Design and implementation of a digital site-less clinical study of serial rapid antigen testing to identify asymptomatic SARS-CoV-2 infection

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Abstract

Background: Rapid antigen detection tests (Ag-RDT) for SARS-CoV-2 with emergency use authorization generally include a condition of authorization to evaluate the test's performance in asymptomatic individuals when used serially. We aim to describe a novel study design that was used to generate regulatory-quality data to evaluate the serial use of Ag-RDT in detecting SARS-CoV-2 virus among asymptomatic individuals. *Methods:* This prospective cohort study used a siteless, digital approach to assess longitudinal performance of Ag-RDT. Individuals over 2 years old from across the USA with no reported COVID-19 symptoms in the 14 days prior to study enrollment were eligible to enroll in this study. Participants throughout the mainland USA were enrolled through a digital platform between October 18, 2021 and February 15, 2022. Participants were asked to test using Ag-RDT and molecular comparators every 48 hours for 15 days. Enrollment demographics, geographic distribution, and SARS-CoV-2 infection rates are reported. *Key Results:* A total of 7361 participants enrolled in the study, and 492 participants tested positive for SARS-CoV-2, including 154 who were asymptomatic and tested negative to start the study. This exceeded the initial enrollment goals of 60 positive participants. We enrolled participants from 44 US states, and geographic distribution of participants shifted in accordance with the changing COVID-19 prevalence nationwide. *Conclusions:* The digital site-less approach employed in the "Test Us At Home" study enabled rapid, efficient, and rigorous evaluation of rapid diagnostics for COVID-19 and can be adapted across research disciplines to optimize study enrollment and accessibility.

Introduction

Over-the-counter rapid antigen SARS-CoV-2 tests (Ag-RDT) present unique opportunities for widespread COVID-19 testing. However, the authorization of these tests under the Food and Drug Administration's (FDA) Emergency Use Authorization (EUA) generally imposes a requirement on companies to evaluate their test's performance for detecting asymptomatic infections with serial screening [1]. To satisfy this requirement, it was necessary to conduct a longitudinal study to observe the onset of SARS-CoV-2 infection and performance of Ag-RDT across the course of infection [2]. This required an innovative research design to generate regulatory-quality, representative data, capture new-onset infections amidst a changing pandemic and understand asymptomatic infections, which represent a small proportion of all SARS-CoV-2 cases.

This study describes the design, implementation, and completion of a novel, digital, site-less study called "Test Us at Home" funded by the National Institutes of Health (NIH) Rapid Acceleration Diagnostics (RADx) Program. In this study, we outline the rationale for key decision-making and describe findings of the operational effort needed to successfully collect data under this paradigm, to provide rapid, rigorous evaluation of over-the-counter diagnostics across diverse participants of all ages in community-based settings.

Methods

Study Design

This prospective cohort study recruited participants over 2 years old who were asymptomatic and self-reported absence of SARS-CoV-2 infection in the 3 months prior to enrollment. Participants were asked to test for SARS-CoV-2 via Ag-RDT and molecular comparator every 48 hours for 15 days. This study was approved by the Institutional Review Board of the WIRB-Copernicus Group.

Study Objectives

The primary objective of this collaboration between the FDA, NIH, and the RADx Tech Clinical Studies Core at UMass Chan Medical School was to generate right-of-reference data that could be used towards FDA EUA. To accomplish this, we aimed to evaluate the performance of serial use of three different Ag-RDT to detect a new-onset SARS-CoV-2 infection, as determined by a laboratory-based molecular test.

Study Population and Recruitment: To approximate the performance of Ag-RDT in the general public, the FDA suggested against preferentially enrolling participants with a known SARS-CoV-2 exposure (oral communication, August 3, 2021). The goal of the study was to recruit at least 60 participants who started the study without any symptoms and with a negative SARS-CoV-2 molecular test and subsequently tested positive during the study period. Due to the fluctuating rates of COVID-19 positivity and the importance of recruiting asymptomatic participants, we employed a decentralized study design whereby eligible participants from anywhere in the mainland USA except for Arizona could participate. Residents from the state of Arizona were excluded because Quest Diagnostics, the laboratory performing molecular tests, did not provide direct-to-consumer tests in that state. Additional inclusion and exclusion criteria are listed in Table 1. Recruitment relied on the engagement of community stakeholders to advertise the study and reach communities nationwide. Periodic

Table 1. *Inclusion and exclusion criteria*

Inclusion Criteria
• At least 2 years old • Access or parental access to a smartphone or device to download and use study app • Reside in mainland United States • Able to receive mail at home • Willing to drop off comparator samples at FedEx drop-off site or allow for pick-up service to retrieve samples • Report no COVID-19 symptoms within 14 days prior to study enrollment

Exclusion Criteria
• Self-reported positive test for SARS-CoV-2 infection in the previous 3 months • Facial trauma interfering with nasal swabs • Lack capacity to consent • Do not understand English or Spanish • Currently in the correctional justice system • No internet access on smartphone while at home

analyses were conducted to inform enrollment goals based on observed precision for positive percent agreement.

