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SHORT COMMUNICATION

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Clinical validation of novel dried blood spot based collecting device using serum separation for measuring SARS-CoV-2 antibodies

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Abstract

Accurate surveillance of coronavirus disease 2019 (COVID-19) incidence includes large-scale antibody testing of the population. Current testing methods require collection of venous blood samples by a healthcare worker, or dried blood spot (DBS) collection using finger prick, however this might have some logistic and processing limitations. We investigated the performance of the Ser-Col device for detecting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibodies using a finger prick: DBS-like collection system that includes a lateral flow paper for serum separation and allows for automated large scale analysis. For this prospective study, adult patients with moderate to severe COVID-19 were included 6 weeks post-symptom onset. Healthy, adult volunteers were included as a negative control group. Venous blood and capillary blood using the Ser-Col device were collected and the Wantai SARS-CoV-2 total antibody ELISA was performed on all samples. We included 50 subjects in the study population and 49 in the control group. Results obtained with venous blood versus Ser-Col capillary blood showed 100% sensitivity (95% CI: 0.93–1.00) and 100% specificity (95% CI: 0.93–1.00). Our study shows the feasibility of SARS-CoV-2 total antibody screening using a standardized DBS technique with semiautomated processing for large scale analysis.

KEYWORDS
antibody detection, COVID-19, dried blood spot, SARS-CoV-2

1 | INTRODUCTION

In the coronavirus disease 2019 (COVID-19) pandemic, testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) specific antibodies is critical for monitoring immune responses after vaccination, as well as in epidemiological studies.[1] However, large-scale serological testing by traditional venipuncture can be challenging, especially in rural areas or developing countries, where access to healthcare is often limited. Capillary blood sampling using a finger prick and collection with a dried blood spot (DBS) technique gives the opportunity to self-collect blood samples at home and can be stored for months before analysis.[2–5] However, DBS technique might have several limitations such as a lack of standardization of blood sampling and elution, assay interference from whole blood components, the manual processing, and storage of DBS cards.[6]

The aim of this study was to validate the performance of the Ser-Col device for detecting SARS-CoV-2 antibodies in comparison to standard venipuncture. Ser-Col is a newly developed device

containing a microfluidic paper that separates serum from blood cells within minutes after taking blood samples by finger prick. This blood collection and serum separation device was developed in the SCAUT project under the Horizon Europe Framework Program from the European Union.[7] One of the main objectives of the SCAUT project was to develop an automated Ser-Col processing platform to allow for automated large scale analysis[7,8]; in order of magnitude of 500–1000 samples per day. For effectively handling low or medium number of samples per day, the SCAUT project also involved the development of a semiautomated processing platform, including manual addition of buffer to elute dried serum from the microfluidic paper.

In light of these potential advantages, we report the clinical validation of this blood collection device combined with the semiautomated elution system for measurement of SARS-CoV-2 antibodies after moderate to severe COVID-19.

2 | METHODS

For this prospective study, subjects were eligible if they were 18 years of age or older and had laboratory confirmed COVID-19. Clinical data, as well as their SARS-CoV-2 vaccination status was collected. For the control group, subjects were eligible if they were 18 years of age or older with no known history of SARS-CoV-2 infection or vaccination. Healthcare workers and volunteers at hospital outpatient clinics were included. The study was approved by the medical research ethics committee of the VUmc (METc VUmc; 2021.0043; March 25, 2021).

After informed consent, blood was collected at a hospital visit 6 weeks after the first day of symptom onset by venipuncture and a finger prick using the Ser-Col device.

For routine laboratory methods blood were collected in a 5 mL serum tube. The tubes were stored at −20°C in the Laboratory of Streeklab Haarlem.

Blood collection and processing of the Ser-Col device to obtain serum was performed according to the manufacturer's instruction for use and as described previously.[9,10] In short, blood was spotted onto the Ser-Col device (Labonovum) and left to dry at ambient temperature after which the Ser-Col device was transported to the lab at 4°C and stored at −80°C until used. In the laboratory the Ser-Col device was processed semiautomatically because of the low number of samples. The device was taken apart to release the microfluidic paper containing dried serum. Dried serum was eluted manually in 100 µL Ser-Col buffer containing phosphate-buffered saline.

