Large-Scale Testing of Asymptomatic Healthcare Personnel for Severe Acute Respiratory Syndrome Coronavirus 2

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Large-scale, 1-time testing of >12,000 asymptomatic healthcare personnel in California, USA, during April–June 2020 showed that prevalence of severe acute respiratory syndrome coronavirus 2 was low (<1%). Testing might identify asymptomatic and presymptomatic persons, including some with high viral burden, enabling prompt implementation of measures to limit nosocomial spread.

Healthcare personnel (HCP) represent a unique group of concern for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease (COVID-19), because of their increased exposure risk from infected patients under their care and risk for onward transmission to patients and coworkers. The current evidence on the large-scale testing of HCP has focused on symptomatic persons (1). However, the potential for asymptomatic transmission of SARS-CoV-2 is well-recognized (2–4), and presymptomatic HCP might contribute to nosocomial outbreaks (5).

Testing HCP before symptom onset represents an opportunity for early detection of infectious persons. In this study, we assessed the prevalence of SARS-CoV-2 infection through mass real-time reverse transcription PCR (rRT-PCR) and IgG testing of asymptomatic HCP and describe the clinical and laboratory characteristics of infected persons.

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The Study

This study was approved by the Stanford Privacy Office, and individual consent was waived. Stanford Medicine, which comprises Stanford Health Care (SHC), Stanford Children's Health, and Stanford School of Medicine, is located in the San Francisco Bay area, California, USA, and is staffed by >26,000 HCP. We performed a SARS-CoV-2 testing study of asymptomatic HCP during April 20–June 8, 2020. Both patient-facing and non–patient-facing SHC HCP were invited for testing on a voluntary basis through messaging across all hospital departments to encourage a safe working environment. All HCP were eligible for testing, and risk-based eligibility criteria were not enforced.

rRT-PCR of nasopharyngeal swab samples was performed by using the SHC envelope gene laboratory-developed test and a commercial assay (Panther Fusion SARS-CoV-2; Hologic Inc., https://www.hologic.com), as described (6). The distribution of cycle threshold (C_t) values of positive results with these assays ranged from 10 to 45. Plasma IgG testing was also performed by using a SHC laboratory-developed ELISA specific for the spike glycoprotein receptor-binding domain antigen (Appendix, https://wwwnc.cdc.gov/EID/article/27/1/20-3892-App1.pdf).

Demographic data were extracted from an institutional database for the entire cohort, and chart review for persons with positive SARS-CoV-2 rRT-PCR results was performed by using electronic medical records. We excluded from the study persons with a positive rRT-PCR result and an illness consistent with COVID-19 in the preceding 6 weeks. Only the first rRT-PCR result per person was included for the main analysis. Repeat rRT-PCR or IgG serologic

analysis within 2 weeks was recommended to each HCP who had an initial positive rRT-PCR result. HCP were classified as asymptomatic or presymptomatic on the basis of symptoms developing consistent with COVID-19 within 2 weeks after testing.

Statistical analysis was performed by using Stata version 15.1 (https://www.stata.com) and the χ^2 test or Fisher exact test for categorical variables with ≤ 5 datapoints/cell and the Mann-Whitney U test for continuous variables. Results were interpreted as significant according to a p value <0.05.

After excluding 12 persons who had a positive rRT-PCR result and earlier illness consistent with COVID-19, we included 12,418 asymptomatic HCP in the study (Figure 1). Of these persons, 8,775 (70.7%) were female, and median age was 39.5 years (interquartile range [IQR] 32.4–50.3 years). The SARS-CoV-2 rRT-PCR positivity rate was 26/12,418 (0.2%; 95% CI 0.1%–0.3%), and IgG seropositivity rate was 111/12,373 (0.9%; 95% CI 0.7–1.1). IgG serologic results were not available for 45 persons from the part of the study population for whom only nasopharyngeal rRT-PCR was performed.

