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Research Article

Feasibility and Acceptability of Self-Collected Dried Blood Spots for SARS-CoV-2 Vaccine Response in Community-Dwelling Elderly: A Large Decentralized Prospective Study

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Abstract

Background: The STOP-CoV study is an ongoing longitudinal decentralized cohort study assessing the safety and efficacy of the SARS-CoV-2 vaccine. There are limited longitudinal reports on the use of self-collected dried blood spots (DBS) in the elderly population to assess COVID immunity. **Objective:** To evaluate the feasibility and acceptability of self-collected dried blood spots (DBS) and assess participant characteristics associated with completion rates and specimen adequacy. **Methods:** 1286 ambulatory adults, including 911 older (70+ years old) and 375 younger (30-50 years) were recruited in Ontario, Canada, between May and July 2021. DBS were requested every three months after the initial vaccine series and 3-4 weeks after vaccine boosters. **Results:** Of the participants, 2 did not meet screening criteria and 79 consenting participants did not complete any study activities. Among the remaining 1205, 94.3% submitted at least one DBS, and 68.4% submitted all expected specimens. 98.1% of specimens were submitted within the expected time window, and 93.9% were adequate for serology testing across the study. Higher DBS adequacy rates were observed for females compared to males (OR: 1.60; 95% CI: 1.04-2.47) after adjusting for time, age cohort, race, and level of education. The proportion of specimens that were adequate for testing increased over time. **Conclusion:** Using self-collected DBS for SARS-CoV-2 vaccine response assessment in the elderly ambulatory community is feasible, acceptable, and resulted in high submission rates, specimen adequacy, and retention over 48 weeks. Remote self-collection of DBS can increase recruitment, engagement, and retention of underrepresented and/or vulnerable communities in research.

Introduction

The rapid emergence of the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) elicited an urgent global response to develop a vaccine to protect against viral transmission and disease severity [1,2]. Traditionally, vaccine development and testing have required extensive review, regulatory approval, and several years of pre-clinical and clinical trials prior to public distribution [3]. However, due to the pandemic's unanticipated global impact and mortality, the vaccine development, testing, and rollout timeline was expedited. Early in 2021, the Ministry of Health Canada published an interim order granting expedited authorization of vaccines and other therapies to diagnose, mitigate, treat, or prevent SARS-CoV-2 [4]. The initial randomized clinical trials and cohort studies showed efficacy of the vaccines in preventing infection and severe disease [5-8], but there was much that needed to be learned about the immune response to the vaccines, including its durability, level of protection, and the need for vaccines boosters, especially in populations at higher risk of infection, including the elderly [9-14].

The dysregulation and deterioration of the immune system with age, known as immunosenescence, is associated with lower antibody levels in older adults (age 65 years and older) and less robust immune responses to infections and vaccines compared to younger individuals—as observed with hepatitis B, pneumococcal, and influenza vaccines [15]. This may increase susceptibility to infectious diseases and/or require changes in vaccine strategies [16]. As elderly individuals and people living with comorbidities have disproportionately higher risk of death from COVID-19, we were concerned that different vaccine dosing schedules and/or the use of adjuvants would be needed with the SARS-CoV-2 vaccines [17-20]. To evaluate the immune response and inform the need for booster doses, we designed the STOP-CoV study [21] to evaluate long-term antibody response to COVID vaccines in individuals over 70 years, and compare the outcomes to a younger cohort (30-50 years). Given study restrictions imposed by the pandemic [22,23], this was designed as a completely decentralized study. As such, we needed a means for the self-collection of blood samples for antibody testing.

Dried Blood Spots (DBS) is a blood collection method on a paper card that has been used for decades for the serologic diagnosis of infectious diseases, especially in resource-limited settings [24-31]. Blood is easily collected by a single finger-prick using a lancet, and self-collected blood on DBS cards can be transported via regular mail from diverse locations and is relatively inexpensive. The process thereby enables access to a wider distribution of the population, improving research generalizability and validity. Older adults (≥65 years) are typically excluded from clinical research as studies tend to recruit younger individuals with limited comorbidities, on minimal medications, and who are otherwise physically healthy [32,33]. Additionally, older individuals may be fragile, and may face barriers and limitations related to transportation, time, and access to resources that may be required for study participation [26,34-37]. Collection of blood through DBS can eliminate some of these challenges [38]. A number of groups have been able to show the ability to determine antibody levels to COVID from DBS and good correlation to levels in plasma. [39-45].

