Test to Stay in School: COVID-19 Testing Following Exposure in School Communities

Statistical Analysis Plan

NCT05052580

TABLE OF CONTENTS

Abbreviations

Abbreviation	Definition
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CoC	Certificate of Confidentiality
COVID-19	Coronavirus Disease 2019
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DUHS	Duke University Health Systems
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FERPA	Family Education Rights and Privacy Act
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IRB	Institutional Review Board
NC	North Carolina
NCDHHS	North Carolina Department of Health and Human Services
NIH	National Institutes of Health
PHI	Protected Health Information
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus -2
UNC	University of North Carolina
U.S.	United States

Introduction

This study will evaluate spread of SARS-CoV-2 following known exposure in schools. This information will be critical for determining future policies surrounding COVID-19 testing, quarantine, and mitigation practices in the Kindergarten through 12th grade school environment. Staff and students who participate in this study will provide consent for testing and collection of data on demographic factors, symptoms, quarantine, and test results. The existing partnerships with schools established through the ABC Science Collaborative, a partnership between Duke and University of North Carolina (UNC) faculty and Kindergarten through 12th grade schools in NC, which was formed in the summer of 2020 will be leveraged.

This study will be conducted across multiple age groups of school-age children and staff, multiple educational settings, and multiple different educational cultures to increase the potential generalizability of study results. Additionally, this study aims to prospectively collect real-world data, which otherwise would be unavailable, to guide evidence-based decision- and policymaking surrounding transmission and quarantine.

Study Design

This is a prospective, interventional study with a primary objective of evaluating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission following exposure in Kindergarten through 12th grade schools. Participants will be tested with a COVID-19 testing kit that is Food and Drug Administration (FDA)-authorized under an emergency use authorization (EUA) for non-prescription use for both symptomatic and asymptomatic evaluation in children and adults. Participants who consent to participate in this study will be tested at days 1, 3, 5, and 7 following a known COVID-19 exposure on day 0. If a participant does not know of the exposure until more than one day following they exposure, they will be tested on the day they become aware of the exposure and then resume the aforementioned testing schedule (e.g. participant identifies exposure 3 days after the exposure, test on day 3, day 5, and day 7).

If the COVID-19 tests are negative, the participant will remain in the school environment. A positive COVID-19 test or the development of symptoms on any day after exposure would require isolation according to school, local and state guidelines. Demographic information, daily presence or absence of symptoms, whether the infected person or close contact was masked, setting of the exposure, test results, and school absences will be collected following consent. Data regarding school level mitigation practices will also be collected. Data collected from this study may be combined with school-provided data and publically available community data.

General Statistics Principles

In summary tables of continuous variables, the mean, median, interquartile ranges, 95% confidence interval (CI), standard deviation and standard error will be presented to one more decimal place than the original data. In the event no meaningful information is available through the aforementioned decimal place, the statistician in consultation with the PI or designee will determine the most relevant number of decimals to display. Summaries of continuous characteristics will be based on non-missing observations.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of participants with non-missing values and without 'Unknown' or 'Prefer not to answer/say' for the variable within the population treatment group unless otherwise specified.

All statistical analysis will be performed using SAS® v9.4 or higher (Cary, NC USA). Other software may be used if required and determined to be appropriate.

Quality Assurance Procedure:

Each table shell and figure legend specifies what steps will be performed to ensure quality results. Based on the complexity of project specific analyses or generating analysis data sets, double programming or code review by another programmer/statistician may be implemented.

Manuscript #1 COVID-19 Testing Following Exposure in School Communities

Date	June 27, 2022
Corresponding author	Kanecia Zimmerman, MD, MPH
Lead statistician	Hwasoon Kim, PhD
Statistical advisor	Alan Brookhart, PhD
Project leader	Tara Mann, PhD
Target journal	TBD

History of changes

Date	Version	Summary of changes

1.1 Specific Aims

- Evaluate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission following exposure in Kindergarten through 12th grade schools.
- Characterize the effect of individual-level mitigation measures (e.g., masking) on SARS-CoV-2 spread.
- Characterize the effect of exposure setting on SARS-CoV-2 spread.
- Describe COVID-19-related school absences for up to 14 days following within-school SARS-CoV-2 exposure.

1.2 Study Population

Enrolled Population: Students and staff who meet all the following inclusion and exclusion criteria and contribute to the study until withdrawal of consent or the end of study, which is at the end of the school semester, will be used for all analyses:

1. Consent completed
2. Child or adult that is part of a school community
3. Known exposure to SARS-CoV-2 in the school setting (e.g. school bus, classroom, school sporting event, etc.)

Analysis Eligible Population: There are no exclusion criteria for this study.

1.3 Endpoints

Primary Endpoints:

- Proportion of students with positive COVID-19 test following known within-school exposure.
- Proportion of staff with positive COVID-19 tests following known within-school exposure.
- Proportion of exposures undergoing the test-to-stay protocol that result in additional transmission.
- Time to test positivity among those exposed to SARS-CoV-2 and undergoing the test-to-stay protocol.

