

as informing the public about food shortage while reassuring the public that supply will arrive in a few days. China has provided free, country-wide psychosocial support, funded by the government and institutions (5–7). The accessibility is remarkable compared with that in other countries that depend on health insurance benefits.

Our review suggests that China has overcome resource shortages with coordination and resource allocation in its mental health response. The government, universities, and academic societies provide coordination, and independent organizations provide local support. We recommend integration of assessment in direct support, monitoring of organizations, and advocating for affected persons. These recommendations can inform how other countries can overcome shortage of mental health resources when facing this pandemic.

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Antibody Responses to SARS-CoV-2 at 8 Weeks Postinfection in Asymptomatic Patients

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We compared levels of severe acute respiratory syndrome coronavirus 2 neutralizing antibodies in recovery plasma from 7 completely asymptomatic coronavirus disease patients with those in symptomatic patients in South Korea. We found that serologic diagnostic testing was positive for 71% (5/7) of completely asymptomatic patients, but neutralizing antibody response occurred in all 7 patients.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new strain of betacoronavirus that causes coronavirus disease (COVID-19), quickly spread worldwide; the World Health Organization declared COVID-19 a pandemic on March 11, 2020 (1). Recent studies showed that a substantial number of asymptomatic COVID-19 patients contributed to the rapid dissemination of SARS-CoV-2 (2). In hospitalized COVID-19 patients, neutralizing antibody production was shown to increase after the first week of symptom onset, which correlated with disease severity (3,4). However, the neutralizing antibody response in asymptomatic patients is unclear.

In this study, we analyzed the completely asymptomatic COVID-19 patients who were isolated in a community treatment center (CTC) operated by Seoul National University (SNU) Hospital in response to a huge COVID-19 outbreak in Deagu, South Korea. During the CTC stay, physicians and nurses comprehensively evaluated the patients using a video consultation system twice daily (5–7). The completely asymptomatic patients were defined as those with body temperature $<37.5^{\circ}\text{C}$ and no symptoms (e.g., subjective fever, myalgia, rhinorrhea, sore throat, cough, sputum, chest discomfort) during the entire CTC stay. A total of 15 completely asymptomatic patients were confirmed among 113 patients with SARS-CoV-2 infection in the CTC (8). We also evaluated COVID-19 patients with pneumonia who were admitted to the Biocontainment Unit in SNU Hospital and SNU Bundang Hospital (Seongnam, South Korea). We classified pneumonia cases as subtle pneumonia (infiltrations were observed only in the computed tomography images) or apparent pneumonia (infiltrations were observed in chest radiograph) with mild or severe manifestation; case-patients with severe pneumonia required oxygen therapy.

We semiquantitatively measured SARS-CoV-2 IgG using a commercial ELISA kit (Euroimmun, <https://www.euroimmun.com>) according to the manufacturer's instructions. Optical density ratio (sample/calibrator) was interpreted as positive (≥ 1.1), borderline (≥ 0.8 to < 1.1), or negative (< 0.8) according to the manufacturer's recommendation. We performed neutralization assays as previously described (9), using the BetaCoV/Korea/SNU01/2020 virus (10) and 2-fold serially diluted plasma samples (2-fold to 4,096-fold). We recorded the highest dilution of plasma that showed inhibition activity of SARS-CoV-2 as the neutralizing antibody titer. We performed the assay in duplicate with negative control samples from healthy volunteers and patients 7–12 months after recovery from laboratory-

confirmed Middle East respiratory syndrome coronavirus infection. The Institutional Review Boards of Seoul National University Hospital approved the study (IRB no. H-2004-158-1118).

Seven completely asymptomatic COVID-19 patients from the CTC and 17 patients with COVID-19 pneumonia from SNU-affiliated hospitals participated in this study (Appendix Table, <https://wwwnc.cdc.gov/EID/article/26/10/20-2211-App1.pdf>). Of the completely asymptomatic patients, ELISA showed positive results in 5 (71%) patients, borderline result in 1 (14%) patient, and negative result in 1 (14%) patient. ELISA showed higher optical density value in patients with pneumonia; titers correlated with disease severity (Figure). All patients showed neutralizing antibody response. We calculated the geometric mean titer of neutralizing antibody in all asymptomatic patients and in 4 of each type of pneumonia patient (subtle, mild, or severe); geometric mean titer was 78 in asymptomatic patients ($n = 7$), 256 in patients with subtle pneumonia ($n = 4$), and 3,158 in patients with apparent pneumonia ($n = 8$; 4 mild and 4 severe cases).