Small-scale studies have demonstrated the successful use of DBS samples for SARS-CoV-2 antibody detection in the general population, including those at high-risk for infection and severe disease [46-49]. However, findings from larger-scale prospective epidemiological studies, especially in the elderly, are limited. Despite being minimally invasive and user-friendly, older adults may face challenges in obtaining blood with a lancet due to dexterity or changes in cutaneous microvascular structure and function associated with aging [50]. The ability of an ambulatory elderly population to do the self-sampling of blood and the preparation and mailing of DBS while continuing to be engaged in a longitudinal study was unknown.

The main objective of this analysis is to report on the feasibility and effectiveness of using self-collected DBS to detect antibody levels for 48 weeks after the initial vaccine series in an ambulatory population and to evaluate variables associated with the adequacy of sampling.

Materials and Methods

Study Design and Electronic Consent

The STOP-CoV study inclusion and exclusion criteria have been reported elsewhere [21]. The full STOP-CoV Study protocol is available via the study website: https://stopcov.ca/; Trial registration: Clinicaltrials.gov. NCT05208983. The research study and electronic consent were approved by the University Health Network (UHN) Ethics Review Committee. Consent was obtained from all participants using an online consent form on the study's portal, accessed by individualized study identification (ID) number and password. Our laboratory developed an in-house Enzyme-Linked Immunosorbent Assay (ELISA) to determine the total IgG antibody levels to three SARS-CoV-2 antigens: nucleocapsid protein, spike protein and its receptor binding domain, and adapted it for use with DBS. [45,51]. The correlation of DBS to plasma samples was >90%.

Distribution of DBS kit and DBS Collection

Briefly, participants were asked to submit self-collected DBS taken: one week prior to the first COVID vaccination dose; three weeks after the first vaccination dose; two weeks after second vaccination dose; and then every 12 weeks. Subsequent study amendments requested an additional DBS 7 days before the first booster and 3-4 weeks following the first or subsequent boosters' vaccine doses. Individual study schedules were available on paper and electronically, and email reminders were sent when specimens were due.

Following consent, participants were sent DBS kits using conventional mail. These kits were prepared and distributed by a commercial company. One kit was provided for each collection period. Each kit contained one Whatman™ 903 DBS card, two lancets, first aid supplies, a zip-lock pouch containing a silica gel pack, and a plastic pre-stamped/paid return envelope. Detailed written instructions and a step-by-step video on how to collect, package, and mail in DBS samples for laboratory analysis were provided in the kit and on the study website (https://stopcov.ca/).

The DBS cards were fixed with a bar code to identify participants while maintaining confidentiality. Participants were required to record the day of collection on the DBS card prior to mailing, and to allow blood spots to dry before storing the package in the refrigerator until ready to be mailed. They were asked to mail the DBS card in an envelope with fixed postage within 24 hours of collection. Participants were required to log the date of receipt of vaccine doses and collection date of DBS samples into their study portal using their computers, cell phones or other similar personal device. Contact information (email and phone number) to the study staff was made available for those having difficulty in performing the tasks or answering questions. If participants missed submitting one or more DBS cards, they were able to continue in the study and submit further specimens as per their schedule.

Upon recipient, DBS cards were assessed by trained research assistants for quality and quantity of the blood spots based on previous recommendations—omitting identifying information. The quality of the blood spots was based on how much of each collection circle was filled, the number of blood spot samples provided, and whether the blood spot soaked through the Whatman™ paper. A priori, samples were considered acceptable by the laboratory if they had at least two blood spots completely soaked through that were a minimum of 3 mm in diameter. However, we were able to get full results from just one good punch by eluting in half the volume, but no sample was left for repeat testing if needed.

After quality control, all DBS cards were kept frozen at -80°C with humidity monitoring until they were shipped to the laboratory for antibody analysis.

Outcomes

We assessed the following outcomes: i) the proportion of consenting participants who submitted a sample, ii) the proportion of submitted samples returned within the expected window, and iii) the proportion of submitted samples that were adequate for testing. We assessed six time points: before the second vaccine dose, and then 2, 12, 24, 36, and 48 weeks after the second dose (6 time points in total). In an exploratory analysis, we also assessed outcomes (ii) and (iii) for time points occurring after booster doses during the 48 weeks. Due to drop-out, the denominator for the outcome (i) and the number of submitted samples decreased over time. Specimens were considered within the expected time frame if they were two weeks (+/- 1 week) after the second vaccination dose; and then every 12 weeks (+/- 3 weeks).

