

Detection of SARS-CoV-2 RNA and antibodies in diverse samples: Protocol to validate the sufficiency of provider-observed home-collected blood, saliva and oropharyngeal samples

Patrick Sean Sullivan, Charles Sailey, Jodie Lynn Guest, Jeannette Guarner, Aaron Julius Siegler, Mariah Valentine-Graves, Laura Gravens, Carlos del Rio, Travis Howard Sanchez

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Abstract

Background: The US response to the SARS-CoV-2 epidemic has been hampered by a lack of aggressive testing for infection. Testing for SARS-CoV-2 infection is the cornerstone of an effective public health response. However, efforts to test have been hampered by limited reagents, limitations in the availability of swabs used for collection of nasopharyngeal swab (NPS) specimens, limitations in personal protective equipment (PPE) for healthcare providers collecting the NPS specimens, and limitations in viral transport media for transporting the specimens. Therefore, more flexible options for screening for SARS-CoV-2 RNA and serologic responses are critical to inform clinical and public health responses.

Objective: We aim to document the ability of patients to self-collect specimens for SARS-CoV-2 viral detection and serology.

Methods: In this protocol, patient collection of samples will be done with observation by a provider during a telemedicine session. Participants will be mailed a specimen collection kit, engage in a telehealth session with a healthcare provider through a HIPPA-compliant video meeting, and collect specimens while observed by the provider. Providers will record whether they are confident in the sufficiency of the specimen for laboratory testing that would inform clinical decision making. We will objectively assess the laboratory evidence of sufficient biological material in the mailed-in specimens.

Conclusions: Defining a conceptual framework for assessing the sufficiency of patient-collected samples for the detection of SARS-CoV-2 RNA and serologic responses to infection is critical for facilitating public health responses and providing PPE-sparing options to increase testing. Validation of alternative specimen collection should include objective measures of the sufficiency of specimens for testing. A strong evidence base for diversifying testing modalities will improve the tools to guide public health responses to the COVID-19 epidemic.

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Original Manuscript

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TS is editor-in-chief of JMIR Public Health & Surveillance. Because of this, he was not involved in the editorial handling or peer-review of the paper.



Abstract

Background: The US response to the SARS-CoV-2 epidemic has been hampered by a lack of aggressive testing for infection. Testing for SARS-CoV-2 infection is the cornerstone of an effective public health response. However, efforts to test have been hampered by limited reagents, limitations in the availability of swabs used for collection of nasopharyngeal swab (NPS) specimens, limitations in personal protective equipment (PPE) for healthcare providers collecting the NPS specimens, and limitations in viral transport media for transporting the specimens. Therefore, more flexible options for screening for SARS-CoV-2 RNA and serologic responses are critical to inform clinical and public health responses.

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Background

The global pandemic of SARS-CoV-2 infection and associated illness (Coronavirus Disease 2019, or COVID-19) have emerged very quickly, challenging traditional systems of clinical and public health response.[1, 2] There is broad consensus that adequate testing for SARS-CoV-2 is imperative as a cornerstone of public health efforts to control the spread of the virus.[3-5] The United States response to the SARS-CoV-2 epidemic has been hampered by a slow implementation of screening programs and by a variety of factors that have limited the extent of SARS-CoV-2 testing. Following initial problems with quality control of reagents[6] the US government allowed more liberal policies for the development of Laboratory Developed Tests (LDTs)[7], which allowed a massive expansion of capacity in terms of availability of equipment and staff capacity at commercial laboratories.