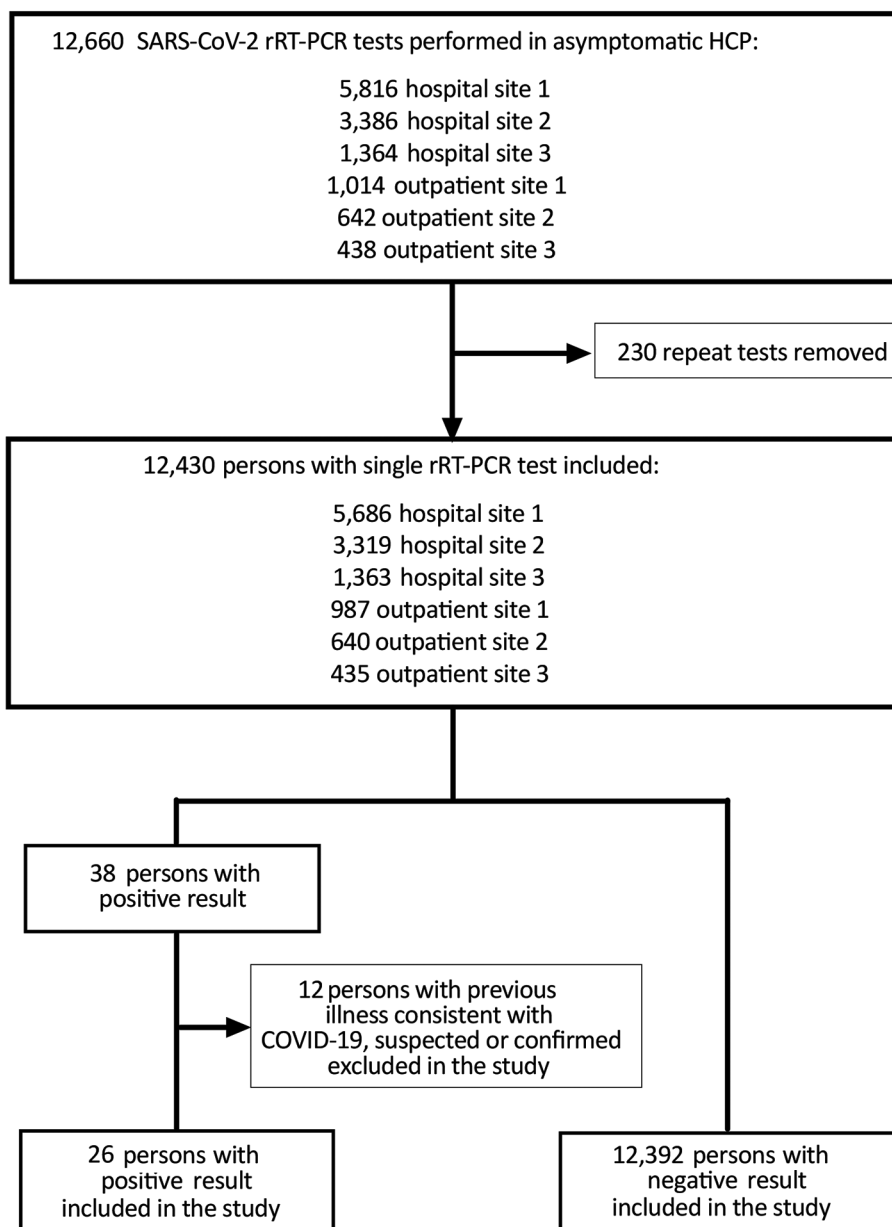Of the 26 persons who had positive rRT-PCR results, 20 remained asymptomatic; for the

Figure 1. Flowchart for study of large-scale testing of asymptomatic healthcare personnel for SARS-CoV-2, California, USA, April–June 2020. COVID-19, coronavirus disease; HCP, healthcare personnel; rRT-PCR, real-time reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table. Clinical and laboratory characteristics for 26 healthcare personnel who had positive initial results by rRT-PCR for severe acute respiratory syndrome coronavirus 2, California, USA, April–June 2020*

