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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

--Manuscript Draft--

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Full Title:	Capillary whole-blood IgG-IgM COVID-19 self-test as a serological screening tool for SARS-CoV-2 infection adapted to the general public
Short Title:	Practicability of COVID-19 self-test
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Keywords:	SARS-CoV-2; COVID-19, Serology; IgG; IgM; Rapid Diagnostic Test; Self-testing; Practicability; France
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. Practicability was defined as the correct use of the self-test and the correct interpretation of the result. The correct use of self-test was conditioned by the presence of the control band after 15-min of migration. The correct interpretation of the tests was defined by the percent agreement between the tests results read and interpret by the participants compared to the expected results coded by the numbers and verified by trained observers. 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. The percent agreement between the tests results read and interpret by the participants compared to the expected results was 98.5% (95% CI: 96.5–99.4) . However, 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.
Order of Authors:	Serge Tonen-Wolyec
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Response to Reviewers:	Responses to journal requirements and to Reviewers Journal Requirements: When submitting your revision, we need you to address these additional requirements. 1. Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming. The PLOS ONE style templates can be found at https://clicktime.symantec.com/3Ab2UDzwphFJFJ5wTH8Dthe6H2?u=https%3A%2F%2Fjournals.plos.org%2Fplosone%2Fs%2Ffile%3Fid%3DwjVg%2FPLOSOne_formatting_sample_main_body.pdf and https://clicktime.symantec.com/3J1bpueumkNeCCUwpeXGyX66H2?u=https%3A%2F

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Our answer: We have checked that the manuscript meets the PLOS ONE'S requirements, including file names and affiliations.
2. Please include additional information regarding the survey or questionnaire used in the study and ensure that you have provided sufficient details that others could replicate the analyses.
For instance, if you developed a questionnaire as part of this study and it is not under a copyright more restrictive than CC-BY, please include a copy, in both the original language and English, as Supporting Information.
Our answer: As requested, the study questionnaires in French (original language) as well as in English have been uploaded in the submission system, as supporting information.
3. Thank you for stating the following in the Acknowledgments Section of your manuscript:
'Dr. Serge Tonen-Wolyec was recipient of ERASMUS+ program between the University of Kisangani, Democratic Republic of the Congo, and the University of Liège, Belgium.'
We note that you have provided funding information that is not currently declared in your Funding Statement. However, funding information should not appear in the Acknowledgments section or other areas of your manuscript. We will only publish funding information present in the Funding Statement section of the online submission form.
a. Please remove any funding-related text from the manuscript and let us know how you would like to update your Funding Statement. Currently, your Funding Statement reads as follows:
'The authors received no specific funding for this work.'
Our answer: In order to acknowledge the journal requirement, we have removed any funding-related test from the manuscript and we have updated our Funding Statement as follow: "This work was partly supported by Biosynex SA. The funders played a role in providing the prototype SARS-CoV-2 test for self-test (Exacto® COVID-19 self-test, Biosynex Swiss SA) and data collection. The study design, analysis, decision to publish, and preparation of the manuscript were not sponsored. Biosynex SA also provided support for this study in the form of salary for Dr. Raphael Dupont. The specific role of this author is articulated in the 'author contributions' section. Dr. Serge Tonen-Wolyec was recipient of ERASMUS+ program between the University of Kisangani, Democratic Republic of the Congo, and the University of Liège, Belgium. There was no additional external funding received for this study."