However, other factors now limit the reach and volume of testing for SARS-CoV-2 infection. Currently, the gold standard specimen for testing for SARS-CoV-2 RNA is a provider-administered nasopharyngeal swab (NPS)[8]; there are currently supply chain challenges, including shortages of rigid swabs for NPS collection, of personal protective equipment (PPE) required for healthcare workers to collect NPS specimens, and of viral transport media required for transporting specimens. [9-12] There are also important questions about site of testing for SARS-CoV-2 infection: should people with mild symptoms that might or might not have COVID-19 disease come into clinics for testing if they don't require immediate clinical care? How can people who have been quarantined receive testing to document viral shedding to guide the time of release from quarantine, without coming into places where patients are congregating? Finally, we have essentially no epidemiologic data about asymptomatic infection, which could be answered with serology data. Decisions about when to end "Stay at Home" curfews should likely be based, in part, on the prevalence of antibodies (and, perhaps, immunity) among populations. All these applications will require mechanisms to collect specimens that minimize needs for PPE and allow flexibility of where specimens are collected. Patient-collected samples have appeal in terms of minimizing PPE requirements and

enabling the possibility of epidemiologic studies to characterize the infection and immune status of populations.

The regulatory environment governing both the development of laboratory developed tests (LDTs) and specifically the testing of patient-collected samples, either in the provider office or at home, is complicated.[13, 14] In response to the urgency of COVID-19 epidemics in the United States, the FDA has relaxed the regulatory pathways for the development of LDTs to increase the national laboratory capacity.[15] With respect to specimen types, FDA has developed two pathways for approval of testing for SARS-CoV-2 infection: (1) develop laboratory data documenting validation or performance to submit to FDA for review as an Emergency Use Authorization; or (2) use state regulatory mechanisms when the test is developed under the jurisdiction of the state in which the lab resides. In the latter case, the State regulators take responsibility for COVID-19 testing by laboratories in their state.

Patient-collected samples have slightly different requirements. FDA has issued clarifications that the ability of states to oversee the validation of LDTs with patient-collected samples is not covered by the general policy for the development of LDTs, and that assays with patient-collected samples will be required to submit data for review through the FDA for an EUA application.[15] FDA recently updated guidance to allow collection of patient-collected mid-nasal turbinate samples collected in the provider office, but specifically noted that this approval did not extend to patient-collected samples collected at home.[16] Guidelines for validation of patient-collected serology specimens do not appear to be explicitly addressed under current FDA guidance, which has focused on collection of samples for viral detection.

Outside of the realm of SARS-CoV-2 diagnosis, FDA has reviewed and approved patient-collected samples for a wide variety of laboratory assays, including HIV serology through dried blood spot (DBS) specimens[17]. In other fields, there is a long history of using patient-collected samples under research protocols to develop data on acceptability and to provide clinical services (e.g., STI

testing) as part of research studies.[18, 19]

We anticipate that there will be biological, immunologic and temporal aspects that will be important to consider in designing the validation studies for alternative specimen types and interpreting the results. When directly comparing provider-collected and patient collected samples of the same type (e.g., provider-collected versus patient-collected oropharyngeal swab [OPS]), it is appropriate to compare the cycle threshold (C_t) for the paired samples to assess comparability. However, RNA concentrations may differ between different specimen types because of differences in RNA shedding in the two sites, such that a direct comparison of C_t results between nasopharyngeal and oropharyngeal swabs might not be an appropriate comparison. Similarly, the timing of onset and waning of IgM titers in patients and detection of IgA in saliva or serum following infection with SARS-CoV-2 are not well understood. Finally, it is unclear whether RNA might persist for variable lengths of time after infection in different specimen types. For example, To et al document the presence of RNA in saliva for nearly 2 weeks post-hospitalization.[20] Ultimately, all of these questions need to be explored to make the most evidence-based recommendations for specimen screening types and collection methods in specific time phases of the infection cycle.

In this manuscript, we lay out a protocol for describing the sufficiency of patient-collected samples for testing for SARS-CoV-2 infection in OPS and saliva, and for immune response to SARS-CoV-2 in DBS and saliva. We consider two aspects of assessment. First, do providers who observe patient-collected samples consider them to be comparable to provider-collected specimens in terms of *specimen sufficiency* for testing for SARS-CoV-2 RNA and antibodies? Second, do assessments of specimen quality (e.g., human nucleic acid for OPS and saliva, specimen saturation and DBS size for DBS cards) document that patient-collected samples contain *sufficient biological material* for accurate testing?