Enrollment: Participants who expressed interest in the study received an email or flyer with instructions for downloading the study app and performing eligibility screening. The study app was a custom interface designed through the MyDataHelps platform. All study surveys and instructions were provided in both English and Spanish. To enroll, participants answered a series of questions to determine their eligibility and prioritization status. All eligible participants underwent automated prioritization based on a priori criteria that were adjusted on a daily or weekly basis (Supplemental Figure 1, Supplemental Figure 2). We adjusted prioritization criteria to preferentially enroll populations based on their region's SARS-CoV-2 transmission rates, community-level vaccination, and sociodemographic characteristics. This step occurred prior to consenting, and data were discarded if the participant did not enroll in the study before the data collection period ended; these data were never accessible to the study team unless the participant consented to take part in the study. Eligible participants who did not match the preferred criteria for enrollment received a note saying that they cannot enroll in the study at this time but would receive communication from the study team when/if they became eligible (Supplemental Figure 3). These participants were placed on a "waiting list," which was reviewed with regard to changing priority criteria throughout the study.

If eligible for enrollment, participants 18 years of age or older were asked to read the e-consent form and provide their signature through the study app (Supplemental Figure 4). Participants younger than 18 years were asked to review the e-assent and e-consent form with the support of their parent(s) or guardian(s) and provide assent for participation, while the parent/guardian provided written consent for participation in the study. Participants were eligible to receive up to $250 for timely completion of all sample collections (Supplemental Figure 5).

Test Distribution: On enrollment, participants were asked to provide their shipping information through the study app. Participants were assigned to one of three Ag-RDT (Quidel QuickVue At-Home OTC COVID-19 Test, Abbott BinaxNOW COVID-19 Antigen Self Test, or BD Veritor™ At-Home COVID-19 Test) using an automated algorithm that was informed by the investigators' discretion based on enrollment numbers and geographic location of the participants (Supplemental Figure 6).

The three Ag-RDT used in the study are authorized for emergency use by the FDA and were selected to provide multiple assessments and facilitate generalizing results to nonparticipating companies. These tests will be hereby referred to as test brands A, B, and C (randomly assigned), as the purpose of the study was not to directly compare different test performances. Participants residing together and enrolling with the same address or enrolled in a group, such as a cohort of classmates, were assigned the same Ag-RDT, to avoid mixing of test types between participants. Groups were given unique codes to input on enrollment, to ensure members were easily identifiable. As a result of this strategy, the assignment of tests to participants was nonrandom, and we intentionally did not pursue a strategy to compare performance between different tests.

Because molecular assays require a prescription by a licensed physician, the study team contracted with PWNHealth, a national clinician network, and developed an automated order filing system with Quest Diagnostics to place the requisite orders (Supplemental Figure 7). A total of 10 Ag-RDT and 7 home-collection kits for molecular comparators were provided to each participant. Participants received Ag-RDT and PCR home-collection kits by mail through separate shipments. The study team provided additional tests to participants if needed (e.g. tests were damaged upon delivery or lost in the mail).

Testing Schedule: Participants were asked to perform the Ag-RDT and collect the specimen for molecular comparator testing on the same day every 48 hours during the 15-day testing period (Supplemental Figure 8). Immediately prior to testing, participants were asked to record any symptoms on the day of testing. The study app provided a push-notification testing reminder at the 44-hour mark and additional notifications every 2 hours until the 52-hour mark if the participant had not completed their tests. Participants were instructed via the app to have at least a 15-minute break between the Ag-RDT and the sample collection for molecular tests. Participants were asked to record the results of the Ag-RDT when available by selecting one of the following options: "Negative," "Positive," "Invalid," or "Don't Know," and upload a photo of the test strip through the app (Supplemental Figure 9). Participants assigned to Test C were also asked to download the Test C company-specific app which contained a test reader. The company test reader asked participants to upload a photo of the test strip and provided Ag-RDT results in real time. Test C users were asked to report the test result given by the test reader, rather than self-interpretation, to the study app. If the participant tested positive by Ag-RDT, they were told to contact their healthcare provider for any medical questions. In the event of an invalid Ag-RDT result, the participant was asked to perform a second Ag-RDT. If the second Ag-RDT result was also invalid, the participant was not asked to perform additional Ag-RDT on that day and was instructed to continue to the PCR sample collection (at least 15 minutes after Ag-RDT sample collection). Participants were responsible for shipping the PCR collection kit containing the sample using the pre-paid FedEx envelope using instructions provided by Quest Diagnostics, which were authorized by the FDA for emergency use.

