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Capillary whole-blood IgG-IgM COVID-19 self-test as a serological screening tool for SARS-CoV-2 infection adapted to the general public

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Ethics Statement Enter an ethics statement for this submission. This statement is required if the study involved: • Human participants • Human specimens or tissue • Vertebrate animals or cephalopods • Vertebrate embryos or tissues • Field research Write "N/A" if the submission does not require an ethics statement. General guidance is provided below. Consult the submission guidelines for detailed instructions. **Make sure that all information entered here is included in the Methods section of the manuscript.**	The study was conducted according to the ethical requirements established by the Declaration of Helsinki. . Ethical approval for this study was obtained from the local scientific committee of Parc de l'Innovation, Strasbourg, France. All participants signed an informed consent form, and were informed of their self-test results, and were referred to care facilities in the event of a positive test.

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Capillary whole-blood IgG-IgM COVID-19 self-test as a serological screening tool for SARS-CoV-2 infection adapted to the general public

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Author's contribution. STW, RD and LB conceived the study. RD performed the experiments, and collected data. STW analyzed the data and generated the figs. STW, MPH, SBA and LB supervised this study. All authors wrote and edited the manuscript.

Abstract

The practicability of a prototype capillary whole-blood IgG-IgM COVID-19 self-test (Exacto® COVID-19 self-test, Biosynex Swiss SA, Freiburg, Switzerland) as a serological screening tool for SARS-CoV-2 infection adapted to the general public was evaluated in a cross-sectional, general adult population study performed between April and May 2020 in Strasbourg, France, consisting of face-to-face, paper-based, semi-structured, and self-administrated questionnaires. A total of 167 participants (52.7% female; median age, 35.8 years; 82% with post-graduate level) were enrolled, including 83 and 84 for usability and test results interpretation substudies, respectively. All participants (100%; 95% CI: 95.6–100) correctly used the self-test. However, 12 (14.5%; 95% CI: 8.5–23.6) asked for verbal help. Overall, 98.5% (95% CI: 96.5–99.4) test results were correctly interpreted, while misinterpretation occurred in only 2.3% of positive and 1.2% of invalid test results. Finally, all (100%) participants found that performing the COVID-19 self-test was easy; and 98.8% found the interpretation of the self-test results easy. Taken together, these pilot observations demonstrated for the first-time, high practicability and satisfaction of COVID-19 self-testing for serological IgG and IgM immune status, indicating its potential for use by the general public to complete the arsenal of available SARS-CoV-2 serological assays in the urgent context of the COVID-19 epidemic.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that causes Coronavirus Disease 2019 (COVID-19), started in the Wuhan province, China, in December 2019, and was declared by the World Health Organization (WHO) as global

pandemic on March 11, 2020 [1-4]. Controlling the outbreak in the community and in hospitals mainly relied on the availability of highly sensitive and specific nucleic acid amplification-based molecular testing for SARS-CoV-2 [5,6]. Furthermore, it was demonstrated that serological testing looking for specific SARS-CoV-2 IgG and/or IgM may be useful for confirming the diagnosis and care of COVID-19 patients [7-9]. On March 2, 2020, the WHO recommended serological testing in addition of molecular diagnosis, for investigating on-going outbreaks as well as for the diagnosis of strongly suspected patients of SARS-CoV-2 infection with negative RT-PCR [10]. Furthermore, antibody tests for SARS-CoV-2 may constitute one of the keys to fight the SARS-CoV-2 epidemic, in particular to overcome the de-confinement period [9]. Seropositivity to SARS-CoV-2 antigens would also allow to identify previously infected individuals, including asymptomatic patients, *a priori* considered to be healed and protected against new reinfection [9].

Recently, rapid lateral flow assays for IgG and IgM antibodies produced during the COVID-19 epidemic have been developed [11]. Several reports have shown that COVID-19 IgG/IgM lateral flow immunoassays may be a reliable tool to diagnose SARS-CoV-2 infection from 14 days of onset of symptoms [12,13]. In some countries, rapid diagnostic testing for COVID-19 has been incorporated into the local guidelines for testing asymptomatic contacts of positive cases, at day 14 of home surveillance [14]. These easy to use IgG-IgM combined tests allow rapid screening with capillary blood samples. The tests are simple, qualitative, visually interpretable, and give a result within 10 to 15 minutes. A positive serology allows to determine whether a person has already been infected by SARS-CoV-2. Serologic tests will be needed to assess the response to vaccine candidates and to map levels of immunity in communities. These rapid tests could be particularly interesting for developing countries for testing patients at the bedside or any other locations where laboratory facilities are lacking.

HIV self-testing constitutes a novel innovative approach to make testing more accessible, confidential, and available at non-traditional venues, such as pharmacies and community venues, as well as in the home, as it offers a discreet, convenient, and empowering way to test [15,16]. HIV self-testing has demonstrated high acceptability with very convenient usability in various adolescent and adult prone populations from developed as resources-constrained settings [17-21].

To our knowledge, there is no currently reported experience in the literature about self-testing for SRAS-CoV-2 infection. Based on our own experience of HIV self-testing evaluation, we herein aimed at evaluating the practicability of a prototype capillary whole-blood IgG-IgM COVID-19 self-test as a serological screening tool for SARS-CoV-2 infection adapted to the general public.

Material and methods

Prototype SARS-CoV-2 test for self-testing. The prototype capillary whole-blood IgG/IgM SARS-CoV-2 self-test (Exacto® COVID-19 self-test, Biosynex Swiss SA, Freiburg, Switzerland) was adapted from the CE IVD-labeled finger-stick whole-blood rapid diagnostic test for IgG and IgM antibodies against SARS-CoV-2 detection (BIOSYNEX® COVID-19 BSS [IgG/IgM], Biosynex Swiss SA), by re-packaging for individual use with the addition of seven components placed in a pouch containing the test cassette, diluent vial, pipette, alcohol wipe, compress, lancet and dressing. The Exacto® COVID-19 self-test (Biosynex Swiss SA) consists of visually read, qualitative, *in vitro* lateral flow immunoassays for the detection of IgG and IgM antibodies to SARS-CoV-2 in human whole blood, serum, or plasma as an aid in the diagnosis of SARS-COV-2 infection. The targeted protein is the receptor-binding domain (RBD) of the spike surface protein of SARS-CoV-2. During testing,

the specimen reacts with SARS-CoV-2 antigen-coated particles in the test cassette. The mixture then migrates upward on the membrane chromatographically by capillary action and reacts with the anti-human IgG in the IgG test line region or/and with the anti-human IgM in the IgM line region. The quantity of blood needed to perform the test is 10 µL.