b. Please include your amended statements within your cover letter; we will change the online submission form on your behalf.
Our answer: We have included our amended Funding statement within our cover letter.
4. Thank you for stating the following in the Competing Interests section:
'The authors have declared that no competing interests exist.'
We note that one or more of the authors are employed by a commercial company: BioSynex
a. Please provide an amended Funding Statement declaring this commercial affiliation, as well as a statement regarding the Role of Funders in your study. If the funding organization did not play a role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript and only provided financial support in the form of authors' salaries and/or research materials, please review your statements relating to the author contributions, and ensure you have specifically and accurately indicated the role(s) that these authors had in your study. You can update author roles in the Author Contributions section of the online submission form.
Please also include the following statement within your amended Funding Statement.
"The funder provided support in the form of salaries for authors [insert relevant initials], but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section."
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Our answer: The authors have read the journal's policy and have the following competing interests: Dr. Raphael Dupont is a paid employee of Biosynex SA. The authors would like to declare the following patents/patent applications associated with this research: https://bases-marques.inpi.fr/Typo3_INPI_Marques/ajoutListe?page=1&idObjet=1484785_202032_tmint&scroll=462.4761962890625. This does not alter our adherence to PLOS ONE policies on sharing data and materials. We have added this highlighting in our cover letter and online submission.
5. PLOS requires an ORCID iD for the corresponding author in Editorial Manager on papers submitted after December 6th, 2016. Please ensure that you have an ORCID iD and that it is validated in Editorial Manager. To do this, go to 'Update my Information' (in the upper left-hand corner of the main menu), and click on the Fetch/Validate link next to the ORCID field. This will take you to the ORCID site and allow you to create a new iD or authenticate a pre-existing iD in Editorial Manager. Please see the following video for instructions on linking an ORCID iD to your Editorial Manager account: https://clicktime.symantec.com/3QJAoi3RwJ4rwEt9UViL8wS6H2?u=https%3A%2F%2Fwww.youtube.com%2Fwatch%3Fv%3D_xcclfuvtxQ
Our answer: We have added a validated ORCID iD (https://orcid.org/0000-0002-5001-0405) of the corresponding author in Editorial Manager.

Reviewers' comments:

Reviewer's Responses to Questions

Comments to the Author

1. Is the manuscript technically sound, and do the data support the conclusions?
The manuscript must describe a technically sound piece of scientific research with data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.
Reviewer #1: Partly
Reviewer #2: Partly
Our answer: We thank the reviewers for their nice comments on our work. However, in order to acknowledge the comments raised by referees, we have made corrections thorough the manuscript; therefore, we hope that our revised manuscript is more technically sound.
2. Has the statistical analysis been performed appropriately and rigorously?
Reviewer #1: Yes
Reviewer #2: Yes
Our answer: We thank the reviewers for their nice comments on our work.

3. Have the authors made all data underlying the findings in their manuscript fully available?
The PLOS Data policy requires authors to make all data underlying the findings described in their manuscript fully available without restriction, with rare exception (please refer to the Data Availability Statement in the manuscript PDF file). The data should be provided as part of the manuscript or its supporting information, or deposited to a public repository. For example, in addition to summary statistics, the data points behind means, medians and variance measures should be available. If there are restrictions on publicly sharing data—e.g. participant privacy or use of data from a third party—those must be specified.
Reviewer #1: Yes
Reviewer #2: Yes
Our answer: We thank the reviewers for their nice comments on our work.

4. Is the manuscript presented in an intelligible fashion and written in standard English?
PLOS ONE does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors here.
Reviewer #1: No
Reviewer #2: Yes
Our answer: In order to acknowledge the comments raised by Reviewer # 1, we have corrected words and grammar as suggested by Referee. We hope that our revised manuscript is presented in an intelligible fashion and written in standard American English.

5. Review Comments to the Author
Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)

Answer to reviewer #1

This study is potentially one of several necessary but not sufficient steps towards translation to practice. However, the discussion must be made much more conservative. The extensive speculation on the role of home serology testing could create safety problems and is of major concern.