Molecular Testing Procedures: Due to concerns of potential false-positive molecular tests, the FDA recommended the use of two types of molecular assays, and potentially, a third assay, if the prior two assays were discordant (oral communication, August 3, 2021) [3–5]. Once participant samples were received at Quest Diagnostics, the sample was divided into aliquots to perform Roche Cobas 6800 SARS-CoV-2 PCR and Quest RC COVID-19 PCR DTC for all participants (Supplemental Figure 10). An additional aliquot was preserved by the laboratory to allow for testing on Hologic Aptima SARS-CoV-2 transcription-mediated amplification (TMA) assay if Roche Cobas and Quest LDT were discordant or inconclusive. All three molecular assays used were highly sensitive, authorized by EUA, and run per instructions per use. Remnant samples of sample fluid from home-collection kits were frozen at $-80\,°C$ and shipped to UMass Chan Medical School for future testing. Results of the molecular PCR assays were available to participants through the Quest results portal and communication from the study team. All participants that tested positive by molecular test received a phone call from a study team member. In the event of discordant results, the participant was contacted by the study staff to explain the results.

Communication with the study team: Participants were provided a study hotline staffed with research coordinators to provide support during extended hours during the weekdays from 8 AM to 9 PM EST. Participants were also able to contact the study team via email at all times. All calls between coordinators and participants were documented in a call log containing the length of the call, the reason for the call, narrative about the call, and whether the issue was resolved.

Data Management: There were three primary sources of data (Supplemental Figure 11). All participant-reported data were collected through the study app and downloaded incrementally through secure file transfer protocol to UMass Chan servers. The molecular testing data were shared by Quest Diagnostics through an established datafeed between Quest and UMass Chan servers. However, the PCR cycle threshold (CT) values and results of the tiebreaker assays were not part of routinely abstracted data and required manual abstraction. Finally, tracking reports were used to document all communications between participants and the study staff. All three sources of data were combined using a participant's unique identifier assigned by the study app. Paired Ag-RDT and PCR data were merged by matching on participant identifier and date of testing. When test dates were not aligned or there were unmatched results, a member of the study team reviewed all testing data from the participants to adjudicate paired findings. The most common reason for mismatched dates was due to missing dates of collection or transcription errors, as date of collection for PCR sample was handwritten by the participant on the Quest requisition form. Study staff reconciled possible mismatched test results by reviewing data for requisition numbers entered in the app, shipment tracking data, and contact reports. If mismatched data could not be adequately aligned, those data were considered ineligible due to failed quality checks. Additional adjudication undertaken by the study team included a manual review of all Ag-RDT images for participants who either had a self-reported positive, don't know, or invalid Ag-RDT result or if they tested positive on molecular test at any point during the study. All data were de-identified and shared with the FDA throughout the study. At the end of the study, the final and cleaned dataset was shared with the FDA and company-specific data were shared with the companies. All data will be made available on the NIH Data Hub once the main findings from this study are published.
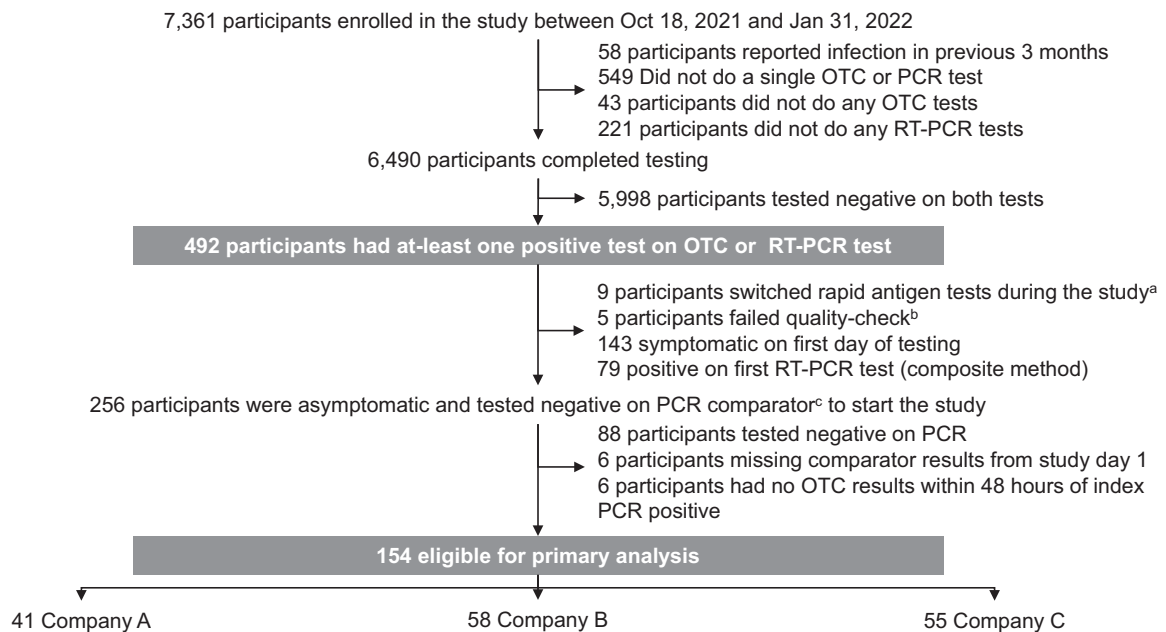
Results