Statistical and Data Analysis

Descriptive statistics are reported as median [Q1 to Q3] or as n (%). A c^2-test for trend was used to compare the proportion within window (the second outcome) between age groups, and to compare the proportion of adequate samples (the third outcome) between time points. In addition, we used a mixed-effects logistic regression model for the third outcome to determine the effects of time, age group, sex, race, and education on adequacy, adjusting for each other. The logistic regression model used a random intercept to account for multiple DBS samples per participant. We report odds ratios and 95% confidence intervals for test adequacy for the fixed effects. The overall model fit and the presence of influential observations were checked. Race and education level were treated as binary fixed effects (Caucasian vs. other, and education level higher than high school vs. other, respectively). Complete-cases were used to estimate the model. Some participants included in the final analysis did not submit samples at all-time points. However, since all consented to the study, we assumed these data were missing at random. An a-level of 0.05 was used. Analyses were performed using R (version 4.2.1).

Results

Study Population

Between May 17, 2021, and July 31, 2021, a total of 1286 adult participants were recruited across Ontario, Canada, for the STOP-CoV Study. Figure 1 demonstrates the recruitment and follow-up. Two participants did not meet the eligibility criteria, 79 consenting participants did not complete any study activities, 18 withdrew from the study, 4 have died, leaving 1205 (94%) active participants at the time of this analysis, reported at 48 weeks after the second vaccine dose. Reasons for withdrawal included: withdrew consent (39%), unable to complete study task (50%),

unavailable for DBS collection (6%), and unable to follow study protocol (5%). 14 participants (all 30-50 years) were enrolled prior to the first vaccine dose, but the majority enrolled prior to the second vaccine dose, reflecting the short timeline between doses as recommended by our public health officials and the time needed for the study start-up. Baseline demographic questionnaires were completed by 1184 (92.2%) participants; 337 (92%) of the young (30-50 years old) cohort and 847 (98%) of the older (≥70 years old) cohort group. Of the 1205 participants active in the study, 1136 (94.3%) submitted at least one DBS sample. Of these, 8 did not receive two vaccine doses and were thus excluded from the analysis, leaving a final sample of 1128.
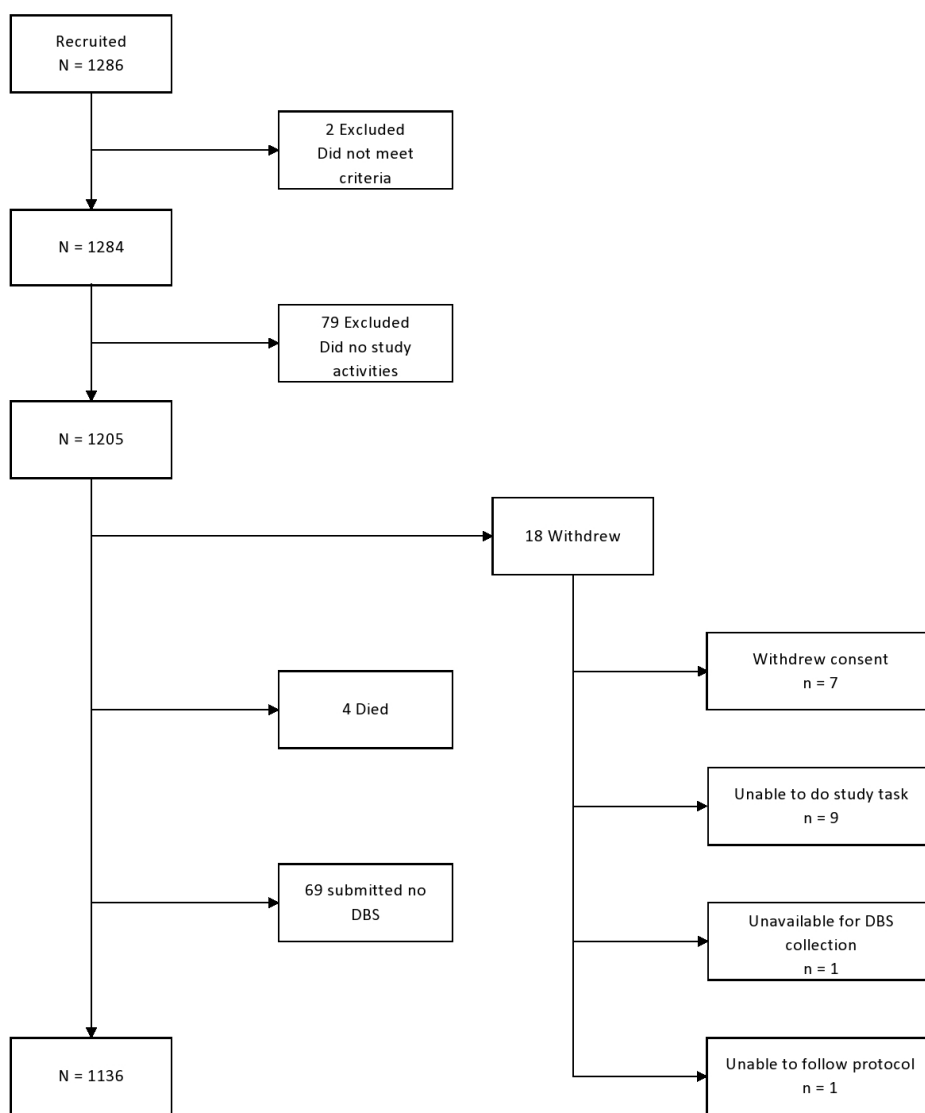