The analytical performances of the BIOSYNEX® COVID-19 BSS (IgG/IgM) (Biosynex Swiss SA) were evaluated during the COVID-19 epidemic in *Grand Hôpital de l'Est francilien*, Jossigny, France, using two serum sample panels obtained from patients with COVID-19 confirmed by positive nucleic acid amplification-based diagnosis at least 14 days after symptoms onset and from patients randomly selected for whom serum samples were collected before the COVID-19 epidemic (from October 1 to November 30, 2019) (instructions for use 2020). The BIOSYNEX® COVID-19 BSS (IgG/IgM) (Biosynex Swiss SA) showed sensitivity of 97.4% and specificity of 100%, demonstrating high analytical performances allowing convenient management of suspected on-going and past-infections. Furthermore, this rapid diagnostic test is recommended for both SARS-CoV-2-specific IgG and IgM detection by the French Ministry of Health [22], because the test fulfilled the criteria of the minimal analytical performances [*i.e.* minimum sensitivity of 90% (or even 95%) and minimum specificity of 98%] of serological tests detecting the antibodies directed against SARS-CoV-2, defined on April 16, 2020 by the so-called *Haute Autorité de Santé* [23]. The simplified instructions for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA) comprised an easy-to-read leaflet in French and English, in A3 format color printing. As an example, the instructions for use are depicted in Fig 1. The online instruction in the video for use was available online from Youtube [24].

Fi Instructions for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA) designed for the general public using typical pictures representative of the principal steps of the man cturer's instructions with explanations written.

Study design and recruitment of participants.

The practicability evaluation of the Exacto® COVID-19 self-test (Biosynex Swiss SA) is a cross-sectional study performed between April and May 2020 by home-based recruitment of adult volunteers using a door-to-door community approach, in 15 neighl oods of Strasbourg and its suburbs, France, consisting of face-to-face, paper-based, semi-structured, and self-administrated questionnaires. Strasbourg is the capital city of the Grand Est province, which was one of the regions affected the most by the SARS-CoV-2 epidemic in France [25].

All participants accepted voluntarily to be included. Eligible participants had an age ≥ 18 years, wanted to know their SRAS-CoV-2 serology status, were capable to speak and read in French, and gave their consent to participate in the study. All trained individuals (physicians, nurses, and biologist) in rapid diagnostic tests were excluded. Informed written consent was signed by all participants. Ethical approval for this study was obtained from the local scientific committee of Parc de l'Innovation, Strasbourg, France.

Practicability study outcomes.

The practicability evaluation was divided into four substudies carried out by trained health care professionals, based on previously acquired experience from WHO recommendations for evaluating the practicability of HIV self-tests [17,18,26]. As depicted in the Fig 2, all participants were included in substudy 1 concerning the understanding of labeling, while they were randomized into two groups for substudy 2 concerning manipulation of the test and substudy 3 evaluating the interpretation of COVID-19

self-test results, using block randomization of 4. Participants in sub-study 4 were each drawn from the satisfaction questionnaires for substudies 2 and 3.

Fig 2. Flow chart showing the recruitment of study participants, their randomization, and affiliation for each substudy.

Data collection and procedures. Paper-based, self-administered, and structured questionnaires were used to obtain the data on the socio-demographic characteristics, medical history of study participants, participants' understanding of the instructions for use, and participants' opinions or levels of satisfaction about the practicability of the Exacto® COVID-19 self-test (Biosynex Swiss SA). All data related to the observation of manipulation and the interpretation of test results were recorded on the standardized sheets by the observers.

Substudy 1. Comprehension of labeling. After receiving a brief explanation of the objectives and conduct of the study, the participants were asked to sign the informed consent form. In a private setting, the participants had the choice between a paper-based instruction for use and a video-based instruction for use, which they were asked to read or watch and understand independently. After their self-declaration of having understood the instruction for use, the participants were asked to fill a questionnaire to gauge their comprehension. To this end, 10 questions restating the key information with closed answers (true, false, or don't know) were asked by the observer on the followings items: 1. Identification of each component of the kit; 2. Manipulation of blood sampling device; 3. Diluent deposit; 4. Possession of a timer; 5. Interpretation of a positive test result; 6. Interpretation of a negative test result; 7. Diagnosis of an invalid test result; 8. Reliability of self-test result; 9. Meaning of a positive result; and 10. Detection of the virus. The participants who correctly answered all 10 questions were considered to have correctly understood the instructions for use.

After this survey, participants were randomized in two groups for evaluation on performing the self-test and the interpretation of test results. In order to achieve this, a sealed randomization envelope was used sequentially. In each group, before starting the survey, a pre-test satisfaction questionnaire was completed by the participants.

Substudy 2. Observation of manipulation. In a private setting supervised by an observer, each participant received a box containing the Exacto® COVID-19 self-test (Biosynex Swiss SA). Participants were then asked to carry out the self-test by themselves in front of a trained observer. The observer was responsible for recording the respect or not of each step, appeal for verbal assistance (mimicking telephone support), difficulty, and errors on a standardized sheet. The successful performance of the SARS-CoV-2 self-test was conditioned by the presence of the control band on test strip, and the test results were read and recorded independently by both the participants and the observers.

Substudy 3. Interpretation of test results. In a private setting supervised by an observer, eight standardized test results including four positive tests (one weak positive for IgM, one clearly positive for IgM, one clearly positive for IgG but weak positive for IgM, and one clearly positive for IgM and IgG), two negative tests, and two invalid tests were proposed to the participants for interpretation after successive random selection of four tests (Fig 3). These standardized tests were coded by numbers to determine the expected results.

Fig 3. Panel of 8 Exacto® COVID-19 self-test (Biosynex Swiss SA) cassettes, including 4 positive tests (n°2, n°3, n°6 and n°7), 2 negative tests (n°2 and n°7) and 2 invalid tests (n°1 and n°5). The n°2 and n°7 are weakly positive for IgM. Each volunteer successively drew 4 tests among a panel of 8 and interpreted them with the help of the reading and interpretation scale. The observer noted the number of the drawn test and the result given by the participant.

Substudy 4. Satisfaction questionnaire. Finally, the participants fulfilled the satisfaction questionnaire concerning their experiences with the COVID-19 self-test including understanding of instructions for use, the identification of the different components of the kit, the sample collection and transfer, the overall performance of the self-test, the reading and interpretation of test results, and the ability to overcome the difficulties encountered.

Statistical analysis. All data were entered into an Excel file and analyzed on SPSS 20.0 (Chicago, IL). Descriptive statistics were computed using mean (standard deviation) or median (interquartile range) for normal or skewed distribution, respectively, then, proportions of all categorical variables were calculated for qualitative data. The labeling index for understanding and usability index were defined as the mean of the correct answers for each question related to the understanding of instructions for use and performing of the COVID-19 self-test, respectively. The Wilson score bounds were used to estimate the 95% confidence intervals (CI). Cohen's κ coefficient estimated the concordance between the results read by participants in connection with the expected results [27]. The degree of agreement was determined as ranked by Landlis and Koch [28]. The comparison of data from the post-test satisfaction questionnaire paired to those from the pre-test satisfaction questionnaire was performed by using Mac Nemar's chi-squared pairing test.