Our answer: The remark of the reviewer is right. To acknowledge the reviewer's concern, we have completed the Strengths and limitations section by adding the following paragraph: "The role of the COVID-19 self-test in fighting the epidemic, caring for infected people and preventing risk of transmission is not yet known. The possible risk of adverse effects of the COVID-19 self-test should not be underestimated, such as a pseudo-insurance of immunity or non-contagiousness. Furthermore, there is limited understanding of adult public acceptability and usability of rapid diagnostic tests in the home setting, as most are currently designed as professional use to be carried out by healthcare professionals. It will of course be necessary to precisely assess all these potential perverse effects. However, the place of the COVID-19 self-test could simply be a complementary public health tool. Indeed, testing a large number of individuals for serological survey for example would be impractical if a blood sample is required for SARS-CoV-2 serologic testing in a laboratory. The solution to use self-sampling and self-testing with participants reporting their results to the clinicians or epidemiologists has been recently reported in a nationally representative serosurvey of SARS-CoV-2 in adults in England, demonstrating its full feasibility [Atchison et al., 2020]."
Atchison C, Pristerà P, Cooper E, Papageorgiou V, Redd R, Piggin M, Flower B, Fontana G, Satkunarajah S, Ashrafian H, Lawrence-Jones A, Naar L, Chigwende J, Gibbard S, Riley S, Darzi A, Elliott P, Ashby D, Barclay W, Cooke GS, Ward H. Usability and acceptability of home-based self-testing for SARS-CoV-2 antibodies for population surveillance. Clin Infect Dis. 2020 Aug 12:ciaa1178. doi: 10.1093/cid/ciaa1178.
Highlight [page 8]: 98.5% (95% CI: 96.5–99.4) test results were correctly interpreted, while misinterpretation occurred in only…

Note [page 8]: L47. What is the definition of the correct interpretation of the test?
Our answer: Since the expected results were known from the code numbers of the eight standardized tests, the correct interpretation of the tests was defined by the percent agreement between the tests results read and interpreted by the participants compared to the expected results coded by the numbers and verified by observers. Thus, misinterpretation corresponded to the percent disagreement between the test results read and interpret by the participants and the expected results coded by the numbers. We have added these clarifications in the abstract and the body of the text.

Note [page 10]: L88 Change ‘as’ to ‘as well as’

Highlight [page 10]: HIV self-testing has demonstrated high acceptability with very convenient usability in various adolescent and adult profane populations from developed as resources- constrained settings [17-21].
Note [page 10]: L88 profane? Don’t think you mean this- suggest remove this word.
Our answer: We have corrected the sentence, as suggested.
Highlight [page 11]: 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.
Note [page 11]: L 119: Have these results been peer reviewed and published elsewhere? If so please provide reference? Why not publish the this study and the performance characteristics of the test in the same paper? They ideally need to be assessed together.
Our answer: While the purpose of our study was not to assess the virological analytical performances of the BIOSYNEX® COVID-19 BSS (IgG/IgM) (Biosynex Swiss SA), this rapid diagnostic test has been fully recommended for both SARS-CoV-2-specific IgG and IgM detection by the French Ministry of Health (https://covid-19.sante.gouv.fr/tests. ; last access 25 August 2020), following an official report from the National Reference Center for Respiratory Viruses [Centre National de Référence Virus des infection respiratoires (dont la grippe)], Institut Pasteur, Paris. We have added this information in the text.

Highlight [page 11]: The online instruction in the video for use was available online from Youtube [24].

Note [page 11]: When the QR code on Figure 1 is scanned it says the video has been taken down. Please provide the video or QR code. Ideally the video could be permanently attached to this paper by the journal rather than relying on a Youtube video that could be taken down again.

Note [page 12]: 132 See latter suggestions about moving full instructions to supplementary materials and using just top half of interpretation panel as Fig 1. Legend needs to state that this was the exact instructions provided to the subjects in this study in both legends.
Our answer: In order to acknowledge the comments raised by Reviewer # 1, we have moved the full instruction for use to supplementary materials. Furthermore, we have provided the video instruction as its supporting information file.

Note [page 12]: L 134: simplify this phrase

Highlight [page 12]: 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 neighborhoods of Strasbourg and its suburbs,…
Our answer: We have simplified this sentence as suggested.

Note [page 12]: How were these neighborhoods selected? Was there a wide range of socio-economic and eductaional status and was this representative of developed countries in Northern Europe? Will need a discussion on how generalizable are these results likely to be.

