Ramy Arnaout rarnaout@bidmc.harvard.edu BIDMC
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PURPOSE OF PROTOCOL

The SARS-CoV-2 pandemic has resulted in an international shortage of the nasopharyngeal (NP) swabs used to collect sample for virological testing. This shortage has become a crisis as testing capacity is growing, and threatens to become the bottleneck at Beth Israel Lahey Health as it already is in other testing centers. To resolve this crisis, a team in the Clinical Microbiology Laboratories at Beth Israel Deaconess Medical Center has been working closely with high-volume domestic manufacturers developing 3D printed NP swabs in an open process involving the hard work of many partners from across the country. This process has resulted in promising prototypes.

We will test these prototypes for non-inferiority relative to existing, already validated NP swabs produced by Copan and/or Puritan ("control swab") for purposes of molecular microbiology: i.e., the PCR tests used for virological testing for SARS-CoV-2 and for multiplex testing using Genmark's ePlex respiratory pathogen panel (RPP). Specifically, we will swab the nasopharynx of patients under investigation (PUI) for Covid-19, the disease caused by SARS-CoV-2, using a prototype, swab using a control swab, and test for concordance of SARS-CoV-2 and RPP results. In all cases we will transport the swab in validated viral transport medium (VTM) as per standard operating procedure at BIDMC.

Primary Objective: To determine whether four newly designed and manufactured NP swabs ("prototype swabs") perform acceptably compared to standard swabs ("control swabs") used for collection of nasopharyngeal samples for molecular microbiology, specifically Covid-19 and respiratory pathogen testing by PCR.

SIGNIFICANCE AND BACKGROUND FOR THE STUDY

The SARS-CoV-2 coronavirus is the cause of the Covid-19 pandemic. This novel coronavirus infection was first described in 2019 in China and testing in the United States first became available in early 2020. A linchpin of fighting the pandemic is diagnostic testing for the virus that causes Covid-19. Unfortunately, NP swabs are in limited supply due to the explosive spread of the virus, including in Italy, home to Copan, a leading manufacturer of NP swabs. Control swabs consist of a plastic shaft with a thin neck and a head (or tip) coated with flock, a filamentous material most often made of rayon, nylon, or Dacron. The swab is inserted into the nasopharynx, swirled around, removed, and the tip broken off into a vial containing VTM. The vial is sealed and sent for testing, for which an aliquot of VTM is taken and used as per testing protocol.

BIDMC has been interacting with manufacturers and testing prototypes according to a three-step protocol: (1) expert evaluation by representatives from clinical pathology, infectious disease, and respiratory therapy for features such as stiffness; pliancy of the head, neck, and shaft; and smoothness of material; (2) sufficiency of collection using microscopic evaluation of Gram stain of the cheek vs. control swabs (as a minimally-invasive proxy for NP swabbing); and (3) PCR compatibility by incubating the swab tip in VTM overnight to soak up or leech out any potential PCR inhibitory substances, spiking with inactivated SARS-CoV-2 viral particles, running our standard test, and confirming positivity.

In addition, working with manufacturers, BIDMC assessed the ability of prototypes to be autoclaved for sterilization, individually packaged, and produced at a rate of hundreds of thousands per day in short order, which are requirements for addressing the pandemic at scale.

Prototypes that passed these tests and assessments were prioritized for the current study.

DESCRIPTION OF RESEARCH PROTOCOL

Study Design – Overview, Methods, Procedures

The study design is a clinical trial to determine whether newly designed and manufactured NP swabs ("prototype swabs") perform acceptably compared to standard swabs ("control swabs") used for collection of nasopharyngeal samples for molecular microbiology, specifically Covid-19 and respiratory pathogen testing by PCR.

The study population will consist of approximately 400 emergency-department, inpatient, and "drive-thru" patients seeking evaluation of respiratory complaints in the context of the Covid-19 pandemic.