Methods

We propose methods to validate multiple sample types for RNA-PCR and for serology tests. A table

of the proposed specimen types and assays is depicted in Table 1.

Specimen	Oropharyngeal Swab	Saliva	Dried Blood Spot
SARS-CoV-2 RNA	X	X	
IgG		X	X
IgM		X	X
IgA		X	X

Table 1. Specimen types and assays to be performed in an evaluation of diverse samples for SARS-CoV-2 RNA and antibody testing

Specimen collection:

Oropharyngeal Swab Self-collection: Patients will be provided with printed instructions for collection (see Figure 1). They will be instructed to insert the swab into their mouth and rub the swab tip against the back of their throat for 20 seconds on the left side, then 20 seconds on the right side. They are advised to avoid touching their tongue, teeth, and gums with the swab. They are instructed to insert the swab in the tube of viral transport media, break the swab at the score, and cap the tube.

Self-collection of dried blood spots (DBS): Patients will be provided with printed instructions for collection (see Figure 2). They will be instructed to wash their hands thoroughly, use an alcohol swab to clean the tip of their middle or ring finger on their non-dominant hand, release the blade of the provided lancet by pressing into the side of the finger near the tip of the finger, and fill each of 5 circles on a Whatman standard dried blood spot collection card. Participants are instructed to allow the blood card to dry for at least 15 minutes before packaging for return shipment.

Saliva self-collection: Participants are asked not to eat, drink, smoke or use oral hygiene products for at least 10 minutes before the collection process (Figure 3). Participants will be instructed to rinse their mouth with water and discard, and then wait 5 minutes after the rinse before collecting the specimen. Participants will be instructed to place their lips over the collection tube funnel and collect saliva until the saliva reaches the red indicator line. The participant will be instructed to

screw the cap on the tube tightly and invert it 20 times to stabilize the sample. The participant will be instructed to write their date of birth on the tube before preparing for shipping.

Testing:

RNA-PCR: Specimens will first be checked for quality. The samples will then undergo total nucleic acid extraction using the Thermo Kingfisher platform (Fisher Scientific, Waltham, Mass). Isolated RNA will reverse transcribed to DNA using a one-step, one-tube system using reagents from Thermo (Fisher Scientific, Waltham, Mass). The second half of the one-tube system will involve qPCR. The reverse-transcribed DNA will undergo qPCR with primers and probes targeting 3 gene regions of the SARS-CoV-2 genome (N, S, ORF1), using reagents from Thermo. The results will be analyzed, and an interpretation will be made based on Ct values and positive identification of the nucleic acid.

Specimen sufficiency for RNA-PCR: We will test OPS and saliva specimens for RNase P as an endogenous internal amplification control and to quantify nucleic acid content of the specimen.[21] We will consider OPS and saliva specimens with C_t values of <30 to indicate sufficient collection of biological material in the saliva sample and the swab, respectively.

Serology tests: Specimens will first checked for quality. For blood, a 6mm punch will obtained from the dried-blood spot and the material will undergo a standard antibody extraction method using TRIS buffer. For saliva, the sample will be aliquoted and used directly in the serology assay. Once the material is added to the reaction tube, the EIA primary and secondary antibodies (SARS-CoV-2 assay, IgG and IgM, Epitope Diagnostics, San Diego, California; IgA: ; EuroIMMUN, Mountain Lakes, New Jersey) will be added using an automated liquid handler instrument (DSX; Dynex Technologies, Chantilly, Virginia). The protocol will follow the manufacturer's guidelines for reaction conditions, data interpretation, and ensuring that internal controls pass.

