PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Monitoring SARS-CoV-2 incidence and seroconversion among university students and employees: a longitudinal cohort study in California, June to August 2020
AUTHORS	Hunter, Lauren; Wyman, Stacia; Packel, Laura; Facente, Shelley; Li, Yi; Harte, Anna; Nicolette, Guy; the IGI SARS-CoV-2 Testing Consortium, N/A; Di Germanio, Clara; Busch, Michael; Reingold, Art; Petersen, Maya L.

VERSION 1 – REVIEW

REVIEWER	Colubri, Andres Harvard University , Organismic and Evolutinary Biology
REVIEW RETURNED	02-Nov-2022

GENERAL COMMENTS	The authors carried our a detailed analysis of a longitudinal cohort of students and staff, studying SARS-CoV-2 test positivity in relation to demographic characteristics of the cohort, and real-time symptom/exposure monitoring. Even though there are limitations in this study due to the low number of SARS-CoV-2 positive cases overall, coverage of one single outbreak due to a super-spreader event, potential enrollment bias, and data being representative of earlier stages of the pandemic, the authors clearly pointed out these limitation and were able to point out to some relevant conclusions that are still applicable, most importantly, that integrated voluntary testing and risk monitoring systems that support targeted case identification can help reduce community transmission of SARS-CoV-2 and arguably other infectious diseases. I only have a few comments: * It would be interesting see the absolute numbers and percentages over the timeframe of the study for the different type of tests (i.e.: symptom- or exposure-based, random, address-based, participant-initiated), either described in the text or ideally as a plot. It will give an idea of how the testing changed over time. * In line 239, when the authors refer to their previous study on "continuous associations between temperature and positivity", I'd add state very briefly the conclusion of that study that temperature screening is insufficient as a primary means of detection. * I'd point out to a recent published study that also showcases an integrated monitoring system at a college campus: https://www.cell.com/med/fulltext/S2666-6340(22)00404-4, which I think it should be added to the references (disclaimer: I'm a co-author in that paper) together with any other recent publication on similar approaches.

REVIEWER	Toh, Zheng Quan Murdoch Children's Research Institute
REVIEW RETURNED	This manuscript by Hunter et al. described an integrated symptom and exposure monitoring and testing system for COVID-19 among a cohort of university students and employees in the United States. The study was carried out between June to August 2020. The authors were able to trace an outbreak within the school compound using genetic testing of nasal swab, and performed several analyses including antibody testing, associations between test positivity and symptoms as well as test positivity and socioeconomic characteristics. However, the number of COVID-19 cases in the cohort was low (2.6%), and therefore the applicability of the study findings and the described monitoring systems, particularly in the current climate of SARS-CoV-2 variants and infectivity, remains in question. Despite that, this system may apply for future outbreaks that may or may not be related to SARS-CoV-2 (worth including in discussion). Overall, the paper was well written, limitations acknowledged, and the approach was sound. Specific comments as follows: - It would be worth describing the settings/COVID-19 situation at the time of the study e.g. how many cases, whether there are lockdowns, masks mandate etc. - Please include serology antigen tested e.g. Nucleocapsid protein, spike protein - While the incentivised system is likely to encourage testing and/or participation, the amount of budget and resources may not be sustainable, particularly when there are huge number of COVID-19 cases in the community/schools due to more infectious SARS-CoV-2 variants and little/no movement restrictions. - Reliance on symptoms for testing will likely to miss a fraction of cases if there is a large outbreak. How would that affect the test system and outcome- would be worth discussing. Also, since the number of positive cases are so low, the IRR for symptoms and test positivity needs to be interpreted with caution. - Should there be any P-values for the associations?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. “The authors carried ou[t] a detailed analysis of a longitudinal cohort of students and staff, studying SARS-CoV-2 test positivity in relation to demographic characteristics of the cohort, and real-time symptom/exposure monitoring. Even though there are limitations in this study due to the low number of SARS-CoV-2 positive cases overall, coverage of one single outbreak due to a super-spreader event, potential enrollment bias, and data being representative of earlier stages of the pandemic, the authors clearly pointed out these limitation and were able to point out to some relevant conclusions that are still applicable, most importantly, that integrated voluntary testing and risk monitoring systems that support targeted case identification can help reduce community transmission of SARS-CoV-2 and arguably other infectious diseases. I only have a few comments: It would be interesting see the absolute numbers and percentages over the timeframe of the study for the different type of tests (i.e.: symptom- or exposure-based, random, address-based, participant-initiated), either described in the text or ideally as a plot. It will give an idea of how the testing changed over time.”