Results

Study population. A total of 194 individuals were assessed for eligibility, but 27 were excluded because they were trained (n=12), less than 18 years old (n=5), and not consenting (n=10). Finally, 167 were successfully enrolled in the study (substudies 1 and 4), and among

them, 83 were assigned after randomization in substudy 2 and 84 in substudy 3 (Fig 2). The demographic characteristics and medical history of study participants are shown in Table 1. Overall, 88 (52.7%) were female. The mean age was 38.6 (SD: 13.8) years, and around one half of participants were aged between 18 and 39 years. The majority (82.0%) of participants had post-graduate education level. The majority (59.3%) had reported no symptoms of COVID-19 in the past two months. Approximately one fifth of participants had previously been screened for SARS-CoV-2 infection by molecular testing of nasopharyngeal swab, of whom 13.4% had a positive result (Table 1).

Table 1. The demographic characteristics and medical history of the 167 study participants.

Variable	Items	Number (%)
Sex		
	Male	79 (47.3)
	Female	88 (52.7)
Age (**years**)		
	18 – 39	88 (52.7)
	≥ 40	79 (47.3)
Mean (SD)		38.6 (13.8)
Educational level		
	College level	14 (8.4)
	High school level	16 (9.6)
	Post-graduate level	137 (82.0)
Had the symptoms of COVID-19 in the past two months[#]		
	Yes	68 (40.7)
	No	99 (59.3)
Previous COVID-19 molecular testing (nasopharyngeal swab)		
	Yes	34 (20.4)
	No	133 (79.6)
Previously diagnosed COVID-19 positive among those previously COVID-19 tested		
	Yes	22 (13.2)
	No	145 (86.8)

[#] Participants who reported having at least one of the following major symptoms associated or not with minor symptoms were considered to have the COVID-19 symptom: fever, fatigue, dry cough, anosmia and dyspnea. Minor symptoms were: pain, nasal congestion, runny nose, sore throat or diarrhea.

244 COVID-19: Coronavirus disease 2019; RT-PCR: Reverse transcription-polymerase chain reaction; SD: Standard deviation.

245

246 **Substudy 1.** This substudy evaluated the ability of the 167 study participants to understand
247 the instructions for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA). A large
248 majority (*n*=155; 92.8%) of participants preferred to use the paper-based instructions whereas
249 only 12 (7.2%) participants used the video-based instructions. The analytical results of the
250 evaluation questionnaire are shown in Table 2. Overall, 149 (89.2%; 95% CI: 83.6–93.1)
251 participants correctly understood the instructions for use, thus correctly answering all 10
252 questions. The labeling index for understanding measuring the mean of the correct answers for
253 each question was 97.1% (95% CI: 93.3–98.8). The question concerning the non-detection of
254 the virus (SARS-CoV-2) by the self-test showed the highest rate (10.2%) of incorrect response.

255

256 **Table 2.** Analytical results of the evaluation questionnaire concerning the ability of the 167 study
257 participants to understand the instruction for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA)
258 (substudy 1).The questions raising specific issues concerning the manipulation of the kit, the interpretation
259 of test results, and the consequence of test results, were asked by the observer and the answers were closed.

Comprehension of labeling checklist*	**Participants' responses**		
	True [*number (%)*]	**False** [*number (%)*]	**Don't know** [*number (%)*]
Q1: "A capital letter is associated with each component of the kit to better identify it during the performance of self-test"	166 (99.4)	-	1 (0.6)
Q2: "The blood collection device (lancet) helps to collect the blood and transfer it immediately into the SQUARE well of self-test with the pipette"	165 (98.8)	1 (0.6)	1 (0.6)
Q3: "Two drops of diluent should be placed in the same well as the drop of blood"	2 (1.2)	163 (97.6)	2 (1.2)
Q4: "A timer (watch or mobile) to clock 10 minutes before reading the result is need"	167 (100)	-	-
Q5: "Presence of a readable strip next to IgM and/or IgG on the self-test cassette means that the test is positive"	166 (99.4)	1 (0.6)	-
Q6: "Lack of band by test results is interpreted as a negative test"	4 (2.4)	162 (97.0)	1 (0.6)
Q7: "Lack of control band by test results should be interpreted as an invalid test"	167 (100)	-	-
Q8: "Having symptoms less than 10 days before the test does not provide a reliable result"	157 (94.0)	7 (4.2)	3 (1.8)

Q9: "If the test is positive it means that they have been in contact with the virus"	163 (97.6)	3 (1.8)	1 (0.6)
Q10: "The Exacto® COVID-19 self-test does not detect the presence of the virus"	148 (88.6)	17 (10.2)	2 (1.2)
Labeling index for understanding (% [95% CI])[£]	97.1 [93.3–98.8]		
Correct understanding of the instruction for use (n; % [95% CI])[#]	149; 89.2 [83.6–93.1]		

[*] Overall, 155 (92.8%) participants preferred to use the paper-based instruction whereas only 12 (7.2%) participants used the video-based instruction;

[£] The labeling index for understanding was defined as the mean of the correct answers for each question;

[#] The participants who correctly answered all 10 questions were considered to have correctly understood the instructions for use.

CI: Confidence interval; COVID-19: Coronavirus disease 2019; Q: Question.

Substudy 2. This substudy evaluated the ability of participants to use the Exacto® COVID-19 self-test (Biosynex Swiss SA) in a supervised setting. The results of the questionnaire are shown in Table 3. Overall, all participants (100%; 95% CI: 95.6–100) performed the self-test and succeeded in obtaining a valid test result with an overall usability index of 98.5% (95% CI: 93.0–99.7). Seventy (83.1%; 95% CI: 75.0–90.6) participants correctly used the self-test without any difficulties, errors, and help, whereas 12 (14.5%; 95% CI: 8.5–23.6) had asked for verbal help. The identification of the different components of the kit, the use of the lancet and pipette, and the transfer of blood were the steps requiring the most frequent verbal help in 1.2%, 2.4%, 8.4%, and 2.4%, respectively (Table 3). Interestingly, all participants (n=6; 7.2%) using the video instructions performed the self-test easily (usability index of 100%) without any difficulties, errors, and help. Overall, the mean time of HV self-test performance (since the opening of the box until the migration step) was 8.8 (SD: 3.0) minutes.