Specimen sufficiency for serology: For dried blood spots, we will conduct a three-point quality check, documenting the visual appearance of the blood spot, whether it is soaked through the paper, and whether the circles are filled, as we have previously reported.[22]

Provider observations:

Providers will observe participants as they collect specimens through a telehealth video session on a HIPPA-compliant video conference service. After establishing a secure connection and confirming the identity of participants using a study identifier, the provider will direct the participant to use the provided instructions to collect the specimen; the provider will identify their role as one of an observer. The provider will document on a case report form (CRF) that they observed the participant collecting the specimens (See Appendix 1 for CRFs). The provider will also record their assessment of whether the specimen collected is sufficient for laboratory testing, and, as secondary assessments, complete checklists of steps in the correct collection of the specimen (e.g., did not smoke or drink while collecting saliva specimen, inverted closed saliva tube 20 times as directed, dropped blood on DBS spots rather than touching the DBS card).

Analysis:

We will tabulate the provider impressions of specimen sufficiency (primary outcome); exploratory analyses for provider observation will include enumeration of how common certain errors in self collection were. For RNA-PCR specimens, we will tabulate the proportion of OPS and saliva samples that had C_t values for RNase P < 30 . As a secondary analysis, we will examine whether the RNase P C_t values for the patient-collected OPS were different from the C_t values from a historical set of provider-collected OPS tested with the same reagents and laboratory equipment in the study laboratory. These analyses will involve comparing means of the two groups using a t-test.

Discussion

There is an urgent need to develop and validate new methods to monitor SARS-CoV-2 infection status and immune experience.[4] Currently, provider and supply chain shortages threaten our national capacity to diagnose people who need care and monitor the growing COVID-19 epidemic. Patient-collected samples, if they are validated and approved through regulatory channels for clinical purposes, offer several advantages from clinical and public health perspectives. From a clinical

perspective, patient-collected specimen options will decrease provider burden, allow for follow up monitoring for viral shedding without the need for return office visits, and reduce risks for provider exposure during specimen collection. From a supply chain perspective, depending on the specimen that is used, self-collection can reduce the need for PPE for providers who would otherwise collect the sample, will reduce the need for rigid nasopharyngeal swabs, and could reduce the need for viral transport media (e.g., saliva samples). From a public health perspective, having options for patient-collected samples will allow for population-based studies to measure the population prevalence of current and past infection with SARS-CoV-2. Such studies are critical to understand the natural history of infection, to develop an understanding of what proportion of the population have asymptomatic infections, to monitor population immunity, and to reach patients who live in remote areas with testing.

We developed this protocol for validation recognizing the extreme urgency of developing new testing options and appreciating the regulatory structures that ensure that clinical testing in the United States meets high standards and produces actionable results. We believe that having providers observe patients collecting specimens is an important steppingstone on the path between relying wholly on provider-collected samples (and the required PPE and clinical visits) and the use of patient-collected samples collected outside of the supervision of providers. We note that FDA has approved SARS-CoV-2 testing on patient-collected midturbinate nasal swabs, but only if the patient-collected swabs are collected in the provider's office.[16] The kappa values of the midturbinate study have not been reported, but the sensitivity of the patient-collected swabs to detect SARS-CoV-2 RNA among those known to be infected was 90%. [16] This approval is a rational decision, because modeling data suggest that testing at this stage of the epidemic is still valuable in blunting the epidemic, even if it is imperfect. [3] Recent data suggest that staff-collected and patient-collected mid-turbinate swabs have high correlation for detection of influenza viruses.[23]

The COVID-19 epidemic has been remarkable for its rapid onset and the very rapid spread into new