Characteristic	Overall, n = 26	Asymptomatic, n = 20	Presymptomatic, n = 6	Unadjusted p-value†
Median age, y (IQR)	39.5 (31–46)	41 (32.5–47)	32.5 (30–40)	0.3
Sex				
M	7 (26.9)	7 (35.0)	0	0.1
F	19 (73.1)	13 (65.0)	6 (100)	
Occupation				
Nurse	8 (30.8)	6 (30.0)	2 (33.3)	1
Physician	4 (15.4)	2 (10.0)	2 (33.3)	0.3
Other, direct patient facing	6 (23.1)	5 (25.0)	1 (16.7)	1
Other, nondirect patient facing	6 (23.1)	5 (25.0)	1 (16.7)	1
Unknown	2 (7.7)	2 (10.0)	0	NT
Suspected exposure‡				
Yes	4 (15.4)	2 (10.0)	2 (33.3)	0.2
No	17 (65.4)	13 (65.0)	4 (66.7)	
Unknown	5 (19.2)	5 (25.0)	0	
Concurrent conditions				
Yes	7 (26.9)	5 (25.0)	2 (33.3)	1
No	18 (69.2)	14 (70.0)	4 (66.7)	
Unknown	1 (3.9)	1 (5.0)	0	
Median days from NP testing to symptom onset (IQR)	NA	NA	3 (1–9)	NT
Signs/symptoms				
Fever (self-reported or objective)	NA	NA	1 (16.7)	NT
Sweats	NA	NA	1 (16.7)	
Cough	NA	NA	5 (83.3)	
Shortness of breath	NA	NA	1 (16.7)	
Sore throat	NA	NA	3 (50.0)	
Rhinorrhea	NA	NA	2 (33.3)	
Malaise/fatigue	NA	NA	4 (66.7)	
Myalgia	NA	NA	1 (16.7)	
Headache	NA	NA	2 (33.3)	
Gastrointestinal	NA	NA	2 (33.3)	
Unknown	2 (7.4)	2 (9.5)	0	
NP C_t				
20–25	1 (3.9)	1 (5.0)	0	0.2
>25–35	3 (11.5)	1 (5.0)	2 (33.3)	
>35–45	22 (84.6)	18 (90.0)	4 (66.7)	
Median NP C_t (IQR)	38.1 (37.8–38.4)	38.1 (37.9–38.4)	38.1 (29.5–38.3)	0.8
Plasma IgG				
Positive	6 (23.1)	6 (30.0)	0	0.3
Negative	20 (76.9)	14 (70.0)	6 (100)	
Repeat rRT-PCR within 30 d, first test result				
Positive	4 (15.4)	2 (10.0)	2 (33.3)	0.3
Negative	19 (73.1)	15 (75.0)	4 (66.7)	
Not performed	3 (11.5)	3 (15.0)	0	
Repeat IgG within 30 d, first test result				
Positive	2 (7.7)	2 (10.0)	0	1
Negative	16 (61.5)	12 (60.0)	4 (66.7)	
Not performed	8 (30.8)	6 (30.0)	2 (33.3)	

*Values are no. (%) unless indicated otherwise. C_t, cycle threshold; IQR, interquartile range; NA, not applicable; NP, nasopharyngeal; NT, not tested; rRT-PCR, real-time reverse transcription PCR.
†By χ^2 test, Fisher exact test, or Mann-Whitney U test.
‡Exposure known or suspected occurring in the community or hospital setting.

remaining 6, COVID-19 subsequently developed within a median of 3 days (IQR 1–9 days) (Table; Figure 2). None of the persons who had positive rRT-PCR results were hospitalized. Of the 20 persons who remained asymptomatic, 6 were IgG positive at the time of their positive rRT-PCR result (median C_t 38.1 [IQR 36.7–38.1]), and 2 of the 15 persons retested with the IgG test seroconverted 12 days later (C_t 20.8 and 38.0).

