Title: COVID-19 Antibody and Reinfection Study

NCT number: 1589316-19

Revised: 8/1/2023

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Goal:
The goal of this study is to establish a cohort of Kaiser Permanente Colorado (KPCO) members who have and have not had COVID-19 infection for serial antibody testing and PCR testing to:
1. Quantify antibody titers among participants over 9 months.
2. Determine the rates of recurrent infection among participants with prior COVID-19.
3. Examine association between antibody titer levels and risk of recurrent infection.

Description:
In this study, the Kaiser Permanente Colorado (KPCO) Institute for Health Research (IHR) will evaluate SARS-CoV-2 IgG antibody titers over time and correlate antibody titers with risk of recurrent infection. The investigators will identify KPCO members who have and have not had prior infection, enroll them into a cohort study, conduct serial surveys for new COVID-19 symptoms, and facilitate serial viral and antibody testing.

All laboratory testing procedures and clinical management of participants will be conducted by KPCO operations. The research team will identify participants, obtain consent, administer surveys to assess COVID-19 symptoms, and direct patients to the appropriate testing. Health outcomes on cohort participants will be tracked with survey data on symptoms, clinical and utilization data from the KPCO electronic health record (e.g., hospitalization), and laboratory data (e.g., viral test results).

This research-operations partnership strategy will generate data to better understand the implications of positive antibody titers to this novel pathogen.

Study Type: Observational

Study Model: Case-control nested in a prospective cohort study
We will recruit participants into a prospective survey and testing cohort who had suspected or confirmed SARS-CoV-2 infection. We will also recruit randomly sampled patients of similar age, sex, and race/ethnicity with no evidence of previous SARS-CoV-2 infection.

Time Perspective: Prospective

Target Follow-up: 10 months

Study Population:
The study population will include individuals who are enrolled in KPCO's health plan. Individuals will be selected who have evidence of prior SARS CoV-2 infection and samples of the general KPCO membership of similar demographic characteristics who appear not to have had SARS CoV-2 infection.

Inclusion criterion:
- KPCO health plan members,
- 18 years and older,
- Have a valid email address or phone number in the electronic health record.

Exclusion criterion:
- Opted out of research
- Participated in the pilot survey

- Need a non-English language interpreter

HIPAA Privacy Rule Authorization and Informed Consent Process:
This study will ask for a waiver of HIPAA Privacy Rule Authorization to identify KPCO members who meet the inclusion and exclusion criteria (see above). It is not feasible to outreach this cohort without the waiver as the study will include large numbers.

This study will consent eligible members. Participants will be consenting to serial surveys, receipt of messaging about testing, and access to antibody testing. This study will consent patients electronically through the REDCap e-consenting process. They will also authorize study staff to track COVID-19 tests performed, testing results, risk factors for severe COVID-19 disease, and health outcomes. Participants' EHR data 24 months prior to enrollment into the study and up to 24 months after completing the study may be included the analyses.

Study Procedures:
After identifying and consenting members, we will administer a REDCap initial survey to inquire about current symptoms of COVID-19, prior symptoms of COVID-19, prior testing for COVID-19 (and results), prior or current quarantine or isolation, interest in getting tested, attitudes about testing, self-protective behaviors (e.g., social distancing, mask wearing), demographic information, employment category, and contact with patients or the public through their employment. We anticipate that the survey will take 10 minutes to complete. Follow-up surveys, conducted every 28 days, will inquire about new symptoms, new testing, current attitudes and current behaviors. Testing procedures and patient notification of viral and antibody results will be conducted by operations as part of routine medical care. Operations has notified us that antibody results will be made available on KP.org or the KP app. We will inform participants that they can obtain results there.

At the time of the baseline or follow-up surveys, based on the responses to questions about prior testing and symptoms on the surveys, individuals will be encouraged to seek viral or antibody testing.

Participants will receive a thank you email and a second email with instructions for obtaining viral and/or antibody testing, depending on their reported previous test(s) and result(s), and symptoms.