Neutralizing antibodies play an essential role in virus clearance and have been considered a critical immune player for protection against viral diseases. Knowledge of the neutralizing antibody response in asymptomatic patients is critical for diagnosing the disease, understanding pathogenesis, and interpreting seroepidemiologic data to define prevalence and risk factors for infection. Production of neutralizing antibodies in asymptomatic COVID-19 patients was reported recently. Wu et al. reported that $\approx 30\%$ of recovered mild COVID-19 patients generated a deficient level of neutralizing antibody titers; in 10 of the 175 patients, the level was below the limit of detection (F. Wu et al., unpub. data, <https://doi.org/10.1101/2020.03.30.20047365>). The difference in results from our study compared with the previous study might be caused by differences in the timing of the test. In the previous study, antibody tests were performed 2–3 weeks after symptom onset, whereas we tested 2 months after symptom onset or laboratory diagnosis. Seroconversion in asymptomatic patients might take longer.

In our study, the neutralizing antibody titer correlated with the severity of the disease. This result suggests that patients with more severe disease might be more protected against reinfection and those with asymptomatic or mild disease could be more vulnerable to waning immunity over time because the initial immune response was not as strong as in patients with more severe disease.

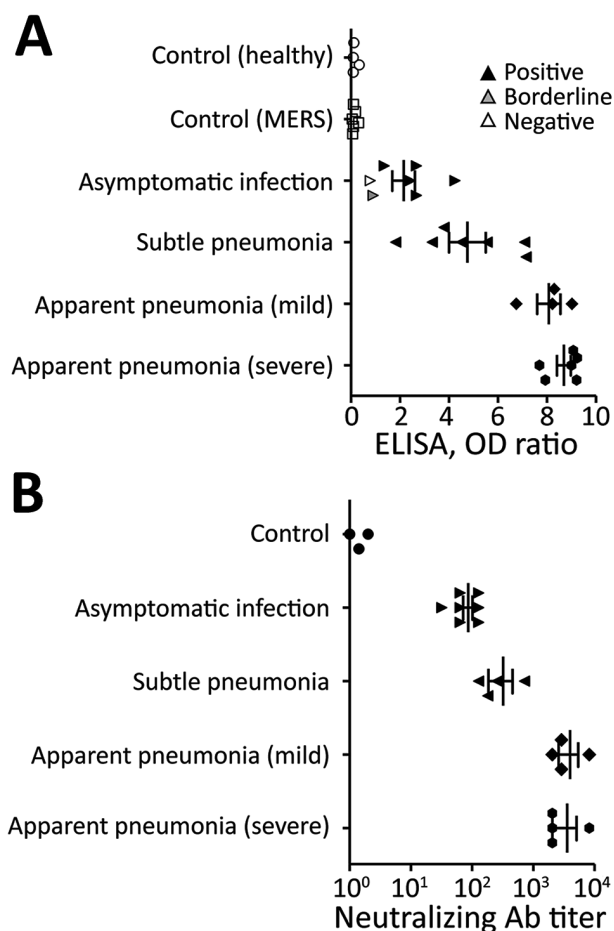


Figure. Antibody response against severe acute respiratory syndrome coronavirus 2 at 8 weeks postinfection among patients and controls in South Korea. A) Serologic diagnostic test (ELISA) results. OD ratio indicates the ratio of the extinction of the patient sample over the extinction of the calibrator. B) Neutralization assay results. For each patient type, an outlined symbol indicates a negative test result, gray symbol a borderline result, and black symbol a positive result, as tested according to manufacturer recommendation. Bars represent mean values and SE. From each patient group other than the completely asymptomatic group, 3–4 patients were randomly selected for neutralization assay. The controls included 1 healthy volunteer and 2 patients with MERS. Ab, antibody; MERS, Middle East respiratory syndrome; OD, optical density.

The ELISA results showed good agreement with the neutralizing antibody results. Negative ELISA results in some asymptomatic patients may be a limitation of the ELISA or may be attributed to patients with cross-neutralizing antibodies in their serum. Despite the limitation of our small sample size, our findings suggest that seroepidemiologic studies may detect mild COVID-19 infection in completely asymptomatic patients by the presence of neutralizing antibodies at 8 weeks postinfection.

