “No infections were detected in…234 tested children [under age 11], despite…living in same household as infected people,” consistent with other evidence that children are much less likely to become infected, and even if infected are typically asymptomatic (as opposed to presymptomatic) carriers 2) (www.washingtonpost.com/opinions/2020/05/29/case-reopening-schools-this-fall/).

The only other evidence cited by Oran and Topal for the role of asymptomatic transmission is from one of the other 16 cohort studies they reviewed, regarding which they conclude: “More than half of [infected nursing facility] residents…were ASYMPTOMATIC at the time of testing and MOST LIKELY contributed to transmission.” In fact, the cited 3) NEJM paper explains that “7 days after their positive test, 24 of 27 asymptomatic residents (89%) had onset of symptoms and were RECATEGORIZED as presymptomatic.” Apparently Oran and Topal have confused here the very same issue (asymptomatic vs presymptomatic transmission) that they attempt to clarify at the onset of their own paper, re “To be clear, the asymptomatic individual…will NEVER develop symptoms.” I petition the journal editors to retract this paper, or at least to request that the authors modify their (perhaps unintentional but clearly misleading) conclusion regarding the contagiousness of asymptomatic SARS-CoV-2 carriers. Surely any objective expert or meticulous reader would also wonder whether the paper’s conclusion, that asymptomatic carriers in point of fact are significant drivers of COVID-19 at the population level, is sufficiently substantiated by the "data" cited by the authors (i.e., that two or three persons in Italy reporting having had contact with asymptomatic carriers MAY thereby have become infected). This article and in its unsubstantiated conclusion has already been widely cited and therefore requires immediate correction.

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Daniel P. Oran and Eric J. Topol • Scripps Translational Science Institute • 11 June 2020

Authors' Response to Cevik, Bogoch, Carson et al

We are puzzled by your critique. In the opening paragraphs of our review, we clearly state that most of these studies are cross-sectional in nature, taking care to label in our table the minority of longitudinal studies. We also clearly explain the ambiguity surrounding asymptomatic versus presymptomatic status.

In our opinion, the unpublished “systematic review” preprint that you refer to, which appeared after our article was published and has not been subject to peer review, fails to adequately address the compelling data that it includes (as did we) from Vo, Italy. Not only is that a large representative sample with longitudinal data, but its findings are supported by other groups that we included. In the study, completed over 14 days, the researchers concluded that the proportion of asymptomatic individuals was 43%. In addition, none of the subjects who were asymptomatic at the beginning of the study had developed symptoms by the end.

In the midst of a global pandemic, we believed that it would be valuable to collect all the currently available data on an ill-defined phenotype and address an important issue: whether a sizable proportion of those infected with SARS-CoV-2 will have no symptoms. As of late May 2020, when we completed our review, which was just five months after the appearance of the first cases of COVID-19, much of that data was in rough and fragmentary form. We think that we faithfully and accurately reported what we found.

Journalism has been described as a first draft of history. In a similar way, our narrative review, which collected the earliest available evidence, is a first draft of science. In the months and years ahead, new evidence — ideally, from well-designed, large-scale studies with representative samples — will appear, adding greater detail and clarity to our knowledge.

We share your perspective that significant gaps remain in what we know about crucial aspects of COVID-19, including the details and frequency of SARS-CoV-2 transmission by infected individuals who have no symptoms, and the harm to the lungs and possibly other parts of the body that might be associated with asymptomatic infection.

We are unaware of any other pathogen that can cause asymptomatic infection in a significant minority of patients — whether that is 20% or 40% — while also having a serious potential of taking lives. We look

forward to collaborating with all interested investigators to expand our knowledge of SARS-CoV-2 and COVID-19.

Zoë Hyde • Western Australian Centre for Health and Ageing, Medical School, University of Western Australia, Perth, Australia • 11 June 2020

Comment on: Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review

To the Editor: In their recent review, Oran and Topol (1) aimed to determine the prevalence of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and concluded 40-45% of infected persons likely remain symptom-free.

Although the authors attempted to distinguish between pre-symptomatic cases (i.e., those yet to develop symptoms) and those who are truly asymptomatic, they base their conclusions on only three studies, two of which are cross-sectional. Furthermore, the remaining longitudinal study considered symptomatic persons to be those with fever or cough, which is an extremely limited definition.

At least two high-quality longitudinal studies were published during the period the authors searched the literature, both reporting a considerably lower prevalence. In a study of 100 laboratory-confirmed index cases and 2,761 close contacts in Taiwan, 22 secondary cases were identified, of which only 4 (18%) were asymptomatic during 14 days of follow-up (2). Following an outbreak in a call centre in Korea, 1,143 people were tested and 97 were found to be infected with SARS-CoV-2. Of these, 4 were pre-symptomatic and 4 (1.9%) remained asymptomatic during a 14-day monitoring period (3). These findings more likely represent the prevalence of asymptomatic infection, given the rigorous testing, contact tracing, and monitoring strategy employed in both settings.

The authors also noted an apparent high proportion of asymptomatic cases (58.4%) among crew members of the U.S.S. Theodore Roosevelt. However, in a serological study of crew and associated personnel published subsequently, only 18.5% were found to be asymptomatic (4). Oran and Top draw attention to the persistent test positivity of crew members, writing that asymptomatic pers “might be able to transmit the virus to others for longer than 14 days.” This thankfully now seems unlikely. While shedding of viral RNA may occur for a month or more, infectious virus was never cultured after the 11th day of illness in patients in Singapore (5). Thus, with the exception of immunocompromised persons and severely ill patients, infectivity is unlikely to persist beyond the second week of illness.