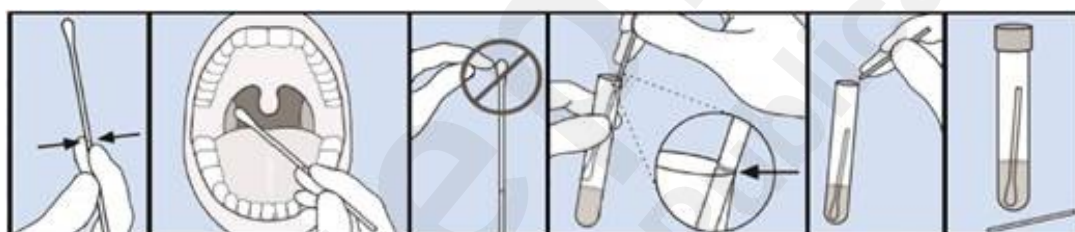
populations. The public health and clinical medicine systems in the United States have not had time to respond in conventional ways to this pandemic. There is a need to be innovative in developing and deploying new strategies to meet the clinical needs of patients who are infected with SARS-CoV-2, but simultaneously to gather data to understand the broad picture of the epidemic and to monitor infections and immunity at the population level. Given the catastrophic demands on our hospitals and medical offices, we must develop ways to move testing for screening purposes and epidemiologic monitoring out of the healthcare system.[24] Self-collection of specimens is widely used for monitoring of other infectious diseases and health conditions, and it is imperative to validate and deploy self-collection tools to understand and respond to this pandemic. We propose a structured and objective process by which patient-collected samples can be evaluated by providers for the process of their collection and by laboratorians for their biological sufficiency. We propose that, as we learn more about the capacity of patients to correctly collect specimens and illustrate the use of internal controls to document biological sufficiency of specimens, there will be opportunities to use SARS-CoV-2 testing in innovative ways to address the COVID-19 epidemic.

Figure 1. Participant instructions for self-collection of oropharyngeal swab

Start Here

- Do not eat, drink, smoke or use oral hygiene products for at least 10 minutes before you start the collection process.
- Rinse the mouth with water and discard. Please wait at least 5 minutes after this rinse to start the collection procedure.
- Please write your Date of Birth on each barcode label in the “DOB: _____” location. One barcode is on the Oropharyngeal (OP tube). A second barcode is on the exterior of the Saliva Collection device.
- Wash your hands thoroughly with warm water and mild soap for at least 30 seconds.

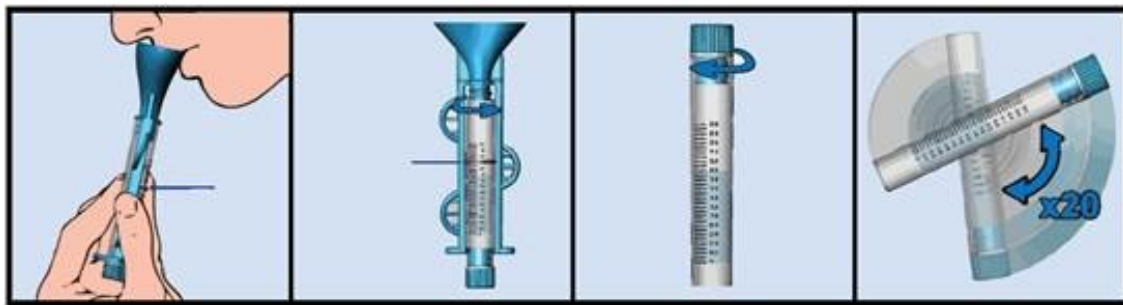
OP Swab & Tube Collection:



1. Hold the swab with the score line above your hand. Do not let it touch anything before or after sample collection, until it is placed in the media tube.
2. Insert the swab into your mouth and rub swab tip against the back of your throat, 20 second on the left side, then 20 seconds on the right side. Avoid touching your tongue, teeth, and gums with the swab.
3. Carefully withdraw the swab and place into the collection tube.
4. Break the swab at the score line by bending against the collection tube.
5. Place lid onto the collection tube and ensure it is closed evenly and tightly.
6. Place specimen into biohazard bag with absorbent pad. Ensure the seal is closed completely. *Note: The thin “paper” sheet in the biohazard bag is the absorbent pad. Please leave in biohazard bag.*