The study endpoint is confirmation or rejection of concordance between each of the four prototypes vs. control swab. This will be achieved through a test of concordance for 10 positive Covid-19 tests, 10 positive RPP tests (any pathogen), and 10 negatives. Because the study is for Covid-19-positive vs. negative and simultaneously RPP positive vs. negative, the total number of tested swabs may be fewer than 30 (but no fewer than 20) per prototype. Note that to economize testing, there may be collection without testing for some swabs (e.g. if 10 negatives are already collected). No patient will be swabbed with more than a single prototype swab.

Study Intervention/Investigational Agent: The agents consist of four prototypes designed and assessed as described in the "Background" section. Like control swabs, these are 15-16cm in length, with 1-3cm radially symmetric heads of diameter 2-3mm, a thin neck of 4-7cm (diameter 1-2mm), and a thicker shaft (diameter 2-4mm), with a break point most often 7-8cm from the tip of the head to facilitate transport. The materials are various FDA-grade plastics and resins.

Consent: Potential participants at the point of testing, whether drive-thru, ER, or inpatient, will be asked if they are willing to have an additional experimental swab test performed by the treating clinician. The participant will be given a written research information sheet (by study staff) that will include contact information for the study doctor if the participant has any questions. For distribution of participant information sheets and instructions to staff, we will be coordinating with the head of respiratory therapy, Joe Previtera, who is a co-investigator on this study.

Research Procedures: Participants who have been swabbed using control swab as part of standard (i.e., non-study/non-experimental) clinical evaluation will be swabbed with a single prototype as experimental. Prototype swab will be placed in a separate vial of the same BIDMC-validated VTM solution and sent to the clinical labs for testing.

For each prototype, prototype swabs will be tested until either 10 Covid-19 positives, 10 RPP positives, or 10 negatives are collected, whichever comes first. Thereafter, prototype swabs may be held and tested following result of the accompanying control swab, to bring totals to 10. (This is to avoid unnecessary testing of e.g. extra negatives if 10 negatives have already been obtained.)

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Results from control and prototype swabs will be compared for concordance. This is a research study. The result of the prototype swab will not be returned to the patient or entered into the patient record and will not be used for clinical decision-making. This is for research use only. If the research swab result is discordant with the standard of care swab, the study team will notify Chris Rowley or contact the highly infectious disease pager to relay the result. Chris Rowley or the physician carrying the highly infectious disease pager will determine next steps.

Regarding management of discordant results: if results are discordant, the discordant result will simply be recorded as such. Swabbing will not be repeated by the research team.

Data and Specimen Banking: Specimens will be labeled with a subject-specific unique identifier without PHI with the format <PROTOTYPE)_0001.

Specimens will be linked to electronic medical record number (MRN), date specimen was taken, and result of Covid-19 and RPP testing. Specimens and data will be analyzed with subject unique identifier labels without any PHI.

De-identified data will be shared with the sponsor for analysis. Data will be transferred using Excel spreadsheets.

Study Timeline: The study involves a one-time collection of a prototype swab from a patient. For an individual participant, the length of participation in the study will be just enough time for sample collection (approximately 1 minute). The study will run for approximately two weeks, followed by one week of analysis. The length of time to complete the study will depend on manufacturers' delivery of swabs and the rates of positive and negative results (currently ~15% for Covid-19 on a volume of ~1,000 tests/day). The anticipated total duration of the study is three weeks.

Statistical Considerations | Sample Size Justification: Approximately 400 participants will be enrolled in the study at BIDMC and will have a prototype swab collected.

For each of the four prototype swabs, we will test 10 positive Covid-19 cases, 10 positive RPP cases, and 10 negatives, for a total of 30 tested prototypes. Thus, given prototypes from four manufacturers, we expect approximately 120 prototype swabs to be tested.In clinical microbiology, it is standard practice to take this approach of identifying 10 positives and negatives to evaluate new swabs (Miller et al. Changing Swabs: To Validate or Not To Validate? J Clin Micro 2013 10.1128/JCM.02023-13).

