MELVIN AND BREN SIMON CANCER CENTER
INDIANA UNIVERSITY

Rapid SARS-CoV-2 IgG Antibody Testing in high risk healthcare workers and candidacy for convalescent plasma therapy/prophylaxis

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1.0 BACKGROUND & RATIONALE

The success of Singapore, Taiwan and Hong Kong in limiting the impact of the sudden acute respiratory syndrome coronavirus-2 (SARS-CoV-2), also know as COVID-19, has been attributed to their preparedness but mostly to the implementation and distribution of SARS-CoV-2 fast diagnostic tests and establishment of decentralized point-of-care (POC) testing (https://www.nature.com/articles/d41587-020-00010-2). So far, the frontline response to the SARS-CoV-2 outbreak has been polymerase chain reaction (PCR) testing. PCR is the gold standard for diagnosing an infectious agent, and it has the advantage that the primers needed for such tests can be produced with relative speed as soon as the viral sequence is known.

The first quantitative reverse-transcriptase-based PCR (RT-PCR) tests for detecting SARS-CoV2 were designed and distributed in January by the World Health Organization (WHO), soon after the virus was identified. The test protocol is complex and expensive, however, and is mainly suited to large, centralized diagnostic laboratories. Tests typically take 4–6 hours to complete, but the logistical requirement to ship clinical samples means the turnaround time is 24 hours at best. A new fast PCR test (45 min) from Cepheid has been approved by the U.S. Food and Drug Administration on March 21st with availability at the end of the month. Rapid POC tests are also needed to accelerate clinical decision-making and to take some of the workload off centralized test laboratories. Most importantly, the current state of the matter in Indiana University Health system, as well as many around the country is that healthcare workers including from the ER and ICU are currently unable to receive adequate testing through existing facilities. Worst, their access to appropriate personal protective equipment (PPE) has been limited, increasing their exposure risk and causing a significant amount of stress and anxiety for front-line healthcare providers across the country.

Back to the Singapore experience, they have used immunoassays that can provide historic information about viral exposure, as well as diagnostic evidence. They exploited antibody–antigen recognition, either by using monoclonal antibodies (mAbs) to detect viral antigens in clinical samples or by using cloned viral antigens to detect patient antibodies directed against the virus. The lateral flow assay format — essentially a dipstick encased in a cassette — contains the capture reagents (either an mAb directed at a viral antigen or a viral antigen that is recognized by patients' antibodies) immobilized at defined locations on a nitrocellulose membrane, as well as labelled detector mAbs that recognize the same target. A positive result, which is triggered by binding between the analyte and capture mAb and binding by the detector mAb, is visible as a colored line. Two drops of blood from a pinprick is enough to detect a virus. They're essentially the same as home pregnancy kits. Several of these assays are available in Asia, and most European Countries have been using them too. In US, RayBiotech has developed such a similar test using knowledge from the Asian tests (https://www.raybiotech.com/covid-19-igm-igg-rapid-test-kit/). This product is CE marked and certified for diagnostic use in the EU. The application for FDA Emergency Use Authorizations of tests was submitted on March 16th, 2020. At the moment, the FDA has only approved PCR testing. No lateral flow tests have been approved as of March 23rd, 2020. However, this lateral flow test can be used legally in the US, for in vitro diagnostic use, as a POC test when administered by a licensed medical practitioner. These kits were developed in-house by Ray Biotech and validated using samples taken in hospital from patients showing clinical symptoms in Guangzhou China (all confirmed via PCR). Current stocks of 10,000 kits are being replenished daily at RayBiotech, with efforts to increase production ten-fold within the next week. The CE certificate can be found here: https://www.raybiotech.com/files/images/CG-COV_CE-Certificates.jpg.

Based on the Singapore, Taiwan, Hong Kong positive experience, and to curb the fast spread of the virus in the US, we propose to use the POC SARS-CoV-2 IgG Antibody in high risk healthcare workers with or

without symptoms, previously quarantine or not. Indeed, we hypothesize that the incidence of seroconversion among ER and ICU healthcare workers is high and higher than current models predict and that several cases are asymptomatic or with mild symptoms.
There are two additional benefits of testing seroconversion.

1) Although there are no official reports, we clearly hear and see selfies of anxiety, stress and exhaustion from our colleagues at the front line. Thus for the healthcare workers knowing that they have seroconverted, will help them be more confident that they are now protected and can work in safer conditions as it has recently been shown that reinfection could not occur in SARS-CoV-2 infected rhesus macaques https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1.

2) The healthcare workers represent an ideal pool of donors for convalescent plasma due to their commitment and the fact that they have usually been tested to give blood or are currently blood donors. The FDA just approved a master protocol for collection and administration of convalescent plasma: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

In sum, "you cannot fight a fire blindfolded, and we cannot stop this pandemic if we don't know who is infected." (World Health Organization Director-General, 16 March 2020).