Figure 3. Participant instructions for self-collection of saliva

Saliva Collection:



1. Open the package containing the saliva collection device. Place contents on a clean and dry surface.
 2. Place lips over the opening of the collection Tube Funnel. Collect saliva until the sample level reaches the red indicator line. (Ensure that the saliva reaches the red indicator line, not just the foam.)
 3. When collection has been completed unscrew the Funnel from the collection tube by rotating the tube in the direction shown until the tube is completely detached from the funnel.
 4. Remove the Cap from the bottom of the collection tube and screw it tightly closed.
 5. Gently invert the vial 20 times to stabilize the sample.
 6. Remove the barcode label from the outside of the saliva device package and apply to the collection tube.
 7. Place collection tube into biohazard bag with absorbent pad. Ensure the seal is closed completely. *Note: The thin "paper" sheet in the biohazard bag is the absorbent pad. Please leave in biohazard bag.*
- ✓ **After specimens are collected, please place all biohazard bags with specimens in to the kit box.**
 - ✓ **Please ensure the barcode label has been applied to the Saliva Colleciton Tube.**
 - ✓ **Please ensure your Date of Birth has been written on each barcode label in the "DOB: _____" location.**

Leftover supplies can also go into the box or be discarded in the trash.

Figure 3. Participant instructions for self-collection of dried blood spots

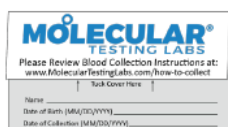


Blood Card Collection Instructions

Tips for proper blood collection

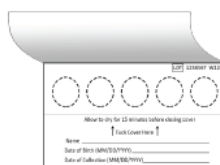
1. Hydration promotes blood flow. Be sure you are not dehydrated when performing collection.
2. Do not perform collection immediately after smoking.
3. Washing and warming your hands under warm water will help promote blood flow in your hands.
4. Shake hands vigorously towards the floor to encourage blood flow to your fingers.
5. Keep blood card and hands below your heart during collection for best blood flow.

1.



Write your name, date of birth, and the date of collection in the designated fields. Use MM/DD/YYYY format.

2.



Open blood card flap to expose the circles on the blood collection paper. Do not touch the blood collection paper.

3.



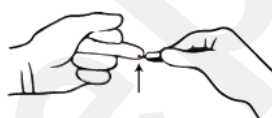
Wash hands with warm water for at least 30 seconds, then shake hands vigorously for 15 seconds to encourage blood flow to your fingers.

4.



Clean fingertip with alcohol pad. It is best to use the middle or ring finger of your non-dominant hand.

5.



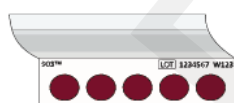
Take the lancet and twist off the cap. Press the small tip firmly into the side of your finger, near the tip, until the needle ejects with a click. Lancet is single use.

6.



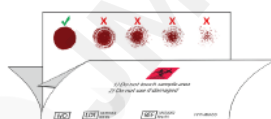
Keeping your hand below your heart during collection, massage finger from base to tip to encourage blood flow. As blood drop forms, touch the drop to the center of the circle. Do not touch the blood collection paper with your finger as this will restrict blood flow, reduce saturation, and may result in sample rejection.

7.



Fill each circle on the blood collection paper completely. It is okay for blood to extend beyond lines.

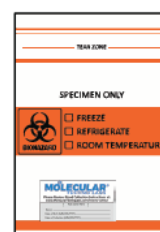
8.



Check the back side of blood collection paper. **Blood should saturate all the way through and fill each circle of the collection paper. More blood is better.**

Allow Blood collection paper to air dry on a flat surface for 15 minutes. Do not heat or blow dry blood collection paper. Heat will damage the specimen.

9.



When blood collection paper is dry, close blood card by tucking flap. Place the blood card into biohazard bag with the desiccant pack. Ensure biohazard bag is properly sealed.

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