We thank the reviewer for this suggestion. We have created the suggested plot, now in the appendix and referenced in-text (lines 253-259). The figure shows the total number of resulted qPCR tests over

time among all participants (a) and separately among participants who received: a symptom-triggered notification to test in a daily survey in the week before the test (b), an exposure-triggered notification to test in an weekly survey in the 14 days before the test (c), an address-based notification to test in the week before the test (d), and/or a surveillance notification to test in the week before the test (e). One limitation of the study is our inability to isolate participants' specific reason(s) for testing during the study period. For example, automated symptom- and exposure-triggered testing notifications and other motivators for testing (e.g., participant-initiated testing, random surveillance testing) could and did overlap with each other and with routine baseline and endline testing. Therefore, the subpanels of the newly added figure are not mutually exclusive but, taken together, provide an idea of how types of testing shifted over time.

2. "In line 239, when the authors refer to their previous study on "continuous associations between temperature and positivity", I'd add state very briefly the conclusion of that study that temperature screening is insufficient as a primary means of detection."

We have added the conclusion to the text (lines 252-253).

3. "I'd point out to a recent published study that also showcases an integrated monitoring system at a college campus: https://www.cell.com/med/fulltext/S2666-6340(22)00404-4, which I think it should be added to the references (disclaimer: I'm a co-author in that paper) together with any other recent publication on similar approaches."

We added citations to this and other relevant recent publications (lines 462-464).

Reviewer 2

1. "This manuscript by Hunter et al. described an integrated symptom and exposure monitoring and testing system for COVID-19 among a cohort of university students and employees in the United States. The study was carried out between June to August 2020. The authors were able to trace an outbreak within the school compound using genetic testing of nasal swab, and performed several analyses including antibody testing, associations between test positivity and symptoms as well as test positivity and socioeconomic characteristics. However, the number of COVID-19 cases in the cohort was low (2.6%), and therefore the applicability of the study findings and the described monitoring systems, particularly in the current climate of SARS-CoV-2 variants and infectivity, remains in question. Despite that, this system may apply for future outbreaks that may or may not be related to SARS-CoV-2 (worth including in discussion). Overall, the paper was well written, limitations acknowledged, and the approach was sound. Specific comments as follows: It would be worth describing the settings/COVID-19 situation at the time of the study e.g. how many cases, whether there are lockdowns, masks mandate etc."

We have added context about the setting and COVID-19 situation at the time of the study (lines 129-136).

2. "Please include serology antigen tested e.g. Nucleocapsid protein, spike protein"

We have clarified that the serology test detects antibodies against the SARS-CoV-2 spike protein S1 antigen (line 229).

3. "While the incentivised system is likely to encourage testing and/or participation, the amount of budget and resources may not be sustainable, particularly when there are huge number of COVID-19 cases in the community/schools due to more infectious SARS-CoV-2 variants and little/no movement restrictions."

We have revised the discussion to highlight this point (lines 465-469).

4. “Reliance on symptoms for testing will likely to miss a fraction of cases if there is a large outbreak. How would that affect the test system and outcome- would be worth discussing. Also, since the number of positive cases are so low, the IRR for symptoms and test positivity needs to be interpreted with caution.”

We agree that reliance on symptoms for testing is likely to miss a large fraction of cases, and we have expanded upon this in describing our monitoring approaching in the discussion (lines 400-404). We have also revised our discussion of the study’s limitations to emphasize the importance of cautious interpretation of the estimated associations due to imprecision caused by low case numbers (lines 444-446).

5. “Should there be any P-values for the associations?”

Many epidemiologists have shifted away from reporting p-values due to concern that they are "inherently confounded [...] - a mix of information about the size of the effect and the size of the study" (Lang, Epidemiology, 1998). We elected to present confidence intervals, rather than p-values, in line with these conventions in epidemiologic research. Confidence intervals provide information about both the effect size and precision around the estimate (Poole, Epidemiology, 2001; Stang, Journal of Clinical Epidemiology, 2011). Many estimates in our study are statistically significant but imprecise (i.e., have wide confidence intervals). Given this, we believe that highlighting confidence intervals, in lieu of p-values, provides the clearest picture of our findings.

VERSION 2 – REVIEW

REVIEWER	Colubri, Andres Harvard University , Organismic and Evolutinary Biology
REVIEW RETURNED	10-Mar-2023

GENERAL COMMENTS	The authors adequately addressed the comments from the initial review, and after going through the revised manuscript I consider that it's ready for publication.

VERSION 2 – AUTHOR RESPONSE