On the basis of the assumption that these 14 persons (6 presymptomatic and 8 asymptomatic who had early or delayed positive IgG results) had true positive results, the clinical specificity of the test was estimated to be 12,392 (99.9%) of 12,404 (Appendix Table). The overall median C_t was 38.1 (IQR 37.8–38.4) and overlapped between asymptomatic and presymptomatic persons (Appendix Figure). One asymptomatic HCP had a C_t value of 20.8, consistent with high viral load.
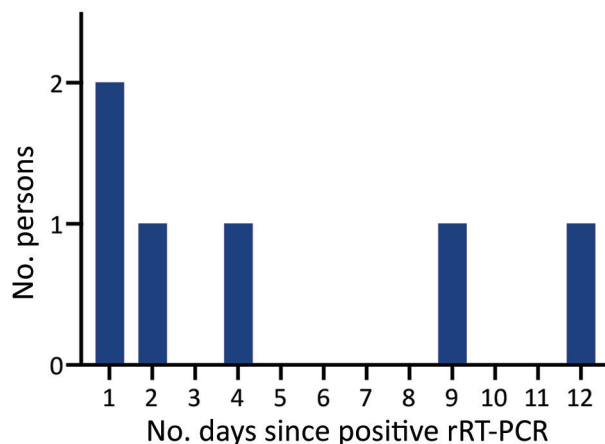
Figure 2. Timing of symptom onset in presymptomatic persons for study of large-scale testing of asymptomatic healthcare personnel for severe acute respiratory syndrome coronavirus 2, California, USA, April–June 2020. rRT-PCR, real-time reverse transcription PCR.

Conclusions

In this cohort of >12,000 asymptomatic HCP from an area that had low COVID-19 in-hospital and community burden at the time of the study, the prevalence of SARS-CoV-2 was low (<1%) by rRT-PCR and IgG serologic analysis. The combined rRT-PCR positivity rate for symptomatic and asymptomatic persons tested during the same period in Santa Clara County was 3.2%, and the county-level proportion of hospitalizations due to COVID-19 was also 3.2% (*7*). Other smaller asymptomatic HCP studies have demonstrated positive rRT-PCR prevalence ranging from 1% to 7% (*3*; E.S. Barrett et al., unpub. data). In addition, point-of-care IgG positivity estimates for asymptomatic persons in studies from Santa Clara and Los Angeles Counties ranged from 1% to 5% (*8*; E. Bendavid et al., unpub. data).

There are limitations in comparability given that rRT-PCR positivity indicates active infection and potentially contagious persons, whereas IgG positivity might indicate past or active infection. However, the findings in the current study suggest that, in low-prevalence settings, HCP SARS-CoV-2 transmission risk might be driven mostly by community exposure, given the limited evidence of nosocomial transmission. In this study, there was no apparent cluster of transmission events from HCP with positive rRT-PCR results. Nonetheless, given that most persons infected with SARS-CoV-2 in this cohort were involved in direct patient care, mass testing that focuses on these persons, as well as implementation in settings lacking personal protective equipment or with a high burden of infection, might show a higher yield (E.S. Barrett et al., unpub. data).

In this study, 1 asymptomatic person was identified who showed high nasopharyngeal viral load, and 6 persons were given a diagnosis before the onset of symptoms. Despite their low frequency, these persons are examples of key groups to identify given the higher likelihood of onward transmission with high viral loads. This study confirmed the overlap in SARS-CoV-2 RNA levels between asymptomatic and presymptomatic HCP, supporting the need for testing both groups to prevent transmission (*9*).

There is increasing evidence from congregate settings that relying on the presence of symptoms to initiate testing is insufficient (*2,4*). As laboratory capacity increases, asymptomatic mass testing programs might facilitate earlier and more accurate case detection and help maintain workforce readiness, especially in high-prevalence settings (*10*). This testing approach was strengthened by its large scale and comprehensiveness, including tests for viral RNA and SARS-CoV-2 antibodies. Such HCP testing might help build public confidence in the safety of the hospital environment and thus limit delays in care for persons who have non–COVID-19 illnesses.

However, there are limitations to this approach. Previous symptoms were assessed by self-report, which might result in bias. In addition, although the rRT-PCR–positive results in this study could not all be confirmed as true positive results, the estimated clinical specificity of rRT-PCR was 99.9%. Finally, this approach necessitates adequate infrastructure to support intensive clinical triaging, testing, and follow-up. Sample pooling might increase testing throughput, lower cost, and enable SARS-CoV-2 detection in persons who have high viral load and represent a priority group to prevent transmission.

In summary, large-scale testing of HCP might identify asymptomatic and presymptomatic persons, including some with high viral burden. Early detection might enable prompt implementation of infection control measures to limit nosocomial spread.