Table 3. Analytical results of the manipulation observation concerning the ability of the randomly selected 83 study participants to correctly use each step of the Exacto® COVID-19 self-test (Biosynex Swiss SA) autonomously or with verbal help (substudy 2).

Usability checklist*	Successful manipulation		Need for verbal help
	Yes [*number (%)*]	**No** [*number (%)*]	**Yes** [*number (%)*]
1. Did the participant read the instruction for use?	83 (100)	-	-
2. Did the participant easily identify the different components of the kit?	82 (98.8)	1 (1.2)	1 (1.2)
3. Did the participant wash his hands?	83 (100)	-	-
4. Did the participant properly remove the test cassette from the aluminum pouch?	81 (97.6)	2 (2.4)	-
5. Did the participant open the diluent vial correctly?	83 (100)	-	-
6. Did the participant disinfect his finger correctly?	83 (100)	-	-
7. Did the participant wipe residual alcohol with the compress?	82 (98.8)	1 (1.2)	-
8. Did the participant have difficulty lancing their finger?	2 (2.4)	81 (97.6)	2 (2.4)
9. Did the participant have difficulty forming a blood droplet?	1 (1.2)	82 (98.8)	-
10. Did the participant have difficulty using the pipette correctly until it was filled up to the blank line?	7 (8.4)	76 (91.6)	7 (8.4)
11. Did the participant correctly transfer and deposit the blood into the SQUARE well of the test cassette?	81 (97.6)	2 (2.4)	2 (2.4)
12. Did the participant shed two drops of diluent in the ROUND well of the test cassette?	83 (100)	-	-
13. Did the Participant obtain an interpretable result at the end of the process despite a missed or incorrect step?[#]	83 (100)	-	-
Usability index and overall need for help (% [95% CI])[£]	98.5 [93.0–99.7]		14.5 [8.5–23.6]
Correct use without difficulties, errors, and helps (n; % [95% CI])	70; 83.1 [75.0–90.6]		
Average time of manipulation (minutes [SD])	8.8 [3.0]		

[*] 6 (7.2) participants had used the video-based instruction for use; among them the usability index was estimated to 100% without any difficulties, errors, and help;

[#] The result was considered interpretable when a control strip was readable after the migration time recommended by the manufacturer; in the present series, 11 (13.3%) participants had a positive self-test result;

[£] The usability index was defined as the mean of the correct answers for each question.

CI: Confidence interval; SD: Standard deviation.

Substudy 3. This substudy evaluated the ability of participants to read and interpret the COVID-19 self-test results after successive random selection of four tests from a panel of eight standardized tests. The results are depicted in Fig 4. Overall, 336 standardized tests were read and interpreted by the 84 participants, including 171 positive, 84 negative, and 81 invalid test results. A total of 331 (98.5%; 95% CI: 96.5–99.4) tests were correctly interpreted, whereas 5 (1.5%; 95% CI: 0.6–3.5) tests were misinterpreted. Misinterpretation occurred in 2.3% (n=4)

of positive tests (all tests were weakly positive for IgM tests falsely interpreted as negative) and in 1.2% (n=1) of invalid tests falsely interpreted as negative. Cohen's κ coefficient between the results of reading by participants and the expected results was 0.98, demonstrating an excellent concordance.

Fig 4. Stacked columns showing the ability of participants to read and interpret (correctly or incorrectly) the 336 results of the Exacto® COVID-19 self-test (Biosynex Swiss SA) obtained from successive random selection of a panel of 8 standardized tests, including four positive, two negative, and two invalid test results.

Substudy 4. This substudy assessed the pre-test and post-test satisfaction of participants concerning the instructions for use (substudy 1), performing the COVID-19 self-test (substudy 2), and the interpretation of test results (substudy 3). The results of the questionnaire are shown in Table 4. The understanding of the instructions for use of the self-test was considered easy in pre-test satisfaction questionnaire as well as in post-test period (100% *versus* 97.6%; not significant). However, 92.8% of participants found that the sample collection was very easy in pre-test satisfaction questionnaire whereas this satisfaction decreased after self-testing to 71.1%, yielding a difference of -21,7 (95% CI: -31.7 to -11.7; $P<0.001$). Similar decrease was observed with the satisfaction of sample transfer (81.2% *versus* 60.2%; difference: -21.0% [95% CI: -30.9 to 11.1]; $P<0.001$). Concerning the interpretation of test results, the participants found it easy in pre-test satisfaction questionnaire as well as in post-test period (100% *versus* 98.8%; not significant). Finally, when asked about the ability to surmount the difficulties encountered during COVID-19 self-testing, all (100%) participants found it easy (97.0% very easy; 3.0% rather easy).

323 **Table 4.** Items and results of the pre-test and post-test satisfaction questionnaire and concerning the
324 instruction notice (substudy 1), the performing of the Exacto COVID-19 self-test (Biosynex Swiss SA)
325 (substudy 2), and the interpretation of test results (substudy 3).

Satisfaction questionnaire	**Pre-test satisfaction** [*number (%)*]	**Post-test satisfaction** [*number (%)*]	**Difference**[*] *% [95% CI]*	**P-value**[#]
How did you find the understandability of instructions for use of self-test? (N=167)				
Very easy	156 (93.4)	153 (91.6)	-1.8 (-5.1 to +1.5)	NS
Rather easy	11 (6.6)	10 (6,0)	-0.6 (-3.3 to +2.1)	NS
Rather difficult	0 (0)	2 (1.2)	+1.2 (-1.8 to +4.2)	NS
Very difficult	0 (0)	2 (1.2)	+1.2 (-1.8 to +4.2)	NS
How did you find the identification of the different components of the self-test kits (N=83)				
Very easy	81 (97.6)	80 (96.4)	-1.2 (-6.5 to +4.3)	NS
Rather easy	2 (2.4)	3 (3.6)	+1.2 (-4.1 to +6.5)	NS
Rather difficult	0 (0)	0 (0)	-	NA
Very difficult	0 (0)	0 (0)	-	NA
How did you find the sample collection? (N=83)				
Very easy	77 (92.8)	59 (71.1)	-21,7 (-31.7 to -11.7)	<0.001
Rather easy	5 (6.0)	20 (24.1)	+18.1 (+11.3 to +27.7)	<0.001
Rather difficult	0 (0)	1 (1.2)	+1.2 (-4.1 to +6.5)	NS
Very difficult	1 (1.2)	3 (3.6)	+2.4 (-3.5 to 8.3)	NS
How did you find the sample transfer? (N=83)				
Very easy	68 (81.2)	50 (60.2)	-21.0 (-30.9 to 11.1)	<0.001
Rather easy	14 (16.9)	25 (30.1)	+13.2 (+4.3 to +22.1)	0.043
Rather difficult	0 (0)	2 (2.4)	+2.4 (-3.5 to +8.3)	NS
Very difficult	1 (1.2)	6 (7.2)	+6.0 (-1.3 to +13.3)	NS
How did you find the overall performance of self-test? (N=83)				
Very easy	80 (96.4)	77 (92.8)	-3.6 (-10.1 to +2.9)	NS
Rather easy	2 (2.4)	6 (7.2)	+4.8 (-2.1 to +11.7)	NS
Rather difficult	1 (1.2)	0 (0)	-1.2 (-6.5 to +4.3)	NS
Very difficult	0 (0)	0 (0)	-	NA
How did you find the reading of strips after migration? (N=84)				
Very easy	73 (86.9)	70 (83.3)	-3.6 (-10.0 to +3.0)	NS
Rather easy	8 (9.5)	10 (11.9)	+2.4 (-3.4 to 8.4)	NS
Rather difficult	2 (2.4)	3 (3.6)	+1.2 (-4.0 to +6.4)	NS
Very difficult	1 (1.2)	1 (1.2)	-	NA
How did you find the interpretation of self-test results (N=84)				
Very easy	76 (90.5)	76 (90.5)	-	NA
Rather easy	8 (9.5)	7 (8.3)	-1.2 (-6.4 to +4.2)	NS
Rather difficult	0 (0)	0 (0)	-	NA
Very difficult	0 (0)	1 (1.2)	+1.2 (-4.0 to +6.4)	NS
How did you find your ability to surmount the difficulties encountered (N=167)				
Very easy	-	162 (97.0)	NA	NA
Rather easy	-	5 (3.0)	NA	NA
Rather difficult	-	0	NA	NA
Very difficult	-	0	NA	NA