Our answer: Due to the limited movement during the lockdown period, the choice of these neighborhoods and its suburbs was based on their easy accessibility and their

	high prevalence of reported cases of SARS-CoV-2 infection. We have added this sentence in the “Study design and recruitment of participants” section for more highlighting. Note [page 14]: L189: Change appeal for to provide Highlight [page 14]: 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. Our answer: We have changed the words as suggested. Note [page 14]: L196: change proposed to provided Highlight [page 14]: 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… Our answer: We have changed the words as suggested. Note [page 14]: L196: delete successive Note [page 14]: L201- 202: suggest change No to # Highlight [page 14]: 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). Our answer: We have changed the words as suggested. Note [page 14]: L202: change successively to randomly Highlight [page 14]: Each volunteer successively drew 4 tests among a panel of 8 and interpreted them with the help of the reading and interpretation scale. Our answer: We have changed the words as suggested. Note [page 15]: L228: change and to or Highlight [page 15]: excluded because they were trained (n=12), less than 18 years old (n=5), and not consenting (n=10). Our answer: We have changed the words as suggested. Note [page 18]: L277: delete HIV Highlight [page 18]: Overall, the mean time of HIV self-test performance (since the opening of the box until the migration step) was… Our answer: It was a mistake, we have deleted it. Note [page 19]: L293: delete successive- not clear what this means Highlight [page 19]: COVID-19 self-test results after successive random selection of four tests from a panel of eight standardized tests. Our answer: We have deleted it. Note [page 20]: L308: would be interesting to know if there were any differences in the results from substudy 4 for those previously in subsidy 2 versus 3. Highlight [page 20]: Substudy 4. Our answer: We did not assess such comparisons. Note [page 22]: L349 Europeans of high educational attainment Highlight [page 22]: 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.
Our answer: We thank the reviewer for this clarification, which we have added to the text.

Note [page 23]: L 376: ..error, however numbers in this group were small.

Highlight [page 23]: In the present series, all participants using the video instructions did not need any help and used the pipette without any difficulty or error.
Our answer: We have added this precision related to the small sample size in this discussion as follows: “Although a small sample size of participants used the video instructions in this series, all of them did not need any help and used the pipette without any difficulty or error.”

Note [page 24]: L379: Change delicate to critical

Highlight [page 24]: considered as a delicate step in self-testing [34].
Our answer: We have changed the words as suggested.

Note [page 24]: L395 to 396: Is this really established for SARS-CoV-2 infection. Please provide references

Highlight [page 24]: Furthermore, the presence of IgM alone or with IgG means that the contact with the virus was relatively recent.
Our answer: To acknowledge the reviewer’s remarks, we completed as follows: “Furthermore, according to the kinetic profile of the systemic humoral response against SARS-CoV-2 and the lifespan of circulating immunoglobulins, the presence of IgM alone or with IgG means that the contact with the virus was relatively recent [37]”.

Note [page 24]: L401: Change neuropsychiatric disorders to psychological distress and not psychologically prepared to who has not received pre-test counseling.

Highlight [page 24]: This misinterpretation of positive test results can provide unfortunate consequences such as self-medication or neuro-psychiatric disorders of variable intensity, especially in a person not psychologically prepared [38].
Our answer: We have changed the sentence as suggested.

Note [page 25]: L419: limit the study’s power to detect….what?

Highlight [page 25]: Furthermore, the low sample size could reduce the study’s power.
Our answer: The low sample size could reduce the study’s power to detect a relative difference between groups with high precision.

Note [page 25]: L425: novel rather than original

Highlight [page 25]: During the COVID-19 epidemic, original approaches using individual involvement were proposed in addition to the collective public health approach, and both strategies were furthermore sometimes combined.
Our answer: We have changed the words as suggested.

Note [page 26]: L439: suggest delete ‘, but this….study”

Highlight [page 26]: 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.
Our answer: We have deleted the sentence as suggested.

Note [page 26]: L442: change has made too had

Highlight [page 26]: 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 (…
Our answer: We have changed the words as suggested.