About the Author

Dr. Hogan is an infectious diseases physician and medical microbiologist at Stanford University School, Palo Alto, CA, and currently a visiting instructor in the Department

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References

1. Kluytmans-van den Bergh MF, Buiting AG, Pas SD, Bentvelsen RG, van den Bijllaardt W, van Oudheusden AJ, et al. Prevalence and clinical presentation of health care workers with symptoms of coronavirus disease 2019 in 2 Dutch hospitals during an early phase of the pandemic. JAMA Netw Open. 2020;3:e209673. https://doi.org/10.1001/jamanetworkopen.2020.9673
2. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al.; Public Health–Seattle and King County and CDC COVID-19 Investigation Team. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med. 2020;382:2081–90. https://doi.org/10.1056/NEJMoa2008457
3. Treibel TA, Manisty C, Burton M, McKnight Á, Lambourne J, Augusto JB, et al. COVID-19: PCR screening of asymptomatic health-care workers at London hospital. Lancet. 2020;395:1608–10. https://doi.org/10.1016/S0140-6736(20)31100-4
4. Rivett L, Sridhar S, Sparkes D, Routledge M, Jones NK, Forrest S, et al.; CITIID-NIHR COVID-19 BioResource Collaboration. Screening of healthcare workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission. eLife. 2020;9:9. https://doi.org/10.7554/eLife.58728
5. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al.; Public Health—Seattle & King County; CDC COVID-19 Investigation Team. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility—King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020;69:377–81. https://doi.org/10.15585/mmwr.mm6913e1
6. Hogan CA, Sahoo MK, Huang C, Garamani N, Stevens B, Zehnder J, et al. Comparison of the panther fusion and a laboratory-developed test targeting the envelope gene for detection of SARS-CoV-2. J Clin Virol. 2020;127:104383. https://doi.org/10.1016/j.jcv.2020.104383
7. County of Santa Clara. Open data portal; COVID-19. 2020 [cited 2020 Aug 23] https://data.sccgov.org/browse?category=COVID-19
8. Sood N, Simon P, Ebner P, Eichner D, Reynolds J, Bendavid E, et al. Seroprevalence of SARS-CoV-2-specific antibodies among adults in Los Angeles County, California, April 10–11, 2020. JAMA. 2020;323:2425–7. https://doi.org/10.1001/jama.2020.8279
9. Lee S, Kim T, Lee E, Lee C, Kim H, Rhee H, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. JAMA Intern Med. 2020 Aug 6 [Epub ahead of print]. https://doi.org/10.1001/jamainternmed.2020.3862
10. Black JR, Bailey C, Przewrocka J, Dijkstra KK, Swanton C. COVID-19: the case for health-care worker screening to prevent hospital transmission. Lancet. 2020;395:1418–20. https://doi.org/10.1016/S0140-6736(20)30917-X

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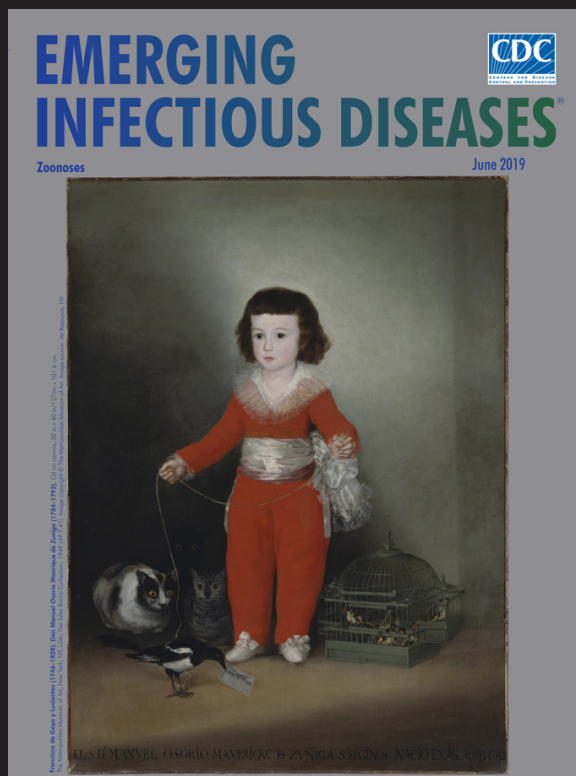
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Appendix

