

Risk of SARS-CoV-2 reinfection in a university student population

Lior Rennert, PhD^{1*} and Christopher McMahan, PhD²

¹Department of Public Health Sciences, Clemson University, Clemson, SC, USA

²School of Mathematical and Statistical Sciences, Clemson University, Clemson, SC, USA

*Corresponding author:

Lior Rennert, Ph.D.

Department of Public Health Sciences

Clemson University, Clemson, SC, USA

liorr@clemson.edu

© The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

ABSTRACT: We assess protection from previous SARS-CoV-2 infection in a population of 16,101 university students (2,021 with and 14,080 without previous infection). The risk of re-infection during the Spring 2021 semester was 2.2% among previously infected students; estimated protection from previous SARS-CoV-2 infection was 84% (95% CI: 78%-88%).

Key words: SARS-CoV-2; COVID-19; reinfection; immunity; epidemiology.

Accepted Manuscript

INTRODUCTION

As of April 10, 2021, over 130 million confirmed cases of the 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 causing 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, implementation of public health interventions, and assessing vaccine effectiveness and durability.³ In this study, we evaluate 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

METHODS

In this retrospective cohort study, we examine SARS-CoV-2 reinfection during the Spring 2021 semester among students previously testing positive for Covid-19 during the Fall 2020 semester at Clemson University in South Carolina. Prior to receiving access to campus facilities in Fall 2020, university students and employees were required to provide a negative Covid-19 PCR test result within 10 days of campus return (accepted methods: nasal, throat, or saliva swabs) or positive serologic antibody tests within 40 days of return.⁶ During in-person instruction of Fall 2020 (9/21-11/25), all students with access to main campus facilities were subjected to mandatory surveillance testing through one of two 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 $\geq$ 95%,⁶ test specificity $\geq$ 99.5%).^{6,8} Residential students, i.e., those living in university residence halls, were subject to two weeks of surveillance-based informative testing followed by repeated weekly testing, while non-residential 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 (1/6). During this period, all university students and employees accessing main campus facilities were subjected to mandatory weekly saliva tests (same test used during Fall 2020 semester). Individuals failing to comply were denied access to campus facilities after 10 days of their last test date. Prior to campus return (12/28/20-1/3/21), all students and employees were required to provide a Covid-19 test result or positive serologic antibody test (similar protocol to Fall 2020 semester).

We restrict the population to all 17 to 24 year-old students tested in the Fall 2020 semester between online instruction (8/19) and end of in-person instruction (11/25). Because it is possible for SARS-CoV-2 RNA to be detected up to 12 weeks after infection,⁹ students testing positive between 10/06/20 and 12/28/20 are excluded from these analyses since these individuals were not eligible for mandatory surveillance testing by start of the Spring 2021 semester.⁶ The selection process for the study population is illustrated in Supplementary Figure 1. Ethical review for this study was obtained by the Institutional Review Board of Clemson University.

We evaluate the risk Covid-19 reinfection among all students initially testing positive between 8/19/20 (start of online instruction) and 10/05/20 (Fall 2020 positive group). The follow-up period for this study is 12/28/20 to 5/1/2021. Because the likelihood of reinfection in a fixed time period depends on current disease prevalence, a comparison group is needed to assess the effectiveness of previous SARS-CoV-2 infection against repeat infection. We therefore compare the infection rate among previously infected students to 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 in 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 $1 - \text{adjusted RR of SARS-CoV-2 infection}$.⁵

We conduct 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 non-residential students in the Fall 2020 semester, it is possible that SARS-CoV-2 infections went undetected in this population. We therefore repeat 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 includes a total of 16,101 students. Mean age was 20.30 years (SD=1.47), 33.8% lived in residential buildings, 51.4% were female, 48.4% were male, and 0.2% did not specify. Of the 2,021 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 testing negative throughout the Fall 2020 semester ($p < .0001$). Estimated protection against repeat infection was 84% (95% CI: 78-88%). We did not have enough evidence to conclude the proportional hazards assumption was violated for group ($p = .7381$). Among those reinfected, median time to reinfection was 129 days (range: 86-231 days). The Kaplan-Meier estimate of the probability of no reinfection for at least 8 months was 97.2% (Supplementary Figure 2).

When excluding reinfections without a confirmatory negative test between original infection and reinfection, 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%).

DISCUSSION

This study is 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 reinfection rates of SARS-CoV-2 under 1%^{3,5,11} and estimated protection from previous infection between 80-83% in populations younger than 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 non-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 months of 2020 or after in-person instruction ended (between Thanksgiving and Christmas holidays of 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 a non-previous infection 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 two 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 previously testing 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 to other individuals in this age group. Finally, emerging SARS-CoV-2 variants may reduce the protective effect of previous infections.¹³

CONCLUSION

In a university student population subjected to mandatory repeated testing, we estimate that previous SARS-CoV-2 infection protects 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 over half of SARS-CoV-2 transmission.¹⁵ Since 16% of this population remains susceptible to reinfection, precautions should still be employed by previously infected individuals (e.g., 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.