326 [*] Difference and CI were assessed with the Wilson score bounds using data collected in the post-test satisfaction questionnaire paired to those
327 from the pre-test satisfaction questionnaire;
328 [#] *P*-value calculated using Mac Nemar's test of paired data.

CI: Confidence interval; NA: Not applicable; NS: Not significant.

Discussion

We herein report on our recent experience during the last COVID-19 epidemic peak period of the practicability of a prototype capillary whole-blood COVID-19 self-test for IgG and IgM against SARS-CoV-2 serological screening among adult volunteers living in France. Our assessment of usability was made with reference to our previous experience in evaluating HIV self-testing according to the WHO recommendations [26]. Overall, the vast majority of participants correctly understood the instructions for use, showed good ability to carry out the self-testing procedure in order to obtain a valid test result, and demonstrated to be capable to correctly interpret the test results with high degree of satisfaction. Only a minority of participants needed verbal help, and only 1.5% of test results were misinterpreted. Taken together, our pilot study generated for the first-time to our knowledge evidence on generally good practicability of COVID-19 self-testing for serological IgG and IgM immune status, despite some limitations. These findings also provide the observational basis for the possibility of using with high confidence self-tests harboring 3 bands of interest, *i.e.* in the case of the prototype COVID-19 self-test, the control, IgG and IgM bands. Finally, our observations lay the foundations for the potential large-scale use of COVID-19 self-test in lay adults, at least Europeans, to complete the arsenal of available serological tests used to assess the immune status vis-a-vis SARS-CoV-2.

Substudy 1. The learning process in different fields of science needs to link theory to practice [29]. The expected results of substudy 1 are, therefore, important for the following practicability substudies 2 and 3, because it is mandatory to check that the instructions for use

354 can be read and understood by all users. Our findings showed that 89.2% of participants
355 correctly answered all 10 questions indicating generally correct understanding of the key
356 messages delivered by the instructions for use of the Exacto® COVID-19 self-test (Biosynex
357 Swiss SA), with an overall rate of good responses of 97.1%. These satisfactory results may be
358 explained in part by the high post-graduate education level of the majority of study participants.
359 Indeed, previous experience from HIV self-testing showed that insufficient educational level
360 constitutes a great challenge in the comprehension of the instructions for use [18,30-32].
361 Although systematic reviews and meta-analysis have shown that HIV self-testing can be
362 successfully conducted by untrained users without in-person demonstrations [31], our
363 observations emphasize the need to complete the classical paper instructions for use by other
364 instructional tools such as short video film, which was preferred by 1 of 13 study participants
365 for better instructions for use understanding. These findings are reminiscent to previous WHO
366 recommendations for HIV self-test stating that all self-testers should have the possibility to
367 access or receive assistance over the phone, through the internet, or with additional instructions
368 such as video, animations, or diagrams [15].

369 **Substudy 2.** All study participants carried out the COVID-19 self-test and
370 succeeded in obtaining a valid test result with an overall usability index estimated at 98.5%.
371 Some difficulty in the correct use of the pipette to transfer the blood sample was the principal
372 reported concern encountered and was the most common reason for oral help. In previous
373 reports on HIV self-testing, the difficulties in self-lancing and blood transfer to the cassette
374 were also observed by lay users [33]. These features underline the importance of video
375 instructions, when available. In the present series, all participants using the video instructions
376 did not need any help and used the pipette without any difficulty or error. The use of a hotline
377 could also offer direct distant assistance.

Substudy 3. The ability to correctly read and interpret the self-test results is considered as a [illegible]cate step in self-testing [34]. This refers not only to the visual subjectivity related to good visual acuity (*i.e.* eye without illness) when reading and interpreting the results, but also to the number of bands to read on the test strip. Indeed, the Exacto® COVID-19 self-test (Biosynex Swiss SA) has three bands, one of which is for the internal control and two for the detection of IgG and IgM antibodies. The interpretation of a weak positive band may be therefore difficult for untrained users. In our series, the rate (98.8%) of correct interpretation of COVID-19 self-test results was high, as previously reported with HIV self-test using similar cassette [17,18]. However, the majority (80%) of misinterpreted test results concerned a weak positive IgM band. This difficulty in reading some weak positive bands and in final interpretation of test results can even occur in lay users as well as trained-users during professional testing [35].

On the other hand, the interpretation of positive results with the serological IgM and IgG test of SARS-CoV-2 presents particularities in this period of the ongoing outbreak. While positive serology for other viral infections such as HIV means an active infection [36], a positive test result with the Exacto® COVID-19 self-test (Biosynex Swiss SA) rather indicates ongoing or previous SARS-CoV-2 infection, with serological immune IgG or IgM immune responses to SARS-CoV-2. Furthermore, the p[illegible]ence of IgM alone or with IgG means that the contact with the virus was relatively recent. The presence of IgG means that the contact with the virus occurred at least 14 days ago [37]. Thus, a positive test result on the COVID-19 self-test does not mean that the SARS-CoV-2 infection is still active. Despite the explanations were clearly given in the instructions for use, 10.2% of study participants were not aware that the COVID-19 self-test does not detect the presence of the virus. This misinterpretation of positive test results can provide unfortunate consequences such as self-medication or neuro-p[illegible]hiatric disorders of variable intensity, especially in a person not psychologically prepared [38].