Real-Time Reverse Transcription PCR and IgG Testing

The documentation on the Stanford Health Care real-time reverse transcription PCR performance that led to US Food and Drug Administration emergency use authorization is reported (*1*). Plasma IgG testing by ELISA specific for the spike glycoprotein receptor-binding domain antigen was performed by using a Stanford Health Care laboratory-developed test. The test was implemented on an automated ESP 600 ELISA platform (Inova Diagnostics Inc., https://www.inovadx.com) and had a specificity of 99.75% determined by testing of 397 prepandemic plasma samples. High sensitivity of the Stanford Health Care receptor-binding domain laboratory-developed test was demonstrated by manual testing of several hundreds of samples from COVID-19 patients collected at different timepoints postsymptom onset (K. Roltgen et al., unpub. data).

Reference

1. US. Food and Drug Administration. Stanford Health Care Clinical Virology Laboratory SARS-CoV-2 test EUA Summary; 2020 [cited 202 Oct 2]. https://www.fda.gov/media/136818/download

Appendix Table. Estimated clinical sensitivity and specificity of SARS-CoV-2 rRT-PCR testing for asymptomatic healthcare personnel*

Characteristic	SARS-CoV-2-infected	SARS-CoV-2-uninfected	Total
rRT-PCR positive	14	12	26
rRT-PCR negative	0	12,392	12,392
Total	14	12,404	12, 418

*SARS-CoV-2 infection was established as a composite reference standard including rRT-PCR results, IgG serologic results, and development of symptoms consistent with COVID-19. Of the 26 persons who had positive rRT-PCR results, 14 were considered to have true-positive results. Of these 14 persons, symptoms consistent with COVID-19 developed 1–12 days after the positive rRT-PCR was obtained for 6 of these persons. The other 8 persons remained asymptomatic but showed either a positive initial (n = 6) or delayed (n = 2) positive IgG response. Estimated clinical test performance of rRT-PCR testing: sensitivity: 14/14 = 100% (95% CI 100%); specificity: 12,392/12,404 = 99.9% (95% CI 99.8%–100%); positive predictive value: 14/26 = 53.8% (95% CI 34.7%–73.0%); negative predictive value: 12,392/12,392 = 100% (95% CI 100%); overall true case detection rate: 14/12,418 = 0.11% (95% CI 0.06%–0.2%), or 1.1 cases/1,000 tested; true case detection rate for those at higher risk for transmission (Ct<35): 4/12,418 = 0.03% (95% CI 0.01%–0.08%), or 3.2 cases/10,000 tested. COVID-19, coronavirus disease; rRT-PCR, real-time reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
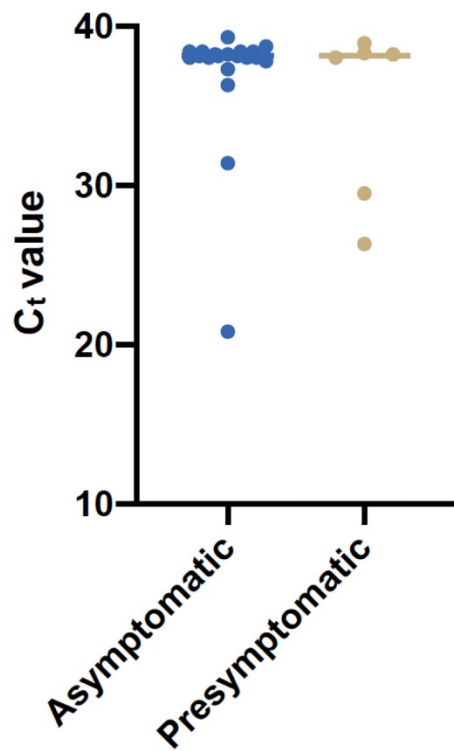
Appendix Figure. Cycle threshold values of symptomatic and presymptomatic persons. Blue circles indicate asymptomatic cases, and gray circles indicate symptomatic cases. Horizontal bars indicate C_t value for each group. C_t, cycle threshold.