

An open letter to Oran and Topol, authors of

“Presence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review” *Annals of Internal Medicine*. 2020 June 3. <https://doi.org/10.7326/M20-3012>

and Christine Laine (editor-in-chief *The Annals of Internal Medicine*)

Authors: Muge Cevik¹, Isaac I Bogoch², Gail Carson³, Eric D’Ortenzio⁴, Krutika Kuppali⁵, Nicola Low⁶, Sara Loree⁷, Alasdair Munro^{8,9}, Lina Moses⁷, Harish Nair¹⁰, Piero Olliaro³, Louise Sigfrid³, Renaud Vatrineton⁴ behalf of the [CORRE Network](#) (International COVID-19 Rapid Evidence Reviews Group)

Dear Editor,

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 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 poor-quality 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.](#)

References:

1. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med*. 2020.
2. Buitrago-Garcia DC, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. The role of asymptomatic SARS-CoV-2 infections: rapid living systematic review and meta-analysis. *medRxiv*. 2020:2020.04.25.20079103.
3. Zhang W, Cheng W, Luo L, Ma Y, Xu C, Qin P, et al. Secondary Transmission of Coronavirus Disease from Presymptomatic Persons, China. *Emerg Infect Dis*. 2020;26(8).
4. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *New England Journal of Medicine*. 2020;382(22):2081-90.
5. Chau NVV, Thanh Lam V, Thanh Dung N, Yen LM, Minh NNQ, Hung LM, et al. The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. *Clinical Infectious Diseases*. 2020.

Affiliations:

¹Division of Infection and Global Health Research, School of Medicine, University of St Andrews, UK

²Division of Infectious Diseases, Toronto General Hospital and University of Toronto, Canada

³ISARIC Global Support Centre, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK

⁴INSERM (The Institut national de la santé et de la recherche médicale), Paris, France

⁵Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Palo Alto, CA, USA

⁶Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

⁷The Global Outbreak Alert and Response Network (GOARN), Geneva, Switzerland

⁸NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

⁹ Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, Hampshire, UK

¹⁰ Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK

Paper/Report	Symptoms considered	Follow up	Infectivity	Notes
Iceland residents	Cough, fever, body aches, and shortness of breath	No follow up. “Notably, 43% of the participants who tested positive reported having no symptoms, although symptoms almost certainly developed later in some of them.”	Does not provide Information about onward transmission from asymptomatic individuals	Although we asked participants who had respiratory symptoms that they described as more than mild not to participate in population screening, close to half the participants reported symptoms, most commonly rhinorrhea and coughing
Vo’ Italy residents	Fever and/or cough	They have not tested the same population	Does not provide Information about onward transmission from asymptomatic individuals	
Nursing Facility Residents in King County, Washington	Fever (oral or temporal temperature measurement), cough, shortness of breath, sore throat, or any other respiratory symptoms	In the 7 days after their positive test 24 of the 27 asymptomatic residents (89%) had onset of symptoms and were recategorized as presymptomatic	Does not provide Information about onward transmission from asymptomatic individuals	Atypical symptoms if their symptoms included only chills, malaise, increased confusion, rhinorrhea, nasal congestion, sore throat, myalgia, dizziness, headache, nausea, or diarrhea
Diamond princess cruise ship	fever or respiratory symptoms	No follow up, only modelling provided	Does not provide Information about onward transmission from asymptomatic individuals	
Boston homeless shelter	Cough, shortness of breath, fever, “other”	No follow up	Does not provide Information about onward transmission from asymptomatic individuals	
New York City Obstetric Patients	No clear symptom definition provided	No follow up	Does not provide Information about onward transmission from asymptomatic individuals	“Fever or other symptoms of Covid-19”
Japanese Citizens Evacuated From Wuhan, China	Fever, cough, and other non-specific symptoms	No follow up	Does not provide Information about onward transmission from asymptomatic individuals	

Greek Citizens Evacuated From Spain, Turkey, and the United Kingdom	No clear symptom definition	No follow up	Does not provide Information about onward transmission from asymptomatic individuals	
New Jersey University Students and Employees	Fever, cough, shortness of breath, vomiting, diarrhoea, or change in smell or taste.	No follow up	Does not provide Information about onward transmission from asymptomatic individuals	
Argentine Cruise Ship Passengers and Crew	No clear symptom definition	No follow up	Does not provide Information about onward transmission from asymptomatic individuals	“COVID-19 symptoms, and body temperatures”
U.S.S. Theodore Roosevelt aircraft carrier	Media report, no details can be found			
Los Angeles Homeless shelter	Media report, no details can be found			
Charles de Gaulle Aircraft Carrier	Media report, no details can be found			
Indiana Residents	Media report, no details can be found			
Arkansas, North Carolina, Ohio, and Virginia	Media report, no details can be found			
San Francisco Residents	Media report, no details can be found			

Table 1: Summary of reports included in Oran and Topol review