Participants will be sent a follow-up REDCap survey every 28 days to track symptoms, testing and results, quarantine or isolation, attitudes about testing, and protective behaviors. After follow-up survey completion, participants will be provided the same instructions about testing, based on their responses, as for the baseline. We will conduct repeat antibody testing on individuals who test positive to assess for reductions in titer levels over time, and among individuals who have negative antibodies to see if they develop new evidence of infection. We will conduct repeat viral testing among individuals who report no symptoms in order to assess for new asymptomatic infections.

Upon completion of the study, all participants will be sent an "Exit Survey" and testing opportunity. After completing the survey, participants will be asked to complete a final nasal and antibody test as part of the study.

Protocol Revisions:

Within this cohort, we opted to conduct a nested case-control analysis to examine the association between antibody status and reinfection. A nested case-control analysis was selected to account for the complexities of pandemic changes over time and various vaccines used during the study period. In addition, antibody status (positive/negative) was used instead of titer levels, as titer ranges differed across test types.

Data Analysis:
We will describe the antibody testing results and rates of reinfection among the study participants. We will use a nested case-control study design to examine the association between antibody seronegativity and reinfection. Reinfection will be defined as a positive SARS-CoV-2 RNA test ≥ 90 days after the first positive RNA test. Participants with reinfections will be matched to controls without reinfections by age, sex, date of the first positive RNA test, date of the last serology test, and serology test type. Using conditional logistic regression, case patients will be compared to control patients on the last serologic test result, with adjustment for potential demographic and clinical confounders.

Privacy, Confidentiality and Data Security:
The primary protection against a breach of privacy and confidentiality is in the structure of the data itself. The data extracted will include the minimum necessary to conduct the described research. Additional procedures will be in place to further protect members from a breach of confidentiality: 1) all data in study datasets will be identified only by a study-assigned unique ID number and will not include the medical record number of the subject; 2) a crosswalk table linking the study ID to a patient medical record number will be separately maintained on password-protected computers only accessible to study staff; 3) members of the study team have completed mandated training procedures and certifications, including special compliance training; new research team members (if any) will complete currently mandated training procedures and certifications prior to working on the study; and 4) the study protocol will be reviewed, approved, and monitored by the IRB. Furthermore, only aggregate data will be released in any public forum or publication.

Risks and Benefits:
This study includes surveys, information about COVID-19 viral and antibody testing, and prompts to get viral or antibody testing, including earlier access to antibody testing being offered at KPCO.

Participation in the study may give participants with symptoms messaging to get viral testing, which may be beneficial for their health and the health of their close contacts. For participants who do not have symptoms, they may learn they have been exposed to COVID-19 through antibody testing. The harms and benefits of obtaining this information are currently unknown. Participants are free to choose whether to get testing. Testing is not a requirement for participation. Testing procedures and medical management will be conducted by KPCO operations.

The primary risk of this study is the potential for loss of confidentiality and privacy of a member, through a loss or inappropriate disclosure of study data. Providing information about a member's COVID-19 symptoms, testing and attitudes may make them feel uncomfortable. They can choose to only answer questions that they are comfortable answering. Additionally, there is also a small risk for discrimination among individuals who have a positive viral test, a negative or positive antibody test, and/or a change in employment location or duties if they disclose the results to their employer. Research staff will not disclose the results of any testing conducted among individual participants to their managers. There are some inherent physical risks in

testing from nasal swabs and blood draws. Finally, the tests KPCO makes available may be under Emergency Use Authorization and any results should be interpreted with caution. Although we will advise them not to, participants may change their behavior as a result of positive antibody test results and could put themselves or others at risk for infection if the test is inaccurate. Alternatively, participants may have an increase in anxiety if their test results are positive or negative. All of these risks described are considered minimal.

There are no known risks to investigators or staff. The benefits outweigh the minimal risks to participants.

Compensation to Participants:
No compensation will be provided to participants.