Figure 1: Study Flow Chart.

Table 1 summarizes the demographic characteristics of the study participants stratified by age cohort. The median age was 41 and 73 years for the two groups, respectively. 257 (76%) of the young cohort and 512 (60%) of the older cohort group identified as female or non-binary.

	30-50	**70+ years**
n (%)	344	861
Age[a] (median, IQR)	41 [36, 45]	73 [71, 76]
Female or NonBinary[a]	257 (75.6)	512 (59.6)
Racial Background		
Arab/West Indian	4 (1.2)	7 (0.8)
Black	11 (3.2)	9 (1.0)
Indigenous/Aboriginal/Indian or Native American	3 (0.9)	2 (0.2)
Latin American	7 (2.1)	0 (0.0)
South Asian	8 (2.4)	7 (0.8)
Southeast Asian	20 (5.9)	12 (1.4)
White	256 (75.3)	800 (93.1)
Other	31 (9.1)	22 (2.6)
Education Level above high school or less	312 (92.9)	721 (83.9)
Comorbidities		
Diabetes	5 (1.5)	123 (14.3)
Cardiovascular Disease	17 (5.0)	414 (48.2)
Cancer	9 (2.6)	171 (19.9)
Transplant or Immunosuppressed	12 (3.5)	36 (4.2)
Chronic Obstructive Lung Disease	0 (0.0)	22 (2.6)
Asthma	48 (14.1)	76 (8.8)

	30-50	**70+ years**
Chronic Kidney Disease	3 (0.9)	17 (2.0)
Hepatitis C	2 (0.6)	3 (0.3)
Chronic Liver Disease	4 (1.2)	9 (1.0)
Chronic Blood Disease	1 (0.3)	12 (1.4)
Chronic Neurologic Disease	4 (1.2)	15 (1.7)
Dialysis	3 (0.9)	4 (0.5)
Total Number of Vaccine Doses		
1	7 (2.0)	16 (1.9)
2	89 (25.9)	96 (11.1)
3	242 (70.3)	342 (39.7)
4	6 (1.7)	407 (47.3)
[a]Six (0.5%) participants are missing baseline data		

Table 1: Baseline Characteristics by Age Cohort.

Dried Blood Spot Submission and Timeline

Of the 69 participants who did not submit any DBS, 38 participants (5.0%) were of the older cohort vs. n=31 (9.9%) of the younger cohort (p=0.003). Overall, 5988 (88.8%) of the expected DBS samples were submitted over the 48 weeks being reviewed; 1493 (80.4%) and 4495 (91.9%) by the young and old cohort, respectively (p<0.001). 97.9% (n=4401) of entries from the older cohort submitted their DBS samples as per schedule (within the allowable window) vs. 98.5% (n=1470) of younger participants according to the initial study protocol (p=0.22).