Data Analysis: Inferential statistics will be done to analyze the extent of agreement of the test results from the two viral collection kits. Quality control checks will be run on the data to detect data that is missing, out of expected ranges, or otherwise questionable.

Data will be recorded using the data collection forms. The data to be collected include (1) demographic data: age, gender, MRN (information available through the electronic health record); (2) date of enrollment; (3) date of specimen collection; (4) Covid-19 positive/negative, using the control swab; (5) RPP pathogen positive/negative, using the control swab; (6) Covid-19 positive/negative, using the prototype swab; (5) RPP pathogen positive/negative, using the prototype swab.

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Statistical plan: We will evaluate using Cohen's kappa, the normed difference between the rate of agreement that is actually observed and the rate of agreement that would be expected purely by chance (Kwiecien et al. Dtsch Arztebl Int. 2011 Jul; 108(30): 515–521).

Study data may be stored for up to 6 years.

Subject Selection | Inclusion Criteria: Individuals presenting to the site for clinical care will be evaluated for clinical screening for Covid-19 testing or other respiratory infection testing. Individuals felt identified clinically as needing Covid-19 testing may be approached for study participation. If the patient provides verbal informed consent, specimen collection with the prototype will be done.

Exclusion Criteria: Known thrombocytopenia of <50,000 platelets/µl (risk of mild bleeding). No other adult patients will be specifically excluded.

POSSIBLE BENEFITS

There is no direct benefit to the participants, but we hope to provide a new resource to areas with critical shortages of Covid-19 sample collection kits.

POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

The need for the viral diagnostic testing will be determined by clinicians as part of their conventional evaluation without regard to this protocol. There is minimal risk to subjects. The primary risks are temporary minor discomfort and minimal nasal bleeding.

RECRUITMENT AND CONSENT PROCEDURES

Recruitment: Patients who have been identified as needing evaluation for Covid-19 using a control swab will be told about the option to provide an additional experimental swab test by the treating clinical staff member. To minimize the spread of Covid-19 and conserve on PPE, the team members will not see the potential participant in person.

Consent: Patients who have been identified as needing the standard viral collection test will be asked by the treating clinician if they are willing to have an additional experimental swab test. Treating clinicians will not be added to the research staffing form as swab testing is a part of their standard clinical role at the hospital. The patient will be given a research information sheet which will provide contact information for the study team. Patients with questions may speak to the study team by phone or email for clarifications. To minimize the spread of Covid-19, the study staff will not see the potential participant in person. Additionally, written informed consent is not necessary as the study is minimal risk and written consent requires paper in the clinical area, which increases the risk of disease spreading.

Participants can withdraw at any time. Participants who withdraw will continue to receive conventional care.

Subject Protection: No subject will be influenced by the study team to participate in this trial.

STUDY LOCATION

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Privacy: Recruitment will occur in private patient rooms or similar private context.

Potential participants will be given the research information sheet by treating clinical personnel already providing conventional care. Participants will be able to call or email the study team to ask questions or address concerns about the study.

Appropriate members of the study team are already credentialed and can access the participants' electronic medical records.

Specimen testing will be done at the BIDMC clinical lab.

Physical Setting: The study recruitment and specimen collection will occur at departments where testing is occurring at BIDMC.

DATA SECURITY

Data will be collected on electronic data collection forms which will be securely stored on firewall-protected servers at the sites, and can only be accessed by the site study team. All study staff will be credentialed for research. With an exception of MRN, the data will not contain identifiers. Rather, participants will be assigned a unique identifier. Only de-identified data will be shared with the coordinating site/sponsor. Data will be emailed securely using Excel spreadsheets.

The study will evaluate the performance of a novel sample collection swab. The results will be not shared with the patients or the treating clinicians and will not be part of the patient's health record.