Nonetheless, the authors’ suggestion that widespread mask use may be necessary is wise. The infectious period begins approximately two days before symptom onset, and pre-symptomatic transmission accounts for a substantial fraction of cases (5). While the authors rightly call for policy changes to minimise the risk of silent transmission, their apparent overestimate of asymptomatic infection risks creating the perception that SARS-CoV-2 is less virulent than in reality.

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Muge Cevik, Isaac I Bogoch, Gail Carson, Eric D'Ortenzio, Krutika Kuppalli • on behalf of the CORRE Network (International COVID-19 Rapid Evidence Reviews Group) • 10 June 2020

A problematic interpretation of a narrative review containing a dearth of poor-quality evidence resulting in an overestimate of asymptomatic infections, which might misinform policy response.

There is a clear need to better understand the contribution of asymptomatic SARS-CoV-2 infections (those with no symptoms at all throughout the infection) in driving the current pandemic. However, there are caveats that in our opinion are pertinent when interpreting the reported findings of this review, including the lack of a clear definition of asymptomatic infection and selective inclusion of cross-sectional studies.

In addition, there is a problematic interpretation of a narrative review containing a dearth of poo evidence resulting in an overestimate of asymptomatic infections, which might misinform policy response. Of the 16 reports included in this review, four defined symptoms of COVID-19 as fever and respiratory symptoms, three had no clear symptom definition, and six were media articles proving no information about symptoms. Respiratory symptoms or fever do not cover the spectrum of COVID-19 presentations, and many individuals with non-specific or mild symptoms are misclassified as being asymptomatic. For instance, Gudbjartsson et al. reported that approximately half of the participants in their population screening had rhinorrhoea and cough despite inquiring for those not to participate (1).

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 found that 71 (86%) later developed symptoms (3). Oran and Topal include 9/16 cross-sectional reports, but describe them as

cohorts, so it is unclear whether some patients might have developed symptoms later on. Only one report included other symptoms (malaise, rhinorrhoea, sore throat etc.) and followed individuals, with 89% of patients 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 the author's conclusions, recent studies assessing longitudinal characteristics of viral load and transmission have found truly asymptomatic patients have significantly lower viral loads than those who develop symptoms and transmit 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 conclude that 15-20% of SARS-CoV-2 infected people remain asymptomatic (2). There remains an immediate need to fill knowledge gaps on COVID-19; however, efforts must coalesce to conducting systematic reviews using robust and transparent methodologies, to avoid selective reporting and to provide a balanced synthesis of evidence. Academic groups should join forces to coordinate efforts, share the burden to deliver timely robust systematic reviews, avoid duplication and improve quality.

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Len Geiger • Alpha-1 Lungs Disease Advocate • 8 June 2020

WHO Statement

I'd like to see the authors' response to The World Health Organization's recent statement, "Asymptomatic spread of coronavirus is 'very rare.'" It seems to me that a "minimum of 30%" and "very rare" are difficult to

equate and border on being mutually exclusive statements.

CNBC article on the subject: https://www.cnbc.com/2020/06/08/asymptomatic-coronavirus-patients-arent-spreading-new-infections-who-says.html

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Andrew N. Cohen, Bruce Kessel • Center for Research on Aquatic Bioinvasions, Richmond CA, USA; John A. Burns School of Medicine, University of Hawaii, Honolulu HI, USA • 7 June 2020

Analysis should address test specificity/sensitivity, and adequate assessment of asymptomatic status

Oran and Topol reviewed 16 studies that provide data on asymptomatic individuals who tested positive for SARS-CoV-2 by RT-PCR, and based on three representative studies concluded that 40-45% of infected individuals are asymptomatic. From this they drew 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 0-52% (i.e. sensitivities of 48-100%) in SARS-CoV-2 RT-PCR tests (1). Though these tests typically have 100% analytical specificity, there are no data yet on their clinical specificity, which includes false positives due to contamination and other human error. In a review of 37 large external quality assessments of RT-PCR viral assays conducted in 2004-2019, false positive rates ranged from <0.6-8.1% (1).

The three representative studies cited by Oran and Topol had positivity rates of 0.8-2.0%; with a false negative rate of 0-52%, false positive rates of 0.3-0.9% would yield enough false positives to account for all the asymptomatic infected individuals reported. In other words, they may not actually have been infected. They also may not have been asymptomatic. Oran and Topol noted that asymptomatic individuals—those who are infected but never develop symptoms—must be distinguished from presymptomatic individuals. This requires checking for symptoms over the period of time in which symptoms could potentially appear, that is, over the maximum reported incubation period starting from the individual's date of infection (if known) or diagnosis. Oran and Topal acknowledged that longitudinal observations were made i the 16 studies they reviewed. However, in 4 of those 5 studies the actual or median observation p were 2 days (obstetric patients), 7 days (nursing home), 0 to about 14 days (Italy), and about 14 days (Greek evacuees), while the maximum incubation period for COVID-19 is reported as more than 14 days (2).

In the three representative studies specifically, there was either no effort to determine symptoms over time (Iceland, Indiana) or an insufficient effort (Italy). We want to be clear that we do not here argue that there are no asymptomatic carriers of SARS-CoV-2. Rather, we suggest that the data reviewed does not support the review's conclusion that a large proportion of infected individuals are asymptomatic.

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Dr. Charles Bens • CEO Health at Work • 7 June 2020

Nearly Half of Coronavirus Spread May Be Traced to People Without Symptoms

This article raises many questions, but provides very few answers. Why get you not explore the Ames Theory of priorities for nutrient use, the existing level of vitamin D3, the negative impact of sugar consumption on white blood cell strength or the overall strength of the immune system measured by the Bens Immune Biomarker Test? Previous Coronavirus exposure many have allowed the COVID-19 virus to think this person has immunity, if so why were lungs still damaged?

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