Figure 2 outline the DBS submission proportions and counts based on the timelines of expected sampling relative to the vaccine doses. There was a similar proportion of participants who submitted all their specimens on time in the age cohorts (89.5% in the older cohort vs. 91.6% in the younger cohort, p=0.34).
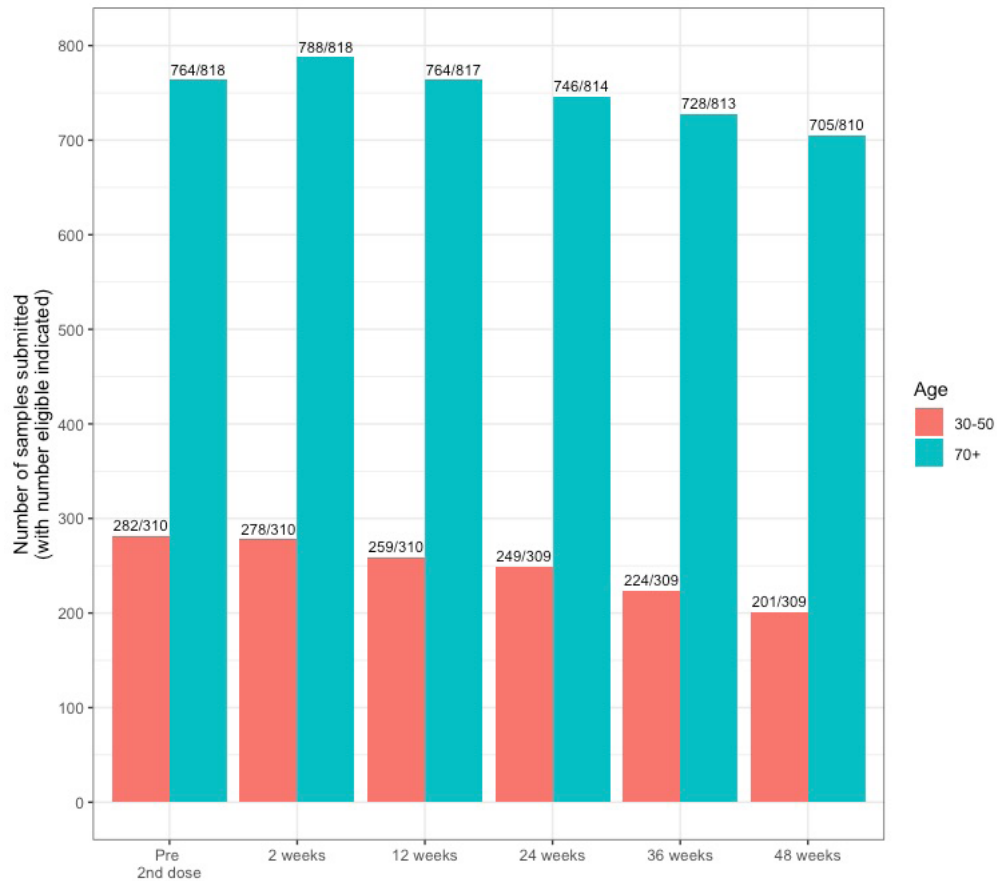
Figure 2: Frequency of eligible dried blood spot specimens submitted at the study time points, stratified by age cohort.

Booster Shot and Extended Retention

88.8% of older participants and 84.8% of younger participants agreed to the extension portion of the study that requested additional DBS prior to and 3-4 weeks after the third dose and 3-4 weeks after subsequent booster and to continue to collect DBS at 3-month intervals until 96 weeks after the second vaccine dose. Of these, 77.8% submitted DBS prior to the third dose, 94.8% 3-4 weeks after the third dose and 41.8% 3-4 weeks after the fourth dose.

Adequacy of Self-Collected Specimen Sample

Overall, 93.9% of specimens were reported adequate for testing, and this number increased with time (e.g. 92.5% before the second dose and increasing to 96.8% at 48 weeks after the second dose, p for trend <0.001). Results of the mixed-effects logistic regression model showed that after adjustment, the effects time remained significant, and that sex was the only other covariate that was associated with the outcome (the odds ratio of adequacy for females was 1.60 compared to males, 95% CI 1.04-2.47, Table 2).