Secondary Endpoints:

- Secondary #1
    - Proportion of students with positive COVID-19 test following known within-school exposure.
    - Proportion of staff with positive COVID-19 tests following known within-school exposure.
    - Proportion of exposures undergoing the test-to-stay protocol that result in additional transmission.
    - Time to test positivity among those exposed to SARS-CoV-2 and undergoing the test-to-stay protocol.
- Secondary #2
    - Proportion of students with positive COVID-19 test after indoor vs. outdoor exposure.
    - Proportion of students with positive COVID-19 test after athletic vs. classroom exposure.
    - Proportion of students with positive COVID-19 test after bus vs. classroom exposure.
- Secondary #3
    - Total number of school days missed due to symptoms after exposure.
    - Total number of school days missed due to isolation after positive COVID-19 test.
    - Total number of school days missed due to quarantine after SARS-CoV-2 exposure.

1.4 Handling of Missing Date

For any partially or completely missing date of testing, the scheduled testing day (Day 1, 3, 5, 7) will be used for days to test positivity.

1.5 Primary Analysis

- Objective: The proportion of students/staff with positive COVID-19 test following known within-school exposure and the proportion of exposures undergoing the test-to-stay protocol that result in additional transmission will be summarized overall, by student or staff, by school district, by school level.

    - To account for the within-school correlation of outcomes, 95% CI will be estimated for the proportion using a generalized estimating equations approach using a working independence correlation structure (Zeger et al. 1988).

    - Objective: Days to test positivity among those exposed to SARS-CoV-2 and undergoing the test-to-stay protocol will be summarized by median and interquartile ranges and nonparametric estimate of test positivity probability will be plotted.

1.6 Secondary Analysis

- Objective: The proportion of students/staff who reported masking and unmasking will be summarized and presented in a bar chart to see the trend by testing day.
    - The primary analysis will be repeated for masked and unmasked participants (students and staff) separately.
    - The primary analysis will be repeated for masked and unmasked source of exposure separately.

- Objective: School absences will be analyzed by absences due to symptoms, positive COVID-19 test, or due to quarantine for exposure to SARS-CoV-2.

    - To account for the within-school correlation of outcomes, analyses will be conducted using a generalized estimating equations approach using a loglink suitable for count outcomes, with a working independence correlation structure (Zeger et al. 1988).

1.7 Subgroup Analysis

Exploratory subgroup analysis may occur from the information collected as part of this study.

Manuscript #2 Test-to-Stay in K-12 Schools after SARS-CoV-2 Exposure: a mitigation strategy for optionally-masked schools?

Date	June 17, 2022
Corresponding author	Melissa M. Campbell, MD
Lead statistician	Hwasoon Kim, PhD
Statistical advisor	Alan Brookhart, PhD
Project leader	Tara Mann, PhD
Target journal	TBD

History of changes

Date	Version	Summary of changes
May 16, 2022	1.0	Manuscript submitted
June 14, 2022	1.0	Revision submitted
June 17, 2022	1.0	SAP was documented

2.1 Specific Aims

- To evaluated the impact of a test-to-stay (TTS) program on within-school transmission and missed school days in optionally masked kindergarten through 12th grade schools during a period of high community severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission.

2.2 Data

TTS data collected from K-12 students and staff with a non-household, within or outside of school exposure to SARS-CoV-2 between November 29, 2021 and January 28, 2022 under school districts in North Carolina (NC) employing optionally masking.

2.3 Study Population

- **Enrolled population:** participants with at least one test with valid results.
- **Analysis eligible population:** participants who were tested positive or had a negative follow-up test at day 5 or later, and completed follow-up among those enrolled

2.4 Endpoints

Primary Endpoints:

- Within-school tertiary attack rate (TAR) among tertiary TTS participants is defined as transmission from a positive TTS participant to a within-school close contact who enrolled in the TTS study once notified of close-contact status

- Days of school saved is defined as the number of days a participant was allowed to attend in-person work or education after being designated as a close contact instead of being required to undergo school exclusion in the absence of TTS.

Secondary Endpoints:

- Proportion of test-positive participants, including both secondary and tertiary close contacts
- Number of additional school-acquired cases due to TTS.

2.5 Handling of Missing Date

No imputation will be performed; Missing data will be excluded from all denominators.

2.6 Primary Analysis

Primary analysis over the entire study period (11/29/2021–1/28/2022, excluding winter break)

- Objective: Describe demographics for the enrolled and analysis eligible populations
- Objective: Report secondary attack rate and TAR for the enrolled and analysis eligible populations
    - To account for the within-school correlation of outcomes, the 95% confidence interval (CI) for the proportion was estimated using a generalized linear mixed model with districts as a random effect.
    - Re-exposure cases are reported and counted as unique cases.