Serum obtained from venipuncture blood and Ser-Col were tested using the Wantai two step incubation antigen "sandwich" enzyme immunoassay for SARS-CoV-2.[11] The Wantai assay was performed according to the manufacturer's instructions.[12] In short, from each blood sample (either obtained using venipuncture or Ser-Col), 100 µL of serum was used. Following all incubation and washing steps, the color intensity (optical density [OD]) in each sample well was measured. The OD is proportional to the amount of antibody captured inside the wells, and to the specimen respectively. For each patient sample, the ratio of signal to cut-off (S/CO) was calculated based on the samples OD and the OD measured for positive and negative controls. An S/CO value of <1 was interpreted as having no SARS-CoV-2 antibodies (negative) and ≥1 having SARS-CoV-2 antibodies (positive).

Sensitivity and specificity of antibody detection in capillary blood versus venous blood were calculated with 2 × 2 contingency tables, 95% confidence intervals (CI) were calculated with the Wilson CI. For the analysis of the Wantai signal-to-cut-off ratio values (S/CO) a

TABLE 1 Cohort characteristics.

	Study population (*n* = 50)	Negative controls (*n* = 49)
Median age (years)	57 (51.3–65.8)	31.5 (26.8–49.3)
Male sex, *n* (%)	26 (52.0)	18 (36.7)
Median BMI (kg/m^2)	28.8 (25.5–31.9)	24.0 (20.9–26.1)
Use of immunosuppressives, *n* (%)	2 (4.0)	1 (2.0)
History of cardiovascular disease, *n* (%)	10 (20.0)	0 (0)
Median weeks post-symptom onset (IQR)	6.9 (6.1–7.9)	na
Median days hospitalization (IQR)	7 (4–11)	na
Need for mechanical ventilation, *n* (%)	3 (6.0)	na
Vaccinated for SARS-CoV-2, *n* (%)[a]	16 (32.0)	na

Abbreviations: BMI, body mass index; IQR, interquartile range, SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

[a]Included are vaccinations administered at the time of sampling and after at least one vaccination. Missing data: 2 participants from the study population had an unknown vaccination status.

Bland–Altman plot was constructed by calculating the mean and difference of the two measurements. A 95% CI was constructed by 1.96 x the standard deviation of the difference of measurements.

3 | RESULTS

A total of 102 participants were included in this study, of which 50 met the inclusion criteria for the study population and 52 for the control group. The samples were drawn between March and July 2021. The samples of 3 (2.9%) of the Ser-Col devices contained insufficient amounts of blood and those subjects were excluded from the study. Cohort characteristics of all 99 included volunteers are listed in Table 1.

The blood samples of the study population were drawn at a median of 6.9 weeks after SARS-CoV-2 infection. All patients in this group had been hospitalized due to COVID-19; 3 (6%) needed mechanical ventilation. Sixteen (32%) participants of the study group were vaccinated against SARS-CoV-2 between initial infection and blood sampling.

There was 100% concordance between the methods, resulting in a 100% sensitivity (95% CI: 93%–100%) as well as 100% specificity (95% CI: 93%–100%) of the Ser-Col device compared to the venous blood samples (Table 2).

For the comparison of Wantai S/CO values we constructed a Bland–Altman plot (Figure 1). A minimal, nonrelevant systematic difference between serum and Ser-Col of 0.28 was seen. No association in favor of serum or Ser-Col with increasing S/CO values was seen as S/CO values are evenly distributed above and under 0.

TABLE 2 Contingency table of 99 paired serum samples collected via venipuncture and Ser-Col device.

Qualitative result of total SARS-CoV-2 antibodies		Venous serum Positive	Negative	Total
	Positive	50	0	50
Ser-Col	**Negative**	0	49	49
	Total	50	49	99

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

4 | DISCUSSION

Our study shows the feasibility of serological screening for SARS-CoV-2 total antibodies using a standardized dried blood device combined with semiautomated processing, showing excellent correlation with serum obtained by venipuncture. The clinical performance of the SARS-CoV-2 antibody assay using the Ser-Col device for blood collection appeared at least equal to other DBS systems.[2–5]

Several other studies have evaluated DBS sampling for SARS-CoV-2 antibody testing. In those studies, including mostly patients with mild disease severity, similar test characteristics were reported, with sensitivity values ranging from 89% up to 100% and specificity values of 97.1% up to 100%.[2–5] However, some studies were limited by the lack of serum serological testing as a reference test.[2]

Our study has limitations. First, self-collection of capillary blood was done in-hospital with help of an investigator, instead of a home