	Note [page 26]: L443: Need to emphasize that it is not yet known if antibodies are protective and if so how durable this protection is and if antibodies guarantee they cannot infect others. Must emphasize the importance of conveying this to the subjects self-testing and of their need to continue to take precautions to protect themselves and others. Highlight [page 26]: Thus, COVID-19 self-testing 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 epi… Our answer: To acknowledge these reviewer's remarks, we have added the following sentence: "However, it should be emphasized that the level of protection of seropositivity for SARS-CoV-2 as well as its duration are not known, and even that the presence of specific antibodies does not mean that the person is not contagious, particularly in onset of infection. It will therefore be important to pass this information on to subjects who self-test so that they continue to take precautions to protect themselves and others." Note [page 26]: L448: "refer.." change to seek confirmatory antibody test by a clinical laboratory and clinical follow-up" Need to comment on the burden this will place on the health care system. Highlight [page 26]: 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… Our answer: We have changed the sentence as suggested, and added that "which could contribute to accentuating tensions in the healthcare system, in particular during epidemic periods". Note [page 26]: L449: change to It should be emphasized that it is not known if a positive antibody test represents protection and the concept of an "immunological passport" cannot be supported at this time. Highlight [page 26]: 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 antibod… Our answer: We have deleted the ambiguous sentence: "…..because it is not known if anti-SARS-CoV-2 antibodies are protective at this time…..". Note [page 27]: L454 Change most excitement to interest Highlight [page 27]: "presumptive immunity" will be determined and used do not exist, this potential use has probably generated the most excitement in the lay public [47]. Our answer: We have changed the words as suggested. Note [page 27]: L456-457: delete: …and would…individuals" No evidence to support his statement. Highlight [page 27]: In any case, an IgG positive COVID-19 self-test result may indicate recovery of a previous SARS-CoV-2 infection, even asymptomatic or mild, and would allow to take more moderate precautions and also to comfortably interact with other COVID-19-seropositive individuals. Our answer: We have deleted it as suggested. Note [page 27]: L459: delete would be hugely beneficial to public health. The is conjecture. Suggest 'is worthy of further study' Highlight [page 27]: Interestingly, serological home testing could be associated with at-home saliva or swab self-sampling for further SARS- CoV-2 molecular diagnosis, and the widespread use of both home approaches would be hugely beneficial to public health. Our answer: We have corrected the sentence as suggested.

Note [page 27]: L461: should consider themselves potentially infected and self-isolate until the results of clinical testing for the virus is known.

Highlight [page 27]: Those whom the viral test indicates an active SARS-CoV-2 infection (including silent carriers and patients with early or mild symptoms) will be able to take informed actions, such as self-isolation.
Our answer: We agree with the reviewer. We have changed “patients” by “individuals”.

Note [page 27]: L465: Change ‘would allow’ to ‘may facilitate’. All of this discussion is too much conjecture and should be toned down.

Highlight [page 27]: Importantly, a confirmed population of “recovered” individuals would allow many to return to work, lead to partial lifting of “stay
Our answer: We have corrected the sentence as suggested.

Note [page 27]: L451: change will to may and indicate how this could be study to support such policies. Discuss how cost-effectiveness would have to be studies.

Highlight [page 27]: Removing financial barriers to self-testing by making publicly-funded tests available free to the entire population will help maximize rapid implementation and help COVID-19-affected country to recover and get back to work.
Our answer: We have deleted this ambiguous sentence.

Note [page 27]: L476: change the general public to ‘by at least some groups with high levels of education.

Highlight [page 27]: Our features demonstrate that COVID-19 self-testing for serological immune status assessment is highly feasible with potential for use by the general public.
Our answer: We have changed the sentence as suggested.

Note [page 27]: L477: change will to may

Highlight [page 27]: If deployed wisely, it will be complementary to other serological screening tools and
Our answer: We have changed the word as suggested.

Note [page 28]: L478: change ‘offer an immediate and easy solution for’ to facilitate uptake of SARS-CoV-2 serology and delete rest of sentence.

Highlight [page 28]: could offer an immediate and easy solution for SARS-CoV-2 serology, especially during recovery or de-confinement periods.
Our answer: We have changed the sentence as suggested.

Note [page 33]: Figure 1. Impractical to include the entire instruction in the main body of the paper. It should be moved to supplementary materials. The top half of the interpretation panel with an appropriate legend would be more appropriate. Given this is the peer reviewed study examining the issue of interpretation the comment under performance about the 98.5% correct interpretation should be removed. Also the reference to support the performance characteristics of the test shown above that statement needs to be provided.