If successful and validated, we will hope to rapidly scale it up to propose the rapid SARS-CoV-2 IgG Antibody testing to the general population as has been done in countries that have had almost no death due to COVID-19.

2.0 OBJECTIVES

2.1 Primary Objective

1. To validate the use of a rapid, at home, point-of-care (POC) SARS-CoV-2 IgG antibody test in high risk healthcare workers

2.2 Secondary Objectives

1. To evaluate the incidence of seroconversion in this high-risk population
2. To identify possible candidates for convalescent plasma donation for therapy/prophylaxis (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds)

3.0 STUDY DESIGN

This is a non-interventional study to validate the use of a rapid, at home, point-of-care (POC) SARS-CoV-2 IgG antibody test in high risk healthcare workers.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria:

1. High risk healthcare workers, prioritizing those who are exposed to aerosol generating procedures (physicians and respiratory therapist) working in the emergency room or intensive care units at Indiana University Health or IU school of Medicine affiliated facilities. A second tier of prioritization, to be approached if testing capacity remains after the initial testing phase, will be nurses working these same areas

2. Health care workers who are currently out sick or quarantined due to possible/known exposure to COVID-19 and whose physician confirms that a negative test would allow their return to work are also eligible for testing (Subjects in this group may begin study procedures and be registered once they reach the end of their quarantine period)

4.2 Exclusion Criteria:

1. Previously tested for COVID-19

5.0 SUBJECT REGISTRATION

All subjects will be registered in OnCore. Regulatory files will be maintained by the department of Pediatrics Intensive Care Unit. Applicable regulatory documents must be completed and on file prior to registration of any subjects.

6.0 STUDY PROCEDURES

6.1 Recruitment and Enrolment

A recruitment email will be sent out to healthcare workers working at Indiana University and/or Indiana University Health (Appendix I) Healthcare workers will be asked to attend walk in hours at either Methodist or Riley Hospital in Indianapolis, IN. They will then undergo the informed consent process and be registered to study and assigned a unique subject ID.

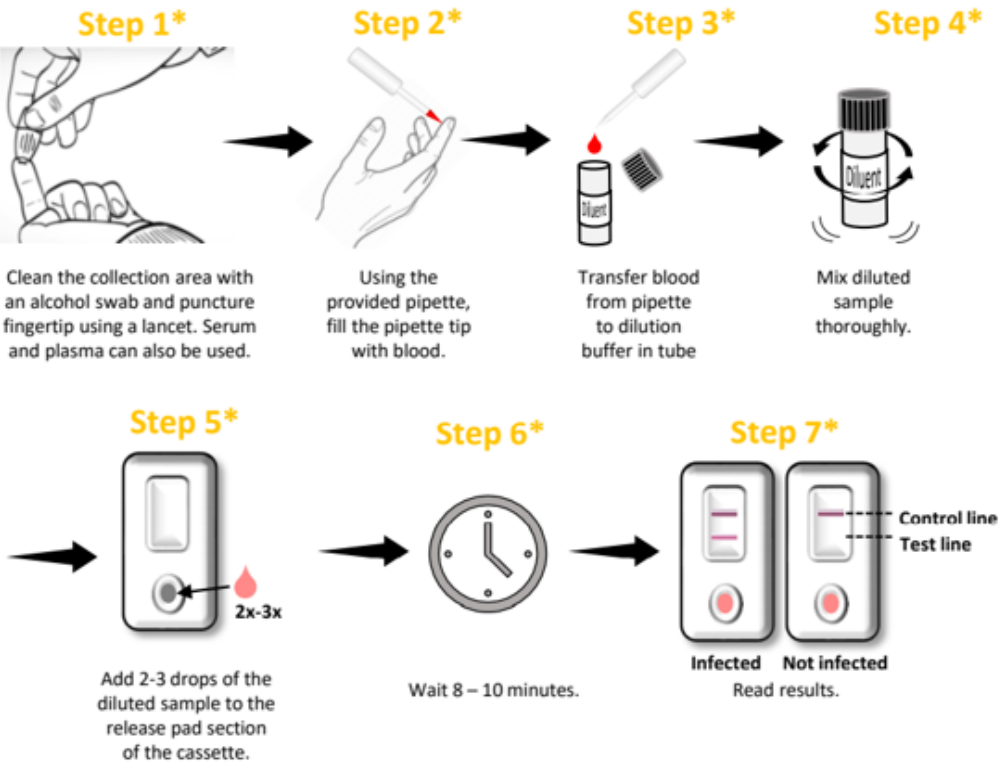
Subjects will be given a link to complete a short data collection form in REDCAP and will be given the SARS-CoV-2 IgG Antibody at home test kit.