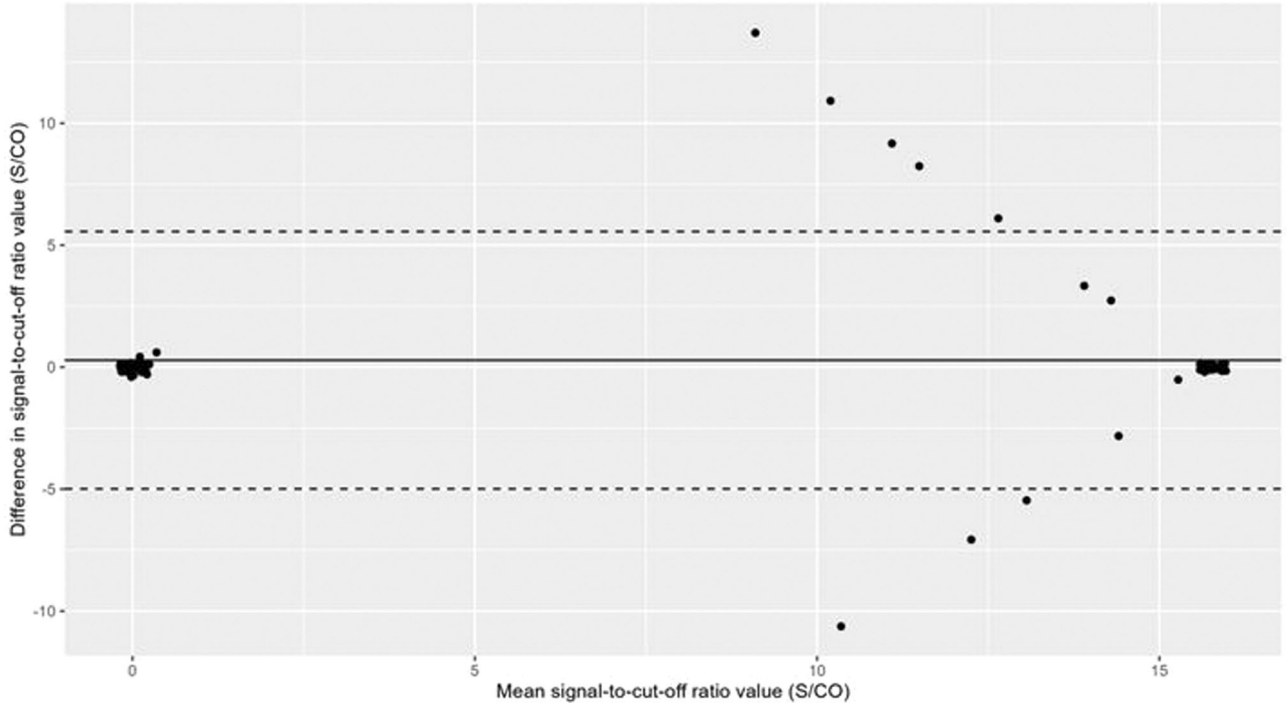

FIGURE 1 Bland–Altman plot with signal-to-cut-off ratio values (S/CO) of the 99 paired serum samples.

setting where individuals might collect smaller amounts of blood in the Ser-Col device than needed.

Second, our study population comprised mainly of moderate to severe COVID-19 cases. Previous studies were mostly performed on mild cases and it is known that mildly ill patients have significantly lower antibody responses as compared with the more severely ill.[13] Therefore, lower sensitivity and specificity might be found in mild cases.

In conclusion, the Ser-Col device can be a valid alternative for detecting SARS-CoV-2 antibodies in serum with the advantage of large scale surveys and self-collection at home, which could be especially useful in areas with limited access to healthcare.

AUTHOR CONTRIBUTIONS

Sophie Jolien Schuurmans Stekhoven, Steven Ferdinand Lodewijk van Lelyveld, Dennis Souverein, and Sjoerd M. Euser participated in conceptualization. Sophie Jolien Schuurmans Stekhoven, Steven Ferdinand Lodewijk van Lelyveld, Brigitte Marlene Sondermeijer, and Kirsten Gerdien te Winkel contributed to data collection. Sophie Jolien Schuurmans Stekhoven and Steven Ferdinand Lodewijk van Lelyveld wrote the original draft. Brigitte Marlene Sondermeijer, Dennis Souverein, Sjoerd M. Euser, Kirsten Gerdien te Winkel, and Marianne A. van Houten contributed in reviewing and editing the paper. Dennis Souverein and Sjoerd M. Euser performed data analysis and visualization. All authors critically reviewed and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University Amsterdam UMC, location VUmc (March 24, 2021/No. 2021.0043).

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