Covariate	Odds ratio (95% CI)	P-value
Age group 70+ years (ref = 30-50 years)	0.75 (0.45-1.26)	0.28
Female sex	1.60 (1.04-2.47)	0.032
Not Caucasian	0.97 (0.49-1.92)	0.94
High school or less education level	0.62 (0.35-1.12)	0.11
Time after second dose (ref = before 2nd dose)		
2 weeks	1.55 (1.03-2.34)	
12 weeks	0.93 (0.64-1.37)	
24 weeks	1.16 (0.77-1.73)	<0.001
36 weeks	1.89 (1.22-2.95)	
38 weeks	3.26 (1.96-5.42)	

Table 2: Results of the mixed-effects logistic regression for modelling adequate specimens.

Discussion

The STOP-CoV study is a large-scale decentralized longitudinal cohort study designed to assess the safety and antibody response of the COVID-19 vaccines. This decentralized study used online consent, and completion of demographic, symptom and vaccine questionnaires. The study used self-collected DBS samples for testing antibody levels in response to the SARS-CoV-2 vaccine. Overall, the DBS technique proved to be feasible and acceptable, with only 9 participants withdrawing from the study because of an inability to provide the blood samples. 98% of specimens were submitted as per the protocol, and of the samples submitted, 93.9% were adequate for testing in a chemiluminescent ELISA-based assay [52]. We were able to include participants from across Ontario, Canada and included a large proportion of individuals over 70 years of age. Over time, the rate of DBS submission decreased, but sample sufficiency for serology testing increased. The elderly cohort submitted more frequently than the younger cohort. The rate of inadequate specimens was similar in the two cohorts and decreased with time. The rate of DBS submission remained the same for those who did or did not consent to the booster vaccine extension of the study. The improved sufficiency could be attributed to practice with time. In a separate study satisfaction survey, most participants reported no difficulty in performing the tasks [53] and felt more confident in the self-collection of DBS with time.

The shift from in-person to remote services due to the COVID-19 pandemic has introduced considerable challenges to health care. Coupled with social distancing measures and in-person restrictions, the rise of COVID-19 cases limited the progression and initiation of many clinical studies [22]. In addition, geographical distance, transportation, and motor function hindrance, may potentially serve as a barrier for older adults to participate in clinical research which is relevant to them. [23,33,54,55]. As a response, our study and other studies have pursued alternatives for SARS-CoV-2 serosurveillance by remote data collection and submission of DBS [27,46,47,49,56-58].

Early seroprevalence and technical studies using DBS to evaluate the immune response to COVID-19 were limited, small-scale, and typically involved a younger, educated population. These studies typically were based on a single test or with infrequent repeat testing. A study conducted in Boston, Massachusetts, examined the seroprevalence of SARS-CoV-2 antibodies among health care workers (n=433) using DBS by finger-prick method [31,55]. Another DBS collection study conducted in Melbourne, Australia (n=74) showed correlations between DBS and serum/plasma collected samples. Likewise, investigators in British Columbia (BC), Canada conducted a cross-sectional study evaluating the accuracy of DBS samples against serum collected samples by cross-validating various small and large scaled studies testing for SARS-CoV-2 antibodies post infection and/or vaccination [44].

Other population-based decentralized studies have since been published which adopted DBS sampling for SARS-CoV-2 serology testing. A Boston study [56] recruited adults within a 45 mile radius and used nasal swabs and DBS to evaluate for natural infection. Of the 10,289 recruited, only 10% were over 70 years. 56% completed 5 or more kits, whereas 19% completed only 1-2 kits at any time point. Non-Hispanic white race, increasing age, better socioeconomic status, and employment were associated with higher rates of engagement and retention. After validation of serology analysis from DBS against plasma, a San Francisco study [40] invited approximately 5500 individuals in each of three sampling phases to investigate changes in seroprevalence. They reported participation rates of 76.8%, 89.8%, and 87.3% per round, respectively. The Action to Beat Coronavirus study (Ab-C) has conducted four serial assessments of SARS-CoV-2 seropositivity, each involving 5000-9000 adults using the Angus Reid Forum, a nationally representative online polling platform for recruitment and DBS for blood collection and serology testing. A United States study conducted three internet-based studies offering serologic testing via DBS[49]. Of 2727 participants 60% consented for serology and 56% returned a usable DBS sample. We expand these findings by the ability to engage participants from rural and urban areas around the province, including a large number of those over aged 70 years, with serial collection over more than one year and additional sampling around vaccine boosters. Research

participation in the elderly population is often limited [32]. In addition to the potential for confounding variables due to high rates of comorbidities within the older population, researchers perceive older adults to be less inclined to participate and anticipate high attrition rates. We demonstrated high completion, acceptability, adherence, and adequacy rates of self-collected DBS specimens, supporting that remote DBS collection is an acceptable and feasible alternative for broader and inclusive testing. Based on our findings, we found that females had an increased odds of submitting an adequate specimen, and did not find any differences according to age, education level, or race.