Author contributions: LR conceived the study and led the study design, co-led and performed the statistical analysis, and wrote the first draft of the manuscript. CM 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.

Additional contributions: We thank the Clemson University's executive leadership, administration, medical staff, and all other testing providers who helped implement and manage SARS-CoV-2 testing. We thank Clemson University's Computing & Information Technology department for their assistance in collecting, managing, and distributing test result data.

Funding/Support: Rennert and McMahan received salary support from Clemson University for public health consulting and modeling during the conduct of this study (project #1502934).

Role of funder: The funder had no role in the development of this study; data collection, analysis, and interpretation; manuscript preparation and review; and the decision to submit the manuscript for publication.

Conflict of Interest Disclosures: None declared

REFERENCES

1. WHO. Coronavirus disease (COVID-19) – World Health Organization. Coronavirus disease (COVID-19) pandemic. Accessed April 10, 2021. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
2. Chen X, Chen Z, Azman AS, et al. Serological evidence of human infection with SARS-CoV-2: a systematic review and meta-analysis. *The Lancet Global Health*. Published online March 8, 2021. doi:10.1016/S2214-109X(21)00026-7
3. Abu-Raddad LJ, Chemaitelly H, Malek JA, et al. Assessment of the Risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Reinfection in an Intense Reexposure Setting. *Clinical Infectious Diseases*. 2020;(ciaa1846). doi:10.1093/cid/ciaa1846
4. Rennert L, Kalbaugh CA, Shi L, McMahan C. Modelling the impact of presemester testing on COVID-19 outbreaks in university campuses. *BMJ Open*. 2020;10(12):e042578. doi:10.1136/bmjopen-2020-042578
5. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *The Lancet*. 2021;397(10280):1204-1212. doi:10.1016/S0140-6736(21)00575-4
6. Rennert L, McMahan C, Kalbaugh CA, et al. Surveillance-based informative testing for detection and containment of SARS-CoV-2 outbreaks on a public university campus: an observational and modelling study. *The Lancet Child & Adolescent Health*. Published online March 19, 2021. doi:10.1016/S2352-4642(21)00060-2
7. Afzal A. Molecular diagnostic technologies for COVID-19: Limitations and challenges. *Journal of Advanced Research*. 2020;26:149-159. doi:10.1016/j.jare.2020.08.002
8. Vogels CBF, Watkins AE, Harden CA, et al. SalivaDirect: A Simplified and Flexible Platform to Enhance SARS-CoV-2 Testing Capacity. *Med*. 2021;2(3):263-280.e6. doi:10.1016/j.medj.2020.12.010
9. Lee JT, Hesse EM, Paulin HN, et al. Clinical and Laboratory Findings in Patients with Potential SARS-CoV-2 Reinfection, May–July 2020. *Clinical Infectious Diseases*. 2021;(ciab148). doi:10.1093/cid/ciab148
10. Boyton RJ, Altmann DM. Risk of SARS-CoV-2 reinfection after natural infection. *The Lancet*. 2021;397(10280):1161-1163. doi:10.1016/S0140-6736(21)00662-0
11. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. *New England Journal of Medicine*. 2021;384(6):533-540. doi:10.1056/NEJMoa2034545
12. To KK-W, Hung IF-N, Ip JD, et al. Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing. *Clinical Infectious Diseases*. 2020;(ciaa1275). doi:10.1093/cid/ciaa1275

13. Wang P, Nair MS, Liu L, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. *Nature*. Published online March 8, 2021. doi:10.1038/s41586-021-03398-2
14. Viner RM, Ward JL, Hudson LD, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. *Archives of Disease in Childhood*. Published online December 16, 2020. doi:10.1136/archdischild-2020-320972
15. Johansson MA, Quandelacy TM, Kada S, et al. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. *JAMA Netw Open*. 2021;4(1):e2035057. doi:10.1001/jamanetworkopen.2020.35057

Accepted Manuscript

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	2,021	44	2.2%	10 (83%)	0.16 (0.12 – 0.22)	84% (78% – 88%)
...confirmed reinfections ^c	2,010	33	1.6%	10 (83%)	0.12 (0.09 – 0.17)	88% (83% – 91%)
Fall 2020 negative	14,080	1,697	12.1%	10 (83%)	1 (<i>reference</i>)	-
Residential students only						
Fall 2020 positive	682	20	2.9%	11 (92%)	0.23 (0.15 – 0.37)	77% (63-85%)
...confirmed reinfections ^c	676	14	2.1%	11 (92%)	0.16 (0.10 – 0.28)	84% (72-90%)
Fall 2020 negative	4,761	603	12.7%	11 (92%)	1 (<i>reference</i>)	-

Fall 2020 positive group consists of all students testing positive between 8/19/20 (start of online instruction) and 10/5/20. Students infected before 8/19/20 or between 10/6/20 and 12/27/20 are not included in this group. Fall 2020 negative group consists of all students testing negative between 8/19/20 and 12/27/20. Follow-up period is between 12/28/20 and 4/9/21.

^a Testing compliance defined as 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 PCR test between original infection and reinfection