Enrollment: In total, 7361 participants enrolled in the study between October 18, 2021 and February 15, 2022 (Fig. 1a). Due to complications with the company app, Test C enrollment began on November 4, 2021, 3 weeks after Test A and B enrollment started
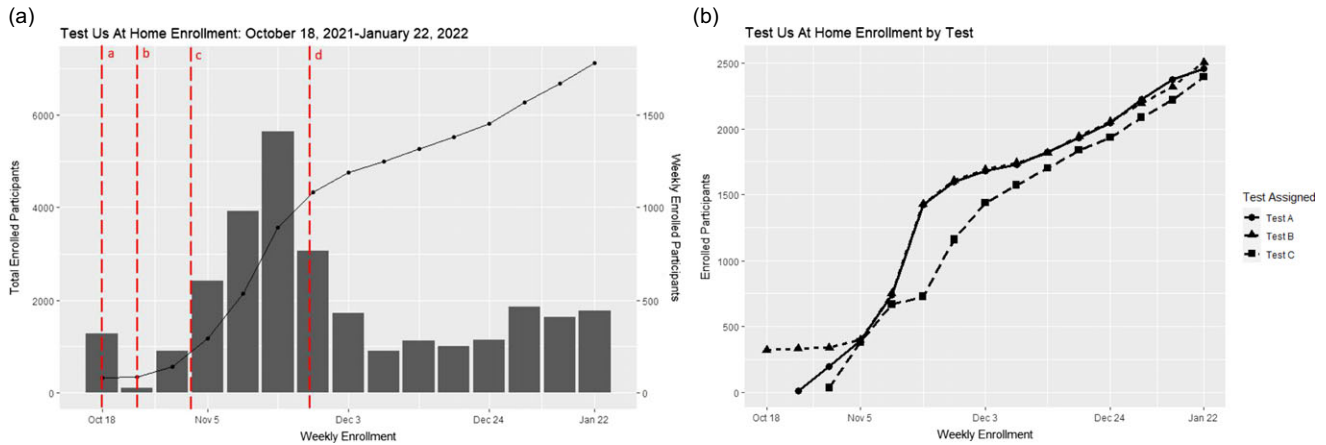
a: Test A and B enrollment opens to individuals with specific group codes on October 18, 2021; b: Enrollment opens nationwide on October 26, 2021; c: Test C enrollment starts on November 4, 2021; d: Enrollment waitlist approach implemented on November 24, 2021

Figure 1. Weekly test us at home study enrollment.

a= participants replaced their assigned rapid antigen tests with commercially obtained rapid antigen tests; b= dates of RT-PCR testing could not be verified based on triangulation of self-reported, shipping, and resulting data; A, B, and C refer to rapid antigen test assignment. c = at-least two positive molecular assays from a single sample per participant (Roche Cobas 6800, Quest LDT, Hologic Aptima)

Figure 2. CONSORT diagram of test us at home.

(Fig. 1b). Following initial surges in recruitment, the enrollment waitlist was implemented on November 24, 2021 to allow for refinement of enrollment from geographic hotspots. In total, 492 participants tested positive on either molecular or Ag-RDT assays during the study, and 154 were eligible for analyses (Fig. 2).