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Retrospective Screening for SARS-CoV-2 RNA in California, USA, Late 2019

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To investigate the possibility of earlier cases of severe acute respiratory syndrome coronavirus 2 infection than previously recognized, we retrospectively tested pooled samples from 1,700 persons with respiratory signs/symptoms seen at Stanford Health Care, Palo Alto, California, USA, during the last 2 months of 2019. We found no evidence of earlier infection.

Phylogenetic analyses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) suggest virus emergence weeks, if not months, before the World Health Organization was notified of the original cluster of cases in Wuhan, China (1). These analyses have estimated that SARS-CoV-2 emerged from October 6, 2019, through December 11, 2019 (2). Given this timeline, interest in retrospectively identifying patient zero in different geographic areas has been growing, to better determine the spread of SARS-CoV-2 and to inform current and future surveillance strategies for emerging infectious diseases.

Given the high volume of international travel before implementation of travel restrictions, travel-

associated coronavirus disease (COVID-19) cases may have occurred in the United States earlier than previously recognized (3). However, monitoring for early community transmission of SARS-CoV-2 in the United States was challenging because the clinical manifestations of COVID-19 are similar to those of other respiratory virus infections, and emergence of COVID-19 overlapped with the annual respiratory virus season. In addition, local COVID-19 case finding and contact tracing efforts were limited by strict indications for testing based on specific risk factors, coupled with limited testing capacity (4,5).

A case of COVID-19 in the San Francisco Bay area, California, was confirmed by autopsy on February 6, 2020. To determine whether the virus had been spreading earlier than previously recognized in northern California, we extended our recently reported pooled screening strategy (4) to a retrospective study that included the last 2 months of 2019.

Our study evaluated all nasopharyngeal swab samples collected October 31, 2019–December 31, 2019, at Stanford Health Care (Palo Alto, California, USA) for which sufficient residual sample volume was available. These samples were collected from inpatients and outpatients who had had negative routine respiratory virus test results (Respiratory Pathogen Panel; GenMark Diagnostics, <https://www.genmarkdx.com>, or Xpert Xpress Flu RSV; Cepheid, <https://www.cepheid.com>) and had not been tested for SARS-CoV-2. Pool size was determined after literature review, accounting for an expected prevalence of <1% (6,7). Pools were created by combining 10 nasopharyngeal samples, and screening was performed by real-time reverse transcription PCR targeting the nucleocapsid gene (region N2) (8). We extracted demographic characteristics for a randomly selected subset of 100 persons. Trends of routine respiratory virus positivity were examined for the same period covered by the retrospective SARS-CoV-2 testing. This study was approved by the Stanford institutional review board, and individual patient consent was waived.

We tested 1,700 individual nasopharyngeal specimens (170 pools) for SARS-CoV-2. Of these, 841 samples had previously tested negative by the Respiratory Pathogen Panel and 859 by the Xpert Xpress Flu RSV. From the subset of persons for whom demographic data had been analyzed, most (67%) were adults. Most (64%) persons had consulted the emergency department for testing, followed by an outpatient clinic (23%) or an inpatient ward (13%). No SARS-CoV-2–positive pools were identified. The study period corresponded to the onset of the 2019–2020 respiratory virus season, during which the number of cases of influenza A, influenza B, and respiratory syncytial virus increased and the frequency

Antibody Responses to SARS-CoV-2 at 8 Weeks Postinfection in Asymptomatic Patients

Appendix

Appendix Table. Clinical characteristics of patients in study of antibody responses to severe acute respiratory syndrome coronavirus 2 at 8 weeks postinfection

Characteristics	Completely asymptomatic	Subtle pneumonia	Apparent pneumonia, mild	Apparent pneumonia, severe
No. patients	7	7	4	6
Male sex, n (%)	5 (72)	3 (43)	3 (75)	5 (83)
Age, median y (range)	25 (20–28)	53 (24–84)	59 (43–78)	75 (55–86)
Isolation period*, median no. days (range)	29 (21–36)	18 (11–21)	17 (11–18)	28 (15–77)
Symptom onset to antibody testing, median no. days (range)	55 (55–60)†	62 (46–66)	45 (39–68)	51 (44–75)

*Patients were deisolated when their SARS-CoV-2 rRT-PCR test results from 2 tests performed with a 24-h interval were negative.

†Duration from laboratory diagnosis to antibody testing in asymptomatic patients. Of the asymptomatic patients, 2 patients had an exposure history.