Substudy 4. The pre-test and post-test answers to the satisfaction questionnaire concerning the instructions for use (substudy 1), performing the self-test (substudy 2), and the interpretation of the results (substudy 2), showed that the large majority of the COVID-19 self-testing steps were considered easy by participants, as previously reported for HIV self-testing using similar rapid test cassette [17,18]. However, the satisfaction with sample collection and blood transfer to the test cassette evolved from "very easy" in pre-test period to "rather easy" after having performed the self-test. This latter observation reminds us our previous experience with HIV self-testing, during which the fear of self-sticking provided capillary blood sample collection difficult in a minority of lay user [18].

Strengths and limitations. Our study is original by highlighting for the first time the usability of COVID-19 self-test, as a novel approach to assess SARS-CoV-2-specific humoral immunity by using rapid diagnostic test and self-interpretation of the results. Our study also shows for the first time the possibility of correctly interpreting three bands on the strip of a rapid diagnostic test by lay users from general adult population. However, the study has some limitations. First, the presence of an observer may lead to a bias in our observations concerning the participants' ability to perform the tests and to interpret the results. Furthermore, the low sample size could reduce the study's power. Finally, further steps are needed to improve mass screening for COVID-19, including the development of other tests such as oral fluid based self-testing, antigen self-testing, as well as home self-sampling.

According to the WHO [39], generalization of COVID-19 testing is key to controlling the spread of SARS-CoV-2 infection. In particular, the findings derived from serological assays can provide valuable information that would help to support the diagnosis, treatment and prevention of SARS-CoV-2 infection [40]. During the COVID-19 epidemic, optional approaches using individual involvement were proposed in addition to the collective public health approach, and both strategies were furthermore sometimes combined. For example, self-

collected upper respiratory tract swabs for COVID-19 test has been shown as a feasible way to increase overall testing rate in South Africa [41], and the US Food and Drug Administration has approved the first kit for self-collected saliva specimen to be used for molecular testing of SARS-CoV-2 [42]. Self-diagnosis of breathing complications from breathing sounds using the smartphone's microphone has been proposed as an appealing resolution for COVID-19 self-testing [43]. Self-reporting of an illness consistent with COVID-19 and artificial intelligence-coupled self-testing and tracking systems for COVID-19 have been developed using mobile phone applications [44,45]. While the place of SARS-CoV-2-specific serology remains controversial [46,47], the indications for the COVID-19 serological self-test have been the matter of poor attention from official agencies until now and remain to be defined [48]. It seems obvious that the motivations for carrying out a COVID-19 self-test would be clearly different than those which push to carry out an HIV self-test, but this problematic exceeds the aim of our study. The COVID-19 self-test allows an individual to test himself simply and quickly, without visiting a care structure, with the essential aim of knowing if the person is in the course of infection (presence of specific IgM alone) or has made a past infection (presence of specific IgG, alone or associated with IgM). Thus, COVID-19 self-test for serological screening could be proposed to identify exposed patients that are presumptively immune to SARS-CoV-2 secondary to ongoing or past-infection and to quantify the prevalence of exposure within a population for epidemiologic purposes. The instructions for use clearly explains that the lack of reactivity does not eliminate a SARS-CoV-2 infection in progress, and that in the presence of any IgG or IgM reactivities the patient must refer to a health care structure for clinical-biological confirmation. In any case, the presence of reactivities could constitute an "immunological passport" of protection [46,47], because it is not known if anti-SARS-CoV-2 antibodies are protective at this time, although the general assumption is that the presence of antibodies will provide at least some immunity [49]. While specific guidelines regarding how

453 "presumptive immunity" will be determined and used do not exist, this potential use has
454 probably generated the most excitement in the lay public [47]. In any case, an IgG positive
455 COVID-19 self-test result may indicate recovery of a previous SARS-CoV-2 infection, even
456 asymptomatic or mild, and would allow to take more moderate precautions and also to
457 comfortably interact with other COVID-19-seropositive individuals. Interestingly, serological
458 home testing could be associated with at-home saliva or swab self-sampling for further SARS-
459 CoV-2 molecular diagnosis, and the widespread use of both home approaches would be hugely
460 beneficial to public health. Those whom the viral test indicates an active SARS-CoV-2 infection
461 (including silent carriers and patients with early or mild symptoms) will be able to take
462 informed actions, such as self-isolation. Furthermore, the risk exposure of the healthy
463 population will be mitigated by the actions taken by the (informed) infected population, thus
464 slowing the spread of the coronavirus and flattening the curve. Importantly, a confirmed
465 population of "recovered" individuals would allow many to return to work, lead to partial lifting
466 of "stay-at-home" or "shelter-in-place" orders, and would help get the economy back to normal,
467 with no loss in protection for the most vulnerable. Recently, the British government, UK, are
468 making available SARS-CoV-2 antibody home tests for healthcare workers and the general
469 public [50]. Home testing will be voluntary, but there is no doubt more people will test if the
470 tests are free. Removing financial barriers to self-testing by making publicly-funded tests
471 available free to the entire population will help maximize rapid implementation and help
472 COVID-19-affected country to recover and get back to work.

473 Until a cure or a vaccine becomes available, antibody and viral testing for SARS-CoV-
474 2 infection will play a critical role in limiting the pandemic and containing its economic damage
475 to individuals and the country. Our features demonstrate that COVID-19 self-testing for
476 serological immune status assessment is highly feasible with potential for use by the general
477 public. If deployed wisely, it will be complementary to other serological screening tools and

could offer an immediate and easy solution for SARS-CoV-2 serology, especially during recovery or de-confinement periods.

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Instruction for use of the EXACTO COVID-19 SELF-TEST

Exacto

COVID-19 SELF-TEST

INTRODUCTION

Exacto® COVID-19 self-test is a rapid immunochromatographic self-test for the qualitative detection of IgG and IgM antibodies against SARS-CoV-2 from a drop of capillary blood. The test contains viral antigens specific to IgG and IgM antibodies of SARS-CoV-2. This self-test determines whether you have been in contact with the virus responsible for COVID-19.

COVID-19 is an acute respiratory illness caused by infection with SARS-CoV-2. SARS-CoV-2 belongs to the same family of viruses that cause Severe Acute Respiratory Syndrome (SARS). The most common symptoms of COVID-19 are fever, fatigue and a dry cough. Some patients may experience pain, nasal congestion, runny nose, sore throat, diarrhea and loss of taste and smell. These symptoms are usually mild and begin gradually. Some people are infected but do not develop any symptoms. Most people (about 80 %) recover from the disease without the need for hospital care.