6.2 SARS-CoV-2 IgG Antibody Testing

The SARS-CoV-2 IgG antibody test will be performed at home by healthcare workers enrolled to study.

Figure 1 provides an overview of the testing procedures with detailed instructions provided in the kit (Appendix II). Once results are obtained, subjects will send the results to the research team by uploading a picture into REDCap or by directly emailing the research team.

Figure 1: SARS-CoV-2 IgG Antibody Testing Workflow



6.2.1 Negative IgG Antibody Test Result

If the test result is negative, there will be no further study procedures and subjects will be advised to continue prevention as usual. Subjects may pick up additional tests and re-test with the finger prick test in 21 days for a maximum of 3 times.

6.2.2 Positive IgG Antibody Test Results

If the test result is positive, subjects will be instructed to have a blood draw for serological testing of IgG to validate the SARS-CoV-2 IgG antibody test. A nasal swab will be performed to confirm the absence or presence of virus by PCR. The blood draw and nasal swab will be conducted at an IU Health testing site and will be analyzed at the centralized IU Health virology lab.

6.2.2.1 PCR Positive Results

If testing is positive and shown to be active for infection by PCR, subjects will be directed quarantine per IUH policy. Prevention as usual should continue at work, including the use of appropriate personal protective equipment.

6.2.2.2 PCR Negative Results

If testing is negative for active infection by PCR and the blood test confirms the results of the seroconversion, subjects will be instructed that they may be a candidate for convalescent plasma donation via a clinical trial and will be referred to a blood center. This is optional and

not mandatory. Prevention as usual should continue at work, including the use of appropriate personal protective equipment.

7.0 COLLECTION OF DATA

Data will be collected from the data collection form completed by subjects and testing results. Data captured includes the following:

- Data required for eligibility verification will be collected from subject self-report.
- Demographics (including, age, sex, race/ethnicity, zip code)
- Potential exposure to SARS-CoV-2.
- Clinical symptoms consistent with SARS-CoV-2

8.0 DATA FORMS AND SUBMISSION SCHEDULE

Data storage for the study will be performed using a secure, web-based, Research Electronic Data Capture (REDCap™). The REDCap® system was developed by Vanderbilt University and is provided by Indiana University through their community license. REDCap® is managed by the Indiana University Department of Biostatistics and secured by University Information Technology Services (UITS) Advanced IT Core. Access to the password-protected database will be limited to the investigators of this study, and any data that is distributed will be either de-identified or authorized by written permission from participants.

All source documents are to remain in the subject's clinic file. All documents will be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Cancer Center Data Safety Monitoring Committee.

9.0 POTENTIAL RISKS AND PROCEDURES FOR MINIMIZING RISKS

Risks related to blood collection include light headedness, pain, bleeding or infection.

There is also a possible risk of loss of privacy and/or confidentiality. In order to minimize these risks, each subject in the database will be assigned a unique study identification (ID) number. Patient-derived material will be linked to patient clinical information through this study ID number. All private health information (PHI), specimen information, and study data will be entered into the access-controlled, password-protected REDCap database. Records and/or data extracted from the database will be identified by the subject study ID number only and without any accompanying individually identifiable patient information. Thus, the code to the study identification numbers will be accessible only to the PI and authorized study personnel.

Emails received from subjects indicating test results will be deleted immediately after receiving or sending and after the results are recorded. All messages containing PHI in inbox, sent, or deleted items folder must be deleted. Any emails containing PHI may only be sent to an outside environment (non IU, IU Health, or Eskenazi accounts) with a valid purpose and will be encrypted.

10.0 STATISTICAL CONSIDERATIONS

The primary objective of this non-interventional study is to validate the use of a rapid, at home, point-of-care (POC) SARS-CoV-2 IgG antibody test in high risk healthcare workers. Since we do not have a current estimate of the seroconversion rate in this high-risk population, we will make a bold estimate that at least 25% will test seropositive. We plan to recruit a sample 306 subjects to estimate the seropositive rate with 95% confident interval of 0.1 width, that if the true rate is 25%, then the sample size is sufficient to obtain a 95% CI of [0.2, 0.3]. Assuming the drop-out rate of 10%, then we would need to recruit a total 340 subjects. The seroconversion rate will be calculated with 95%CI. Additionally, the sensitivity and specificity will be calculated with 95%CI.

11.0 DATA AND SAFETY MONITORING PLAN

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for **Exempt** Trials. Investigators will conduct continuous review of data and subject safety.

11.1 DSMC Monitoring & Auditing

This study will be considered exempt from DSMC review per the IUSCC Institutional DSMP. However, the DSMC may elect to require for cause auditing and/or monitoring any time per their discretion.