Geographic and Sociodemographic Participant Characteristics: The geographic and sociodemographic characteristics of study participants changed over the course of the study, reflecting the shifts in the enrollment approach. In total, participants from 44 of the 48 mainland US states enrolled in the study (Fig. 3). In October, the majority of initial study recruitment occurred on a college campus in Wisconsin, resulting in a young, predominantly white, student population (Fig. 3; Table 2). Additionally, only 3.1% of enrolled participants in October were unvaccinated for SARS-CoV-2. In November, study recruitment was expanded throughout the USA, with enrollment from more than 20 different states.
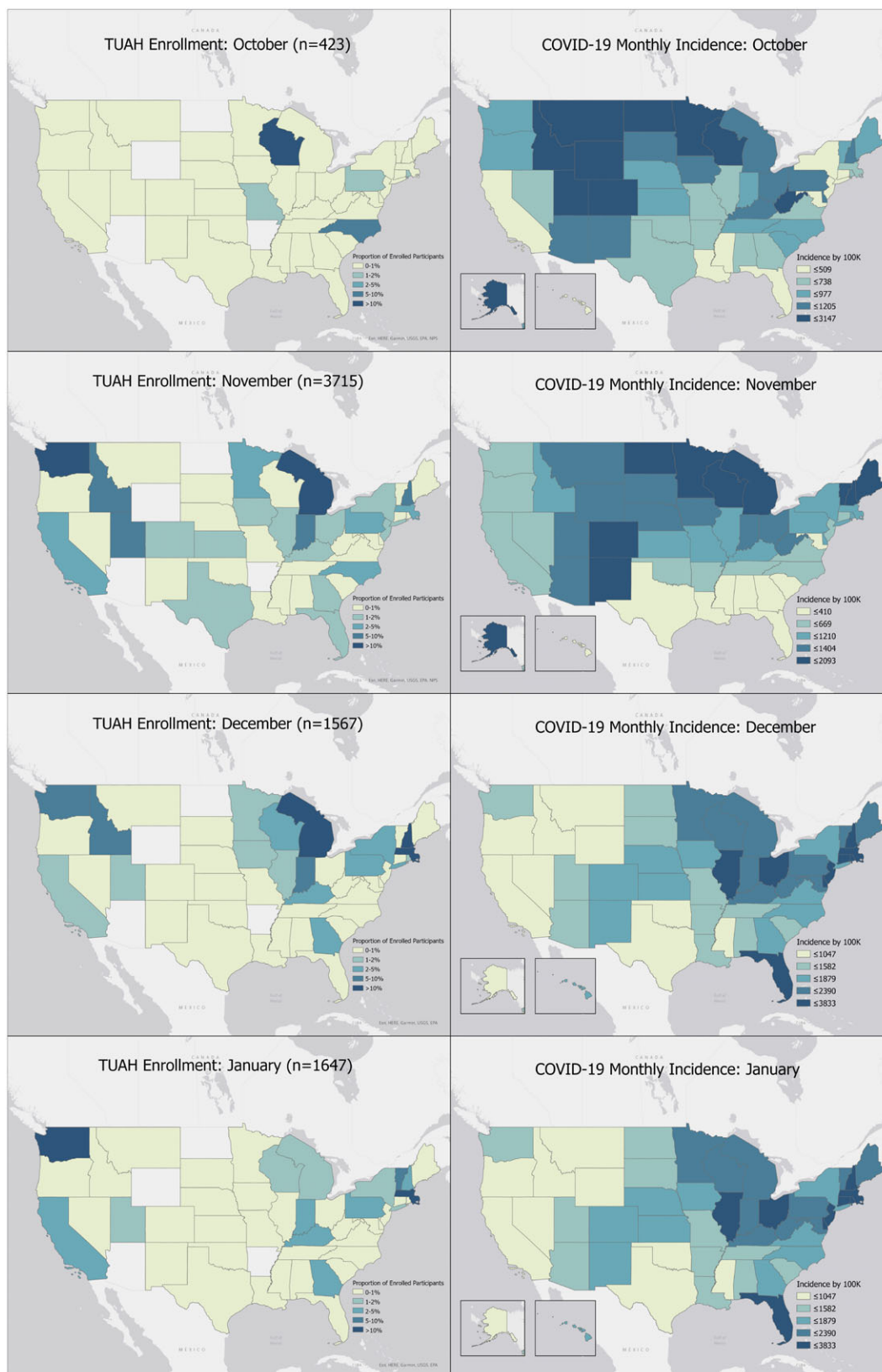
Figure 3. Test us at home enrollment by state and month, October 2021–January 2022.

Participants from rural populations comprised 14% of the participants recruited in November. In December and January, study enrollment shifted to prioritize unvaccinated participants, preferentially pulling these participants from the study waitlist, resulting in 24.6% and 21.4% of monthly enrollment being unvaccinated (Table 2). In January, recruitment efforts also