2.7 Secondary Analysis

- Objective: The primary analysis will be repeated for during the period when the omicron variant comprised most COVID-19 cases (1/3/2022–1/28/2022)

2.8 Sensitivity Analysis

- Objective: Repeat the main analyses among study participants who had a positive test on or after the day of exposure
- Objective: Repeat the main analyses excluding athletic exposures and exposures acquired outside of school because of the higher risk of transmission previously documented in these settings.
- Objective: Broaden the main analyses for considered positives that include presumed positives, defined as those who developed symptoms but did not receive a subsequent negative test

Manuscript #3 Test-to-Stay in K-12 schools after Household Exposure to SARS-CoV-2

Date	June 14, 2022
Corresponding author	Zeni Scott, MD; Diya Uthappa, BS
Lead statistician	Hwasoon Kim, PhD
Statistical advisor	Alan Brookhart, PhD
Project leader	Tara Mann, PhD
Target journal	TBD

History of changes

Date	Version	Summary of changes
May 6, 2022	1.0	Initial version
June 14, 2022	1.0	Clean up

3.1 Specific Aims

- To describe the utility of a targeted TTS strategy in reducing quarantine duration and limiting missed school days for K-12 students and staff with household exposures

3.2 Data

TTS data collected from K-12 students and staff with household exposures within 4 districts and 1 charter school in North Carolina (NC) employing universal masking.

- Establish population cutoff
    - Laura Edwards (Statistical programmer): Here are the number of household exposures with test results on or after days 5, 7, and 9: ≥ Day 5 = 282; ≥ Day 7 = 251; ≥ Day 9 = 214
    - Tara Mann (Project leader): Given that ~65% of population made it into analysis eligible population for day 9, we will use this day as the cutoff, which is consistent with CDC guidance for household close contacts

3.3 Study Population

- **Enrolled population:** participants enrolled after household exposures after treating re-exposures within the FU testing period as one long exposures from the first exposure, n=322

Re-exposures after the FU testing period (treat as unique cases)	**Re-exposures within the FU testing period (treat as one long exposures)** → pick the re-exposed record by A_SL.REEXSEQ in (. 2) because two participants got positives after the re-exposure

Re-exposure records	Confirmed positive	Days to positive, median (min, max)	Note	Re-exposure records	Confirmed positive	Time to positive, median (min, max)	Note
10	5	4 (2, 8)	10 re-exposure records are from 10 participants, which means their initial exposure was not a household close contact.	26	2	8 & 9	26 records are from 13 participants

- **Analysis eligible population:** participants who were tested positive or had a negative follow-up test at day 9 or later, and completed follow-up, n=265

Total records	Exposure period	# enrolled after treating re-exposures (Total records - 13)	# analysis eligible
335	1/8/22 – 2/15/22	322	265

3.4 Endpoints

Primary Efficacy Endpoints:

- Days of in-school work and education saved, defined as the number of days a participant could attend in-person work or learning after being notified of a household member who tested positive for SARS-CoV-2.

Safety Endpoints:

- Primary: Tertiary attack rate (TAR) or within-school transmission of SARS-CoV-2, defined as the rate of transmission to within-school close contacts of positive TTS participants
- Secondary: Secondary attack rate (SAR), defined as rate of transmission or test positivity among TTS participants

3.5 Handling of Missing Date

No imputation will be performed; Missing data will be excluded from all denominators.

3.6 Primary Analysis

- Objective: Describe demographics and vaccination for the enrolled and analysis eligible populations. The primary analysis will be repeated for during the period when the omicron variant comprised most COVID-19 cases (1/3/2022–1/28/2022)
- Objective: Report SAR and TAR for the enrolled and analysis eligible populations.

- To account for the within-school correlation of outcomes, the 95% confidence interval (CI) for the proportion was estimated using a generalized linear mixed model with districts as a random effect.

3.7 Sensitivity Analysis

- Objective: Repeat the main analyses among study participants who had a positive test on or after the day of exposure.
- Objective: Broaden primary analysis for considered positives that include presumed positives, defined as those who developed symptoms but did not receive a subsequent negative test.
- Objective: Estimate range of household SAR by using positivity reported in published literature. For individuals who were tested on day 9 or later, we will use existing TTS data. For participants who did not receive a test on day 9 or later, we will impute values to obtain a range, with the following visual representation as a plot:
    - SAR for the analysis eligible pop
    - SAR for the analysis eligible pop + presumed positives
    - SAR for the analysis eligible pop + presumed positives + 25% of the people with missing data as positive
    - SAR for the analysis eligible pop + presumed positives + 40% of the people with missing data as positive
    - SAR for the analysis eligible pop + presumed positives + 55% of the people with missing data as positive

  → Rationale, reports of SAR in household close contacts range from 25-55% positive. We would like to use published literature to give a range based on our existing data.

  → To account for the within-school correlation of outcomes, the 95% confidence interval (CI) for the proportion was estimated using an over dispersed binomial regression model. For sparse data, confidence intervals for SAR estimates were computed using the Clopper-Pearson approach.

  → The study team decided not to include to the manuscript.

References

Zeger SL, Liang K-Y, Albert PS. Models for Longitudinal Data: A Generalized Estimating Equation Approach. Biometrics. 1988;44(4):1049-1060.