The complete decentralized design of our study using DBS for sample collection has provided opportunities for older and vulnerable populations to benefit from and contribute to relevant clinical research. The advantage of this self-collection technique for recruiting older adults is that they can complete the study activities from home, eliminate the need to travel to a research center, adapt the schedule to their daily routine, and circumvent mobility challenges associated with comorbidities. Additionally, due to the low-cost use of postal service, DBS submission increases the ability to obtain samples from participants living in remote and rural areas, making it an effective alternative to in-person intravenous sample collection. We observed high submission of DBS samples from participants living outside of the greater Toronto area.

Strengths and Limitations

Recruitment, retention, and engagement are known challenges in clinical research, especially when considering a large cohort sample size and for older adults. Given the uncertainty experienced with the COVID-19 pandemic—the constant lifting and reinstating of the lockdown measures, the ongoing changes to vaccines protocol and timelines implemented by the Government of Canada, and increased postal delivery time, our study faced many challenges and changes that could have impacted protocol adherence amongst the participants. However, again due to the completely decentralized nature of our study, we were able to make and communicate changes rapidly. This coupled with the simplicity and ease of DBS self-collection, and the ability to do all study procedures from home, resulted in high retention, follow-up, and DBS sample adequacy. Participation in a study that was of value to an individual during a pandemic filled with uncertainty may have served as a strong motivator for participants to remain active in the study over a long period. We provided participants with their antibody results, as well as a comparator to their age cohort through their individual study portal, which also served to keep them engaged. And although we may have anticipated higher rates of specimen submission during the lockdown period before

persons returned to their daily activities, the rate of submission and commitment to the study remained high following the re-establishment of pre-pandemic routines. The lower rates with time in the younger cohort may reflect a return to usual activities and less focus on the study.

Though our study demonstrated substantial advantages of self-sampled remote DBS collection in the ageing population, some challenges to this minimally method of blood sample collection were noted. In our study, during the early stages of DBS collection, many individuals—irrespective of age—reported having difficulty using the lancet provided, often related to how to use the device and, in some cases, limited blood flow potentially due to the size of the lancet. We received reports of participants resorting to other methods, such as using their personal glucometer devices, needles or other sharp objects to obtain blood. Many participants needed to contact the study team for instruction, who was available by phone and email for rapid consultation. To mitigate the difficulties being experienced, we first developed both a video and a print version demonstrating the proper use of the lancet and strategies to improve the blood draw, and all subsequent sets of kits were distributed with a choice of different-sized lancets for participants to use the one most appropriate for them [59]. With these measures and with experience, the number of inadequate specimens and the need for assistance decreased with time.

Though we successfully demonstrated the feasibility of self-collecting DBS samples from a large-scale elderly cohort, we still have limited generalizability as most participants were white and had a high education level. To participate, they required experience using an electronic device, access to technology and the internet and an understanding of English or interpretive aid. Additionally, in order to undertake a totally decentralized study, the use of remote DBS collection can only be used in studies that do not require in-person procedures (such as a physical examination) and have the technology to do the serologic tests from the small sample provided through a DBS with no need for a blood draw.

Conclusion

In summary, in a large cohort, we have demonstrated the feasibility and acceptability of using self-collected DBS to determine antibody levels in response to COVID vaccines. Our analysis extends existing findings by demonstrating its application for recruitment and engagement in a large longitudinal cohort study consisting of older adults, many living outside of major research centers. Future research using self-collected DBS needs to ensure the clarity of initial instructions to participants. Moreover, developing strategies to engage marginalized or less educated populations can enable better representation in public health-related research.

Acknowledgments

Funding

Conflict of Interest

Dr. Sharon Walmsley has conducted clinical trials, has spoken at CME events, and served on advisory boards with ViiV Healthcare, Glaxo-Smith Kline, Merck, Gilead, Janssen.

Institutional Review Board Statement

The University Health Network (UHN) Ethics Review Committee, REB number 21-5090, approved the research study and electronic consent. Each participant gave electronic consent prior to any study activities.

Data Availability Statement

Data supporting the study results can be provided followed by request sent to the corresponding author's e-mail.

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