Table 2. *Test us at home participant demographics by month of enrollment*

	October N = 415	November N = 3701	December N = 1592	January N = 1653	Total N = 7361
Test Assigned: *n* (%)					
Test A	80 (19.3)	1,474 (39.8)	375 (23.6)	530 (32.1)	2,459 (33.4)
Test B	335 (80.7)	1,231 (33.3)	375 (23.6)	565 (34.2)	2,506 (34.0)
Test C	0 (0.0)	996 (26.9)	842 (52.9)	558 (33.8)	2,396 (32.6)
Vaccination Doses: *n* (%)					
1	51 (12.3)	1,176 (31.8)	418 (26.3)	32 (1.9)	1,677 (22.8)
2	350 (84.3)	2,062 (55.7)	513 (32.2)	352 (21.3)	3,277 (44.5)
3+	0 (0.0)	0 (0.0)	269 (16.9)	915 (55.4)	1,184 (16.1)
Unvaccinated	13 (3.1)	462 (12.5)	392 (24.6)	354 (21.4)	1,221 (16.6)
Don't know	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Age Category: *n* (%)					
Less than 18 years	0 (0.0)	417 (11.3)	199 (12.5)	164 (9.9)	780 (10.6)
18–45 years	384 (92.5)	2,156 (58.3)	851 (53.5)	878 (53.1)	4,269 (58.0)
45–65 years	25 (6.0)	871 (23.5)	392 (24.6)	390 (23.6)	1,678 (22.8)
Over 65 years	6 (1.5)	257 (6.9)	150 (9.4)	221 (13.4)	634 (8.6)
Gender: n (%)					
Female	232 (55.9)	2,340 (63.2)	1,045 (65.6)	1,025 (62.1)	4,642 (63.1)
Male	131 (31.6)	1,208 (32.6)	458 (28.8)	523 (31.7)	2,320 (31.5)
Nonbinary	28 (6.8)	49 (1.3)	20 (1.3)	19 (1.2)	116 (1.6)
Transgender	14 (3.4)	20 (0.5)	11 (0.7)	2 (0.1)	47 (0.6)
No answer	10 (2.4)	84 (2.3)	58 (3.6)	84 (5.1)	236 (3.2)
Race/Ethnicity: *n* (%)					
White	358 (86.3)	3,167 (85.6)	1,249 (78.4)	703 (42.6)	5,477 (74.4)
African American/Black	15 (3.6)	95 (2.6)	94 (5.9)	159 (9.6)	363 (4.9)
Asian	5 (1.2)	98 (2.7)	50 (3.1)	302 (18.3)	455 (6.2)
Pacific Islander	0 (0.0)	1 (0.1)	1 (0.1)	25 (1.5)	27 (0.4)
Native American/Alaskan Native	3 (0.7)	19 (0.5)	9 (0.6)	10 (0.6)	41 (0.6)
Other	9 (2.2)	83 (2.2)	49 (3.1)	192 (11.6)	333 (4.5)
Multiracial	13 (3.1)	137 (3.7)	66 (4.1)	129 (7.8)	345 (4.7)
No answer	12 (2.9)	101 (2.7)	74 (4.7)	133 (8.1)	320 (4.4)
Hispanic: *n* (%)	24 (5.8)	243 (6.6)	88 (5.5)	174 (10.5)	529 (7.2)
Geographic Setting					
Rural	25 (6.0)	521 (14.1)	188 (11.8)	137 (8.3)	871 (11.8)
Suburban	238 (57.4)	1,997 (54.0)	900 (56.5)	797 (48.2)	3,932 (53.4)
Urban	144 (34.7)	1,126 (30.4)	456 (28.6)	643 (38.9)	2,369 (32.2)
No answer	8 (1.9)	57 (1.5)	48 (3.0)	76 (4.6)	189 (2.6)
Highest Level of Education: *n* (%)					
Did not finish high school	0 (0.0)	331 (8.9)	160 (10.1)	131 (7.9)	622 (8.5)
High school graduate	173 (41.7)	328 (8.9)	145 (9.1)	179 (10.8)	825 (11.2)
Some college	155 (37.4)	830 (22.4)	336 (21.1)	378 (22.9)	1,699 (23.1)
Bachelor's Degree or higher	78 (18.8)	2,027 (54.8)	833 (52.3)	830 (50.2)	3,768 (51.2)
Don't know	1 (0.2)	45 (1.2)	18 (1.1)	19 (1.2)	83 (1.1)
No answer	8 (1.9)	140 (3.8)	100 (6.3)	116 (7.0)	364 (4.9)

(Continued)

Table 2. (*Continued*)

	October $N = 415$	November $N = 3701$	December $N = 1592$	January $N = 1653$	Total $N = 7361$
Employment Status: n (%)					
Unemployed	22 (5.3)	414 (11.2)	134 (8.4)	169 (10.2)	739 (10.0)
Retired	8 (1.9)	253 (6.8)	121 (7.6)	170 (10.3)	552 (7.5)
Student	265 (63.9)	656 (17.7)	273 (17.2)	239 (14.5)	1,433 (19.5)
Working now	106 (25.5)	2,230 (60.3)	967 (60.7)	934 (56.5)	4,237 (57.6)
Other	3 (0.7)	55 (1.5)	27 (1.7)	30 (1.8)	115 (1.6)
No answer	11 (2.7)	93 (2.5)	70 (4.4)	111 (6.7)	285 (3.9)

Table 3. *Type of contact and reasons for participant–coordinator contact*

	Number of Participant-Coordinator Contacts
Total	**11,646**
Type of Contact, n (%)	
Phone Call	4627 (39.7)
Voice mail	3455 (29.7)
Email	3564 (30.6)
Unscheduled Push notification	483 (4.2)
Who Initiated Contact?, n (%)	
Participant	5371 (46.1)
Coordinator	5261 (45.2)
Both	825 (7.1)
Missing	189 (1.6)
Reason, n[a]	
App issues	1123 (9.6)
Interpretation of Test Results	16 (0.1)
Symptom reporting	63 (0.5)
Issues with Rapid Antigen Tests	251 (2.2)
Testing Reminder	2228 (19.1)
Compensation	1903 (16.3)
Shipping of Tests	1950 (16.7)
Study testing schedule	1215 (10.4)
Giving Test Results	2833 (24.3)
Other	1794 (15.4)

[a]Reasons for contact were not mutually exclusive.

focused on increasing racial and ethnic diversity in the study population, and the minority of participants enrolled during January identified as White (42.6%). Additionally, 10.5% of participants enrolled in January were of Hispanic origin.