The disease can be spread from person to person through small droplets emitted from the nose or mouth when a person infected with COVID-19 coughs or exhales. Transmission through contact of contaminated hands with the face is common. Hands can become contaminated after touching surfaces that carry the virus. The estimated incubation period for COVID-19 ranges from 1 to 14 days.

The Exacto® COVID-19 self-test, based on antibody detection, can identify individuals who are unaware that they have been infected, either because they have never developed symptoms or because they have symptoms that have never been properly diagnosed. This means that self-testing can identify silent infections, as well as people who have been sick but have recovered. **This self-test does not detect the presence of the virus responsible for COVID-19, but it does detect the response of a patient's immune system against this COVID-19 virus.**

The Exacto® COVID-19 self-test will give a positive result in the majority of cases within 11 days of the onset of symptoms.

A negative result with Exacto® COVID-19 "test in a symptomatic individual does not exclude COVID-19 infection. If symptoms suggestive of COVID-19 are present, a negative result should be followed up with a second test 11 days after the first test.

KIT CONTENTS

TESTING GUIDELINES

-Wash your hands with warm water beforehand and dry them properly. Warm water improves circulation at the fingertips.

-You can let your hand hang for about a minute along your body so that more blood can flow into it. It is recommended that you prick your left hand for a right-handed person and your right hand for a left-handed person.

-If a best to prick the fingertip on the side, this is where there is the most blood and less sensitivity. Avoid areas where the skin is thicker and therefore more difficult to prick.

-It may happen that a drop does not form right away. In this case, you should wait a while and massage your finger lightly from the base to the puncture site.

-Do not hesitate to form large drop of blood at the tip of your finger. This way the pipette will fill up with blood easily and quickly.

BLOOD COLLECTION

1. **Please read the entire manual.** Ensure you have a watch or a stopwatch.
2. Wash your hands with soap and warm water and dry them before proceeding to the next step.
3. Open the box and **remove all items from their packaging.** Don't forget to remove the pipette and lancet from the bag. Place them on a clean, flat surface, identify each item in the kit.

4. Tear the notch in pouch A. Remove cassette B. Use the test within one hour.

5. Unscrew the cap of the diluent bottle C and place it vertically on the work surface.

6. Disinfect the fingertip with the alcohol wipe E.

7. Wipe off traces of disinfectant the compress F.

8. Remove the cap of the lancet G by pulling it off.

9. Place the lancet G against your fingertip (the end covered by the cap is pressed against the finger) and press down firmly to trigger the device and prick your finger.

10. **Squeeze the pricked fingertip strongly** to form a **large drop** of blood at the tip.

11. The pipette D fills automatically at blood contact with the blood drop. **Do not press or pull the plunger.**

Fill pipette D completely with blood up to the white filter.

TEST PROCEDURE

12. Empty the contents of the pipette into the square **cassette** well (a) **reserve** B by **pressing the white pipette plunger.**

13. Place **3 drops** of diluent C in the round **«Diluent»** well (b) reserve B. Leave your cassette on a flat surface.

14. Start the stopwatch or note the time. **Wait 10 minutes to read the result.** Do not read beyond 20 minutes. During this time, you can apply the dressing H.

PERFORMANCE

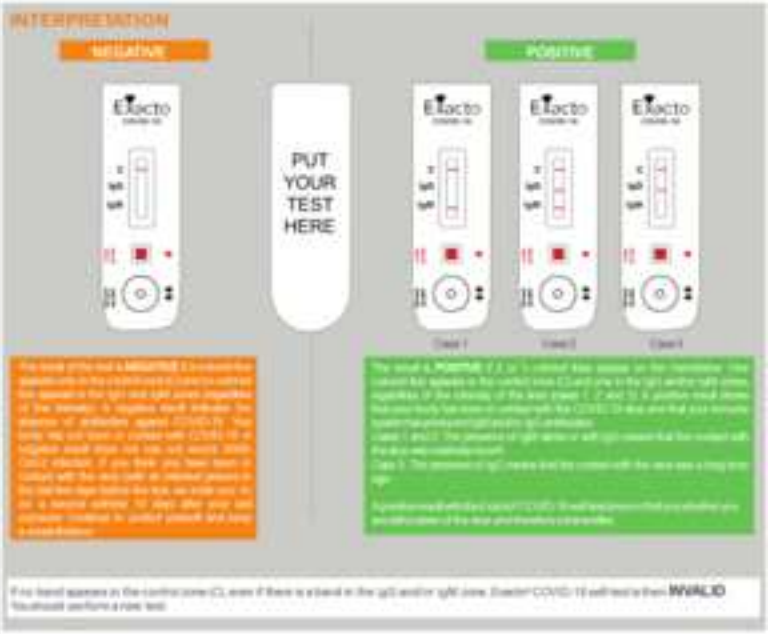
Sensitivity and specificity

Exacto® COVID-19 self-test was compared to the clinical diagnosis (confirmed). The study involved 440 samples for IgG and 438 samples for IgM.

	Sensitivity	Specificity	Accuracy
IgG	100 %	98.3 %	98.8 %
IgM	91.8 %	98.2 %	97.8 %

- A practicability study conducted with a layman population showed that 100 % of participants obtained a correct and interpretable result.
- A readability study confirmed that 99.1 % of the different types of results were interpreted correctly.

INTERPRETATION



If no band appears in the control zone (C), even if there is a band in the IgG and/or IgM zone, Exacto® COVID-19 self-test is then **INVALID**. You should perform a new test.

- Do not interpret the Exacto® COVID-19 self-test if blood is dispensed in the round «DILUENT» well and the diluent in the square «BLOOD» well. In this case, the round «DILUENT» well will be red. You should perform a new self-test or go to a laboratory or to your doctor.
- To dispose of your test and its components, please refer to the rules in force in your country.