11.2 Data Management/ Oncore Reporting Requirements

Despite exemption from DSMC full committee review, this study will comply with the IUSCC Oncore Minimum Footprint requirements for study data collection via the OnCore system.

11.3 Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

11.4 Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery.

12.0 PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

13.0 CRITERIA FOR REMOVAL FROM STUDY

The Principal Investigator may withdraw a subject from the study at any time and for any reason. This may occur at the discretion of the PI and without the subject's consent. Examples of why this might occur

include: informed consent issues, IRB issues, and discrepancies between samples and associated medical information.

APPENDIX I: RECRUITMENT EMAIL

We are conducting a research study to determine if high risk healthcare workers have immunity to the novel coronavirus, SARS-CoV2. The purpose of the research is to determine if a certain marker in your blood (IgG to SARS-CoV-2) can tell if you have been exposed and now recovered from SARS-CoV-2. About 340 healthcare workers affiliated with Indiana University or/and Indiana University Health will take part in this study.
You are eligible for this study if you work in an area of the hospital that exposes you to aerosol generating procedures. We will first focus on physicians and respiratory therapies working in an ICU or ED.

If you have previously been tested for SARS CoV2, you are NOT eligible for this study.
If you agree to take part in the study, your participation will include

1. A very short data collection form
2. A single blood sample taken from a finger prick to be done at home
    a. If you are positive, you will be directed to have a blood draw for serologic testing of IgG and validate the rapid test, and a nasal swab at an IU Health testing site to confirm by PCR that your infection is not active anymore.

If you are interested in participating in this research study, please attend one of the following walk-in hours to be consented and pick up your FREE at home test kit:

XXXXX (to be filled in with the dates and times as we determine them)

Thank you for your consideration,
Sophie Paczesny and Courtney Rowan,

APPENDIX II: SARS-CoV-2 IgG Antibody Detection Kit Instructions

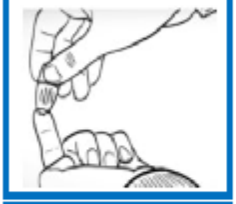
Version 03262020

Coronavirus (SARS-CoV-2) IgG Antibody Detection Kit for Finger Prick Samples

Read the instructions carefully before use.

SAMPLE PREPARATION AND TESTING

Step 1



- Wash your hands with warm water.
- Select the finger you are going to prick and choose a puncture site off center of the fingertip
- Massage and/or shake to stimulate blood flow towards the collection are.
- Clean the collection area and the pipet provided with the alcohol swab (provided in the kit)
- Place the finger with the chosen collection area on a flat surface facing up
- Twist the cap off the lancet (provided in the kit) and press firmly against the collection site to puncture the finger

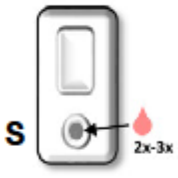
Step 2

- Create a large drop of blood by applying pressure at the base of the finger and massaging upward
- Squeeze the pipet bulb to expel air
- Draw fingertip blood into the pipet by gently releasing the bulb
- The pipet should be filled just up to the indicated line (refer to the figure at left)
- Take care to avoid bubbles

Step 3

- Transfer the blood drawn to the Sample Diluent vial
- Mix thoroughly by squeezing the pipet 3 times

Step 4

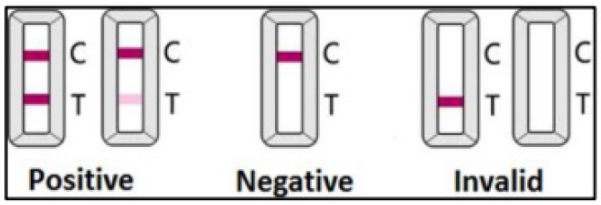


- Use the pipet to add 2-3 drops to the release pad section (S) of the Detection Cassette
- The sample should be run as soon as possible after collection per the instruction above

Step 5

- Wait 8-10 minutes and read the results.
  Results measured after 20 minutes are invalid.

INTERPRETATION OF TEST RESULTS



a. **Positive for coronavirus:** Both the test line (T) and the quality control line (C) are colored. Regardless of the color saturation present of the band on the test line (T), even a very weak band should be judged as a positive result.
b. **Negative for coronavirus:** The test line (T) does not develop color, but the quality control line (C) is colored.
c. **Invalid:** There is no colored control line (C) band. The results are invalid regardless of whether the red band appears on the test line (T); additional testing is required.

REPORTING YOUR RESULTS

a. Take a picture of the Detection Cassette
b. Send picture to the research team via uploading to REDCap or emailing to Dr. Courtney Rowan at coujohns@iu.edu