Operational Support and Logistics: Throughout the study, there were 11,646 contacts between coordinators and 4,389 distinct participants (Table 3). This accounted for 33,356 minutes of coordination time. Coordinators and participants communicated by phone call (39.7%), email (30.6%), voicemail (29.7%), and push notification within the study app (4.2%). The most common reason for contact was to share COVID-19 test results from molecular tests, which accounted for 24.3% of all calls. Other common reasons for contact included testing reminders (19.1%), shipping and receipt of test kits (16.7%), compensation (16.3%), and clarifying the testing schedule (10.4%). The company-generated app for Test C was initially only compatible with certain smartphones; therefore, we delayed enrollment for Test C by 2 weeks and troubleshooted the app with the company, to ensure participants were able to use the app appropriately (Fig. 1a). Further, the decentralized design necessitated an increased reliance on shipping vendors, allowing us to reach participants across the mainland US states. However, this also required a variety of tracking methods to keep track of the 58,888 kits shipped. This study spanned the holiday season, which resulted in additional shipping delays; 1.2% ($n = 728$) of packages were affected by logistical or participant errors that led to an unviable or missing RT-PCR test result.

Discussion

Using an innovative digital, site-less study approach, we developed recruitment and enrollment strategies to capture new onset COVID-19 infections most effectively throughout the country, resulting in the detection of nearly three times as many new-onset COVID-19 cases as originally specified. The digital site-less approach allowed us to seamlessly and dynamically change enrollment patterns and sample different populations based on the evolving nature of the pandemic, to assess rapid diagnostics with agility, efficiency, and rigor among asymptomatic individuals.

The digital site-less approach offered great agility to alter the recruitment strategy to fit our needs throughout the evolution of the study. Initially, to iron out the study logistics, we opened study recruitment in October 2021 to members of a Midwestern university marching band who were traveling together, where we anticipated a high amount of unmasked, close contact interactions. This group enrollment is reflected in the demographics of participants in October, who were younger and had a higher proportion of white participants than participants recruited in November through January. Later, we were able to geographically alter the sampling to enroll participants from throughout the USA and use a waitlist to selectively sample certain populations by zip code, determined by community prevalence of COVID-19 and demographics, to ensure we were curating a representative sample. For example, after seeing low enrollment of participants over age

Table 4. *Summary of features of this study and opportunity for improvement*

Challenges	Innovation	Opportunity for improvement
Widespread outreach to asymptomatic individuals	Democratized participation such that anyone, anywhere, anytime can choose to participate through a smartphone without needing to travel to a clinical study site or recruitment centers	Requirement of smartphone to enroll can prevent some people from participating. Approaches that loan study smartphones or leverage community-health workers as digital studies' liaisons can help overcome this limitation
Engagement of diverse communities	A dedicated team met with county health workers and community stakeholders from across the country to promote awareness of the study and participation among people of color, indigenous heritage, and rural locations	A network of community partners and stakeholders for digital clinical studies that inform, plan, and conduct outreach efforts can help further enhance participation of historically underrepresented populations
Recruitment from SARS-CoV-2 "hotspot"	Use of CDC daily case reports and projects to identify geographical regions where community outreach efforts were enhanced and which were identified as "preferred regions for enrollment"	Promoting peer-to-peer recruitment from hotspots through the use of the smartphone apps
Refinement of enrollment	Adding a layer of prioritization to allow cohort composition such that participants from "hotspots" and those that improve diverse representation of the enrolled cohort	Automatically adaptive priority criteria that does not require manual input or decision-making but can allow manual override
Consenting participants including children >2 years old	Self-contained description of consent, including brief description of key parts of the study displayed through the smartphone app	Use of participatory videos that explain the study objectives and activities embedded within the smartphone app
Assigning rapid antigen tests	Pre-specified criteria that assigned tests to participants automatically	Adaptive algorithm that refines criteria to create balanced cohorts based on multiple variables
Distributing testing kits	Asynchronous assembly and shipment of kits from commercial vendors	Synchronous assembly and shipment of kits such that all materials arrive in box instead of different boxes
Collecting samples for molecular tests	Direct-to-consumer kits for nasal swabs that were returned using FedEx overnight prepaid envelopes	Courier pickup options that can be invoked from within the study app
Performing up to three separate molecular assays in CLIA laboratories	Automated ordering of two tests and manual ordering of additional tests when discordance was observed	Automated ordering of discordant testing with streamlined data collection
Serial testing within a specific window (44-52 hours apart)	Automated app notification and text messages every two hours during the testing window	Providing the option of defining notification frequency during the testing window to the participants
Verification of rapid antigen testing results	In-app widget to allow participants to take an image of rapid antigen tests that were later verified by the coordinators	Automated readers that verify that an image of rapid antigen test was collected and that the test result matches the result manually entered by the participant
Data collection and quality	Data fidelity and timestamp for each element collected within the study app and collation of disparate datafeed from the molecular testing laboratory	Minimizing user entry of free-text or handwritten data
Participant reimbursement	Batch processing of prepaid Bank of America cards that are mailed to participants' home	Automated delivery of reimbursement through smartphone app once the requirements are met

65 years in October through December, in January, we selectively pulled those over 65 years of age off the waitlist, increasing the proportion of participants in this group from 1.5% in October to 13.4% in January. Additionally, the recruitment strategy resulted in 16.6% of all enrolled participants being unvaccinated for SARS-CoV-2, matching nationwide estimates for those over 5 years of age [6].