BIOSYNEX SWISS SA, FRIBOURG - SUISSE

Fig 2

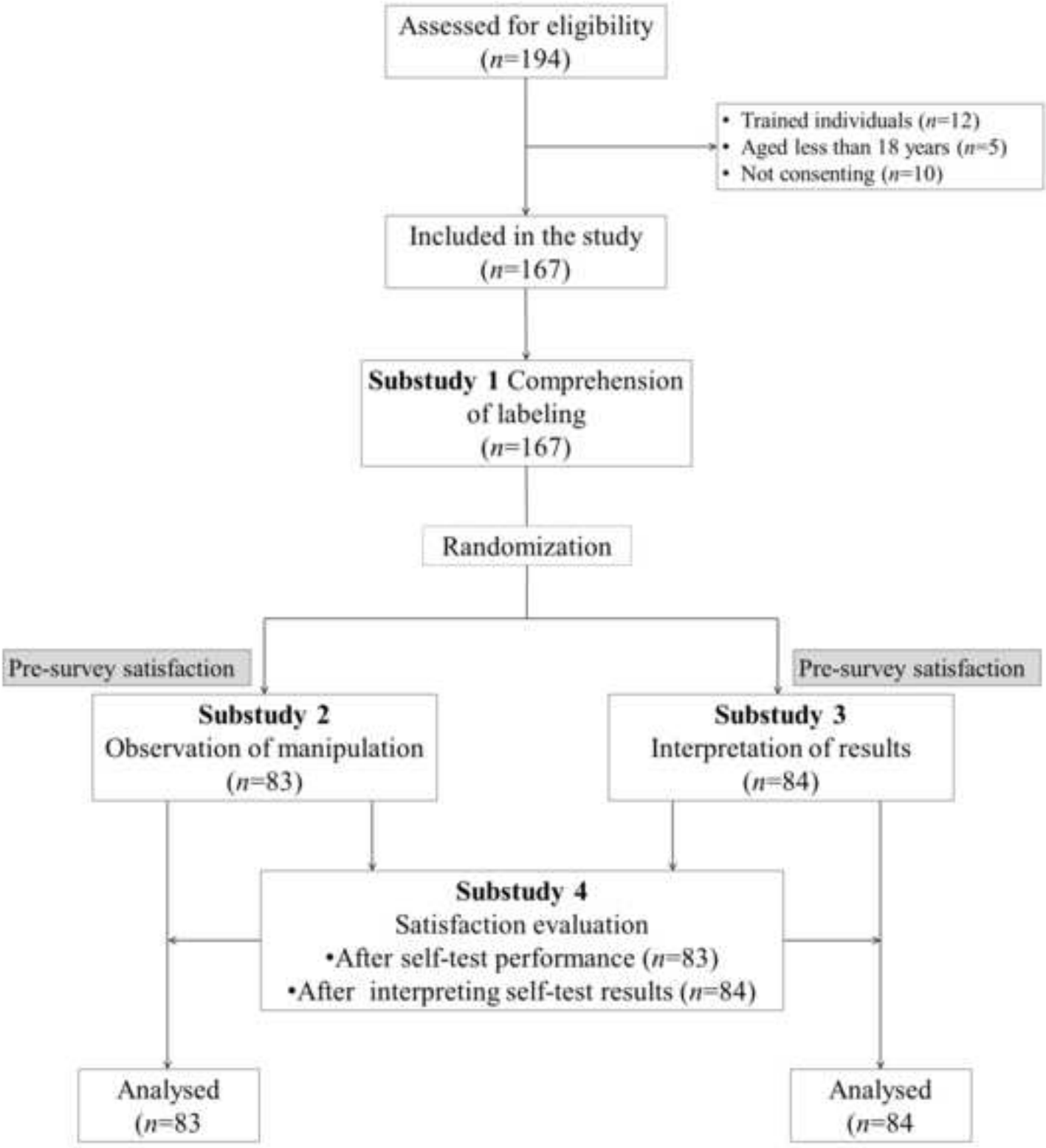


Fig 3

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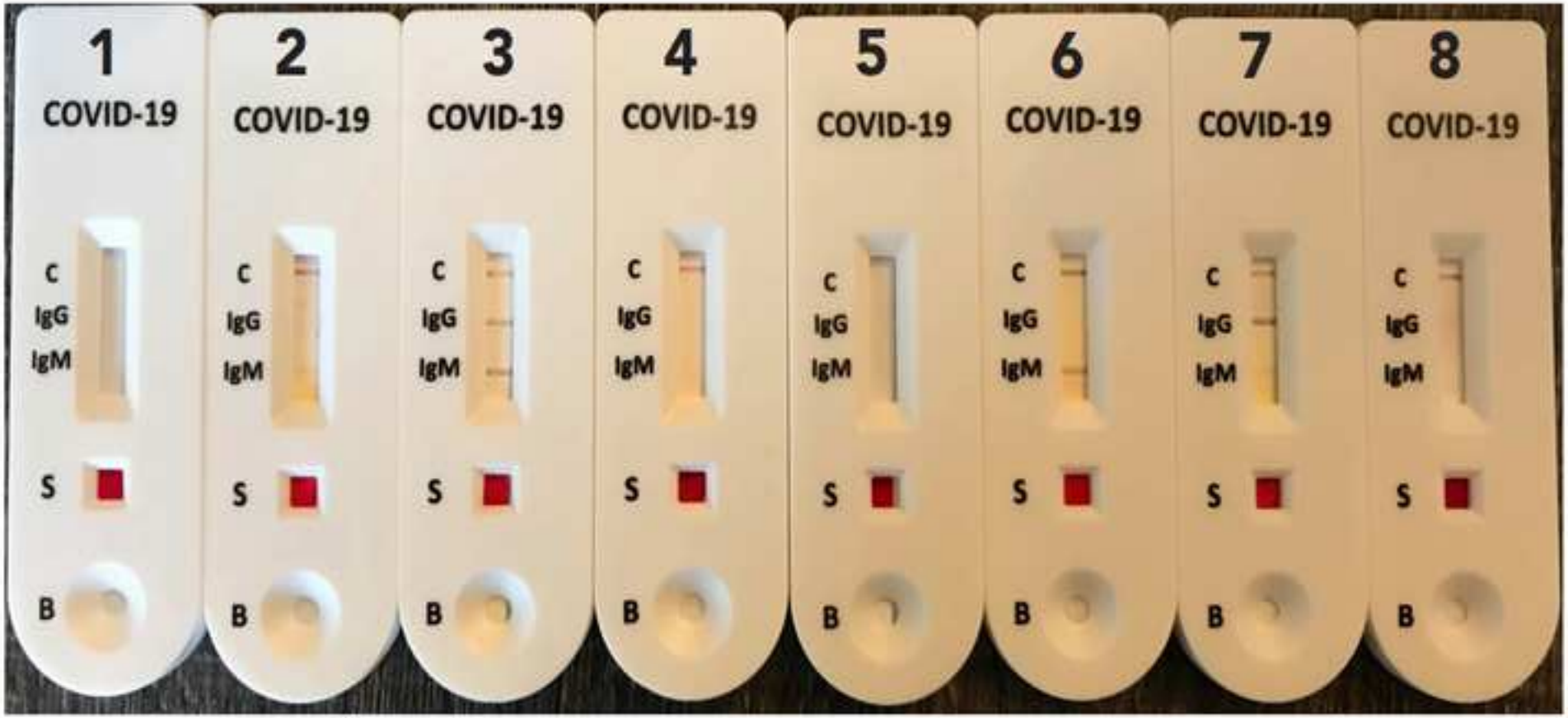

Fig 4

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