Highlight [page 34]: Click here to access/download;Figure;Fig…
None of these links worked on this version.
Our answer: As answered above, we have moved the full instruction for use to supplementary materials. And we have provided the video instruction as its supporting information file. However, we have added a Section A to the former Figure 3 (considered as a Section B) to present the interpretation of the results. Thus, this new figure is entitled Fig 2 in the revised version of our manuscript with legend written as follows: “Fig 2. Interpretation of self-test results. A. The self-test result was interpreted as negative when a Control line (C) was present and readable and the “IgG” and “IgM” lines were absent. It was positive when a “C” and “IgM” (clearly or poorly readable) (case 1), or “C” and “IgG”, or “C”, “IgM” (clearly or poorly readable), and “IgG” lines were present. Finally, it was invalid when the “C” line was absent regardless of the

	presence or absence of the “IgG” and/or “IgM” line. B. Panel of 8 Exacto® COVID-19 self-test (Biosynex Swiss SA) cassettes, including 4 positive tests (#2, #3, #6 and #7), 2 negative tests (#4 and #8) and 2 invalid tests (#1 and #5). The #2 and #37 are weakly positive for IgM. Each volunteer randomly 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”. Concerning the interpretation of results, since the expected results were known from the code numbers of the eight standardized tests, the correct interpretation of the tests was defined by the percent agreement between the tests results read and interpret by the participants compared to the expected results coded by the numbers and verified by observers. Thus, misinterpretation corresponded to the percent disagreement between the test results read and interpret by the participants and the expected results coded by the numbers. We have added these clarifications in the abstract and the body of the text. Finally, the virological analytical performances characteristic of the evaluated self-test are provided in the Material and methods section, in the Prototype SARS-CoV-2 test for self-testing. Answer to reviewer #2 The authors report on 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. They performed their evaluation of this test using a cross sectional, general adult population study between April and May 2020 in Strasbourg, France. The study design consisted of face-to-face, paper-based, semi-structured, and self administrated questionnaires. The study enrolled 167 participants of which 82% had a post-graduate level of education. The study evaluated the participants ability to use the test in a number of different testing settings. The authors conclude that 100% of the participants found that performing the self test was easy and 98% found that the interpretation of the self-test results are easy. Our answer: We thank the reviewer for this perfect summary of our study. While this study is very interesting and brings forward an important POC / self-administered SARS-COv-2 serological assay the authors failed to bench mark the antibody status to a gold standard lab based assay. The absence of this weakens their initial pilot findings. Does it bring value if people can follow directions and get a result if the test does not corelate highly to what would be considered a typical bench mark to an assay performed in the laboratory under a clinical standard? The absence of comparative data is a major flaw in the study design. Our answer: We thank the reviewer for this pertinent remark. However, the objective of this survey was to assess the ability of lay persons to perform or interpret a serological test for SARS-CoV-2 immunochromatography. It was not intended to conduct a self-test performance study as such a study would require a large enough sample size of positive individuals to properly estimate the sensitivity of the self-test. Although this survey was carried out during the epidemic period in France, it should be noted that at that time, only confirmatory molecular testing using RT-PCR was recommended for suspect cases according to the recommendations of the French government to avoid wastage of reagents. Reference serological testing for IgG antibodies to SARS-CoV-2 was only progressively implemented in France during the study period, to be only available at the end of May, after the beginning of the deconfinement. While the purpose of our study was not to assess the virological analytical performances of the BIOSYNEX® COVID-19 BSS (IgG/IgM) (Biosynex Swiss SA), this rapid diagnostic test has been fully recommended for both SARS-CoV-2-specific IgG and IgM detection by the French Ministry of Health (https://covid-19.sante.gouv.fr/tests. ; last access 25 August 2020), following an official report from the National Reference Center for Respiratory Viruses [Centre National de Référence Virus des infection respiratoires (dont la grippe)], Institut Pasteur, Paris. We have added this information in the text. Furthermore, in order to comply with the requirements of the ethical committee, all persons with a positive serological result were referred to the laboratory for diagnostic confirmation and to the hospital for management. In this study, 11 (13.3%) people had a positive result with the self-test and they were oriented to laboratory for result confirmation. We have added these details in the “substudy 2” sections of Methods and results in the revised manuscript.
Additional Information:	