The waitlist approach also allowed us to try to ensure that enrollment was not solely clustered among those who have the greatest access to recruitment strategies, but rather gave the time for information to disseminate to and within various communities, including populations underrepresented in research and device studies [7]. Approximately 12% of our sample came from rural populations, compared with an estimated 14% of the US population living in rural areas nationally [8]. Previous research has found that rural groups are particularly hesitant about the time commitment involved in research studies; therefore, the siteless design may have helped to alleviate this concern [9]. Also, 1.8% of our sample identified as Native American or Alaskan Native only or in addition

to another race, which is reflective of national census rates [10]. Lastly, while many population-level diagnostic studies only include individuals over 18 years old, over 10% of our sample was under age 18 years, increasing our understanding of these devices among both children and adults.

While we intentionally scheduled our study to overlap with the winter months due to the predicted seasonal increase of SARS-CoV-2, the launch of our study nationwide also coincided with the beginning of the Omicron COVID-19 surge throughout the USA, as well as a nationwide shortage of rapid antigen tests. Originally, we planned to prioritize enrollment to select communities that met a threshold for high prevalence of COVID-19; however, during the Omicron surge, nearly all communities throughout the USA quickly met that threshold. Furthermore, health departments and community health workers were very receptive to sharing our study information with their communities, as it filled a clear, immediate need in our ability to supply rapid antigen tests. The overwhelming interest in the study made the waitlist approach particularly effective.

The remote design also resulted in gains in study efficiency, in terms of both coordinator time and cost. Instead of requiring coordinators to schedule and supervise serial sample collections for each participant, the virtual, site-less design allowed participants to test in their homes and on their time, increasing accessibility to individuals with various employment and school schedules, as well as living situations. According to the study coordination logs, direct participant–coordinator phone calls averaged to just over 1-hour per day (82.3 minutes over 161 days of the study) and consisted primarily of testing reminders and returning molecular test results to participants. As clinical research coordinators on average support upwards of seven studies concurrently and approximately two-thirds of coordinators report being expected to work more time on studies than allotted, it is important to optimize study coordination time, while maintaining quality and consistency [11]. Here, we showed the ability for site-less digital trials to run with minimal participant–coordinator interaction, while maintaining high enrollment and adherence to the study protocol.

Site-less cohort studies have become increasingly common, as advances in technology have made virtual recruitment and engagement more feasible [9]. However, digital products and solutions in clinical research remain underutilized [10]. Site-less studies can not only facilitate recruitment and participant engagement, but they can also enhance scientific rigor and design. Through coordination with shipping services, home-test distributors, and clinical labs, we organized shipments of study supplies to participants on enrollment, which allowed participants to start testing at home within 24–48 hours of enrollment. Further, we coordinated the pick-up and shipment of biological samples to the central laboratory, which has seldom been done within the framework of a digital study. The success of these workflows opens the door for the adaptation of site-less studies to answer many complex research questions, by integrating survey responses, biological samples, and home health monitoring.

There are potential limitations to the study. We did not require participants to be under video observation while performing the Ag-RDT or collecting samples for molecular tests. However, our study facilitated use of these tests "as intended" and "as authorized" by the FDA and therefore may represent better approximation of real-world performance of the tests than traditional clinical studies. Additionally, the smartphone app required participants to take images of the Ag-RDT; therefore, we could verify the Ag-RDT results for all participants. Due to the scale and nature of this study, we used commercial vendors for assembly and distribution of the testing kits, which precluded our ability to provide study-specific written instructions enclosed within the kit; we instead relied on providing all study-specific instructions through the smartphone app. This resulted in confusion for some participants who did not start testing immediately after receiving the test kits or did not perform both Ag-RDT and PCR tests concurrently. However, our study team was able to detect these instances and intervene accordingly. Because of the logistical constraints, we could not facilitate a cold-chain transportation of the collected specimen, which precluded our ability to perform viral culture studies. Sample collection for molecular tests required participants to handwrite the date of sample collection, and laboratory data had to be linked with Ag-RDT data based on Participant ID and testing date, which resulted in mismatches and required substantial manual effort for reconciling differences. Finally, the requirement of smartphone ownership to participate in the study disadvantages people without smartphones, as well as those living in areas with poor cellular or wireless access. However, smartphone use is ubiquitous and has been accelerated by the SARS-CoV-2 pandemic.[12] Additionally, we submit that the barrier to participation created by requiring a smartphone is lesser than that created by requiring participants to travel to a clinical study site, multiple times during the study.

These limitations notwithstanding, this study represents the most robust attempt at understanding the performance of Ag-RDT for SARS-CoV-2 detection among asymptomatic participants. We summarize the advantages of our digital siteless approach in Table 4 and outline recommendations for future digital studies. The collaboration between the NIH, FDA, and the RADx Clinical Studies Core allowed for the development of a protocol that was innovative and a study that will provide tremendous value to federal agencies, academic researchers, and companies for elucidating key questions related to raid antigen tests' performance. Future collaborative efforts to develop best practice guidelines and infrastructure for performing digital clinical studies are needed to advance scientific community's ability to perform rigorous clinical research and answer vexing questions.

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