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BRIEF REPORT

# Risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Reinfection in a University Student Population

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We assess protection from previous SARS-CoV-2 infection in 16,101 university students. Among 2,021 students previously infected in Fall 2020, risk of re-infection during the Spring 2021 semester was 2.2%; estimated protection from previous SARS-CoV-2 infection was 84% (95% CI: 78%–88%).

**Keywords.** SARS-CoV-2; COVID-19; reinfection; immunity; epidemiology.

As of 10 April 2021, more than 130 million confirmed cases of coronavirus disease 2019 (COVID-19) have been reported [1]. The true number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, the disease that causes COVID-19, is estimated to be much larger due to a high rate of asymptomatic infections, lack of testing infrastructure, and incomplete case reporting [2]. Understanding protection from previous SARS-CoV-2 infections is important for assessing individual risk of reinfection, implementing public health interventions, and assessing vaccine effectiveness and durability [3].

In this study, we evaluated the SARS-CoV-2 reinfection risk in a large public university student population in the United States. Understanding transmission dynamics in this population is of particular interest since young people substantially contribute to disease spread [4]. Because repeated SARS-CoV-2 testing was mandated for all students, this study setting is ideal for minimizing bias associated with voluntary testing and case underreporting [5].

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## METHODS

In this retrospective cohort study, we examined SARS-CoV-2 reinfection during the spring 2021 semester among students who previously tested positive for COVID-19 during the fall 2020 semester at Clemson University, South Carolina. Prior to receiving access to campus facilities in fall 2020, university students and employees were required to provide a negative COVID-19 polymerase chain reaction (PCR) test result within 10 days of campus return (accepted methods were nasal, throat, or saliva swabs) or a positive serologic antibody test within 40 days of return [6]. During in-person instruction in fall 2020 (21 September–25 November), all students with access to main campus facilities were subjected to mandatory surveillance testing through 1 of 2 PCR tests: anterior nasal swabs (amplification curve cut point values <40 considered positive, test sensitivity = 97%, test specificity = 100%) [6, 7] or saliva tests (quantification cycle values <33 considered positive, test sensitivity ≥95% [6], test specificity ≥99.5%) [6, 8]. Residential students, that is, those living in university residence halls, were subject to 2 weeks of surveillance-based informative testing followed by repeated weekly testing, while nonresidential students were subject to random surveillance testing only [6]. Clinical descriptions of testing procedures and additional details on surveillance testing protocols are described elsewhere [6]. In-person instruction resumed during the spring 2021 semester (6 January). During this period, all university students and employees who accessed main campus facilities were subjected to mandatory weekly saliva tests (same test used during the fall 2020 semester). Individuals who failed to comply were denied access to campus facilities after 10 days of their last test date. Prior to campus return (28 December 2020–3 January 2021), all students and employees were required to provide a COVID-19 test result or positive serologic antibody test (a protocol similar to that for the fall 2020 semester).

We restricted the population to all students aged 17–24 years tested in the fall 2020 semester between online instruction (19 August) and end of in-person instruction (25 November). Because it is possible for SARS-CoV-2 RNA to be detected up to 12 weeks after infection [9], students who tested positive between 6 October 2020 and 28 December 2020 were excluded from these analyses since these individuals were not eligible for mandatory surveillance testing by the start of the spring 2021 semester [6]. The selection process for the study population is illustrated in Supplementary Figure 1. The Clemson University Institutional Review Board provided ethical review for this study.

We evaluated the risk of COVID-19 reinfection among all students who initially tested positive between 19 August 2020 (start of online instruction) and 5 October 2020 (fall 2020 positive group). The follow-up period for this study was 28 December 2020 to 1 May 2021. Because the likelihood of reinfection in a fixed time period depends on current disease prevalence, a comparison group was needed to assess the effectiveness of previous SARS-CoV-2 infection against repeat infection. We therefore compared the infection rate among previously infected students to the rate for those who did not test positive prior to the follow-up period (fall 2020 negative group).

We computed the infection rate for the fall 2020 positive and negative groups as the proportion of (unique) individuals who were COVID-19–positive during the follow-up period. We used Cox proportional hazard models to estimate the relative risk (RR) of infection during the follow-up period between groups, adjusting for age, gender, compliance with mandatory testing, and residential status. The outcome in this model is days between the start of follow-up and date of the first COVID-19 positive test in spring 2021. Individuals who did not test positive during the follow-up period were censored at their last negative test date. Changes in the amount of virus circulating throughout the university throughout the study period are implicitly accounted for through the baseline hazard function of the proportional hazards model. We estimated protection against repeat infection as 1 - adjusted RR of SARS-CoV-2 infection [5].

We conducted sensitivity analyses to address potential limitations of our study. First, to differentiate between reinfection and an existing infection, we excluded individuals who did not provide a negative test between the initial infection and reinfection [10]. Second, because weekly testing was not mandated for nonresidential students in the fall 2020 semester, it is possible that SARS-CoV-2 infections went undetected in this population. We therefore repeated the analyses for residential students only, as these students were subjected to weekly testing for the majority of the fall 2020 semester [6].

## RESULTS

The final sample included 16 101 students. Mean age was 20.30 years (standard deviation = 1.47), 33.8% lived in residential buildings, 51.4% were female, 48.4% were male, and 0.2% did not specify. Of the 2021 previously infected students, 44 (2.2%) were reinfected during the spring 2021 semester (Table 1). This infection rate is significantly lower than the 12.1% rate among the 14 080 students who tested negative throughout the fall 2020 semester ($P < .0001$). Estimated protection against repeat infection was 84% (95% confidence interval [CI]: 78%–88%). We did not have enough evidence to conclude that the Cox model proportional hazards assumption was not violated ($P = .7381$). Among those reinfected, median time to reinfection was 129 days (range, 86–231). The Kaplan-Meier estimate of the probability of no reinfection for at least 8 months was 97.2% (Supplementary Figure 2).

When reinfections without a confirmatory negative test between original infection and reinfection were excluded, estimated protection increased (estimate, 88%; 95% CI: 83%–91%). The corresponding estimates of protection from previous SARS-CoV-2 infection was lower for residential students (main analysis estimate, 77%; 95% CI: 63%–85%; sensitivity analysis estimate, 84%; 95% CI: 72%–90%).

**Table 1. Comparison of Infection Rates During the Spring 2021 Semester (12/28/20 to 5/1/21) Among Students With and Without Previous Infections During the Fall 2020 Semester**

| | Spring 2021 | | | | | |
|---|---|---|---|---|---|---|
| | Population (N) | Infections (N) | Percent Infected | Testing Compliance[a] | Relative Risk (95% CI)[b] | Estimated Protection (95% CI)[b] |
| Main analysis | | | | | | |
| Fall 2020 positive | 2021 | 44 | 2.2% | 10 (83%) | 0.16 (.12–.22) | 84% (78%–88%) |
| Confirmed reinfections[c] | 2010 | 33 | 1.6% | 10 (83%) | 0.12 (.09–.17) | 88% (83%–91%) |
| Fall 2020 negative | 14 080 | 1697 | 12.1% | 10 (83%) | 1 (reference) | … |
| Residential students only | | | | | | |
| Fall 2020 positive | 682 | 20 | 2.9% | 11 (92%) | 0.23 (.15–.37) | 77% (63–85%) |
| Confirmed reinfections[c] | 676 | 14 | 2.1% | 11 (92%) | 0.16 (.10–.28) | 84% (72–90%) |
| Fall 2020 negative | 4761 | 603 | 12.7% | 11 (92%) | 1 (reference) | … |

Fall 2020 positive group consisted of all students who tested positive between 19 August 2020 (start of online instruction) and 5 October 2020. Students infected before 19 August 2020 or between 6 October 2020 and 27 December 2020 are not included in this group. Fall 2020 negative group consisted of all students who tested negative between 19 August 2020 and 27 December 2020. Follow-up period is between 28 December 2020 and 9 April 2021.

Abbreviation: CI, confidence interval.

[a]Testing compliance defined as the number of eligible periods tested (and percentage of eligible periods tested). Length of period is 10 days to account for 3-day grace period. Results reported as medians.

[b]Adjusted for age, gender, testing compliance (measured as percentage of eligible periods tested), and residential status (adjusted for in main analysis only).

[c]Reinfection confirmed through negative polymerase chain reaction test between original infection and reinfection.

## DISCUSSION

We are the first to examine the risk of repeat SARS-CoV-2 infection in a population of young people. Previous studies based on voluntary testing have reported SARS-CoV-2 reinfection rates of less than 1% [3, 5, 11] and estimated protection from previous infection between 80% and 83% in populations aged <65 years [5]. However, studies based on voluntary testing may be prone to bias due to underreporting of infections and differing testing rates between previously infected and not previously infected individuals [5, 11]. The main strength of our study design is that compliance with mandated weekly testing was high in this population (weekly compliance was 83%). We estimated that the reinfection rate 12 to 30 weeks post initial infection was 2.2% in this population; estimated protection from previous SARS-CoV-2 infection was 84%.

There are several limitations to this observational study. First, misclassification of previous infection may lead to attenuation of the protective effect from previous SARS-CoV-2 infection. Surveillance testing was not mandated in the summer of 2020 or after in-person instruction ended (between Thanksgiving and Christmas in 2020). These periods corresponded to the largest surges in COVID-19 cases in South Carolina. It is therefore likely that some students contacted and cleared the virus while away from campus during these periods and may be misclassified as not previously infected in our analyses. Some misclassifications may have also occurred through PCR testing. However, given the high sensitivity and specificity of the surveillance PCR tests, this is expected to have a negligible impact on our findings [5]. It is also possible that reinfections were mistaken for lingering infections. Although we conducted sensitivity analyses that required a negative PCR test between 2 positive PCR tests, distinct sequenced viral isolates on the initial and repeat positive tests are needed to truly differentiate between repeat and lingering infections [10, 12]. Another limitation is that those who previously tested positive may represent a higher risk-taking population. Furthermore, previous infection may lead to riskier behavior [5]. We also note that university students (especially those in congregate housing) tend to engage in high-density social interactions [4] and may therefore be at an increased risk of reinfection compared with other individuals in this age group. Finally, emerging SARS-CoV-2 variants may reduce the protective effect of previous infections [13].

## CONCLUSIONS

In a university student population subjected to mandatory repeated testing, we estimated that previous SARS-CoV-2 infection protected 84% of young people from reinfection in the 3- to 8-month study time period. While this age group is largely asymptomatic and therefore less likely to experience severe outcomes [14], it is estimated that asymptomatic individuals account for more than half of SARS-CoV-2 transmission [15]. Since 16% of this population remains susceptible to reinfection, precautions should still be used by previously infected individuals (eg, face coverings). As natural protection is not guaranteed, these findings strongly support vaccination of those previously infected with SARS-CoV-2. However, individuals without previous SARS-CoV-2 infections could be given prioritization when vaccines are in short supply.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

***Author contributions***. L. R. conceived the study and led the study design, co-led and performed the statistical analysis, and wrote the first draft of the manuscript. C. M. co-led the statistical analysis and contributed to manuscript revisions. All authors contributed to data collection and acquisition, discussion and interpretation of results, and writing of the manuscript. All authors approved the final manuscript.

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