Question	Response
Financial Disclosure Enter a financial disclosure statement that describes the sources of funding for the work included in this submission. Review the submission guidelines for detailed requirements. View published research articles from *PLOS ONE* for specific examples. This statement is required for submission and **will appear in the published article** if the submission is accepted. Please make sure it is accurate. **Unfunded studies** Enter: *The author(s) received no specific funding for this work.* **Funded studies** Enter a statement with the following details: • Initials of the authors who received each award • Grant numbers awarded to each author • The full name of each funder • URL of each funder website • Did the sponsors or funders play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript? • **NO** - Include this sentence at the end of your statement: *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.* • **YES** - Specify the role(s) played. * typeset	This work was partly supported by Biosynex SA. The funders played a role in providing the prototype SARS-CoV-2 test for self-test (Exacto® COVID-19 self-test, Biosynex Swiss SA) and data collection. The study design, analysis, decision to publish, and preparation of the manuscript were not sponsored. Dr. Serge Tonen-Wolyec was recipient of ERASMUS+ program between the University of Kisangani, Democratic Republic of the Congo, and the University of Liège, Belgium.
Competing Interests Use the instructions below to enter a competing interest statement for this submission. On behalf of all authors, disclose any competing interests that could be perceived to bias this work—acknowledging all financial support and any other relevant financial or non-financial competing interests. This statement **will appear in the published article** if the submission is	Dr. Raphael Dupont, who is an employee of Biosynex SA with a salary, had supervised the data collection in Strasbourg, especially during periods of confinement where the movement of individuals was restricted. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

accepted. Please make sure it is accurate. View published research articles from *PLOS ONE* for specific examples. **NO authors have competing interests** Enter: *The authors have declared that no competing interests exist.* **Authors with competing interests** Enter competing interest details beginning with this statement: *I have read the journal's policy and the authors of this manuscript have the following competing interests: [insert competing interests here]* * typeset	
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.

Format for specific study types **Human Subject Research (involving human participants and/or tissue)** • Give the name of the institutional review board or ethics committee that approved the study • Include the approval number and/or a statement indicating approval of this research • Indicate the form of consent obtained (written/oral) or the reason that consent was not obtained (e.g. the data were analyzed anonymously) **Animal Research (involving vertebrate animals, embryos or tissues)** • Provide the name of the Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board that reviewed the study protocol, and indicate whether they approved this research or granted a formal waiver of ethical approval • Include an approval number if one was obtained • If the study involved *non-human primates*, add *additional details* about animal welfare and steps taken to ameliorate suffering • If anesthesia, euthanasia, or any kind of animal sacrifice is part of the study, include briefly which substances and/or methods were applied **Field Research** Include the following details if this study involves the collection of plant, animal, or other materials from a natural setting: • Field permit number • Name of the institution or relevant body that granted permission	
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Describe where the data may be found in full sentences. If you are copying our sample text, replace any instances of XXX with the appropriate details. • If the data are **held or will be held in a public repository**, include URLs, accession numbers or DOIs. If this information will only be available after acceptance, indicate this by ticking the box below. For example: *All XXX files are available from the XXX database (accession number(s) XXX, XXX.*). • If the data are all contained **within the manuscript and/or Supporting Information files**, enter the following: *All relevant data are within the manuscript and its Supporting Information files.* • If neither of these applies but you are able to provide **details of access elsewhere**, with or without limitations, please do so. For example: *Data cannot be shared publicly because of [XXX]. Data are available from the XXX Institutional Data Access / Ethics Committee (contact via XXX) for researchers who meet the criteria for access to confidential data.* *The data underlying the results presented in the study are available from (include the name of the third party*	All relevant data are within the manuscript and its Supporting Information files.

and contact information or URL). • This text is appropriate if the data are owned by a third party and authors do not have permission to share the data. * typeset	
Additional data availability information:	

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. Practicability was defined as the correct use of the self-test and the correct interpretation of the result. The correct use of self-test was conditioned by the presence of the control band after 15-min of migration. The correct interpretation of the tests was defined by the percent agreement between the tests results read and interpret by the participants compared to the expected results coded by the numbers and verified by trained observers. 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. The percent agreement between the tests results read and interpret by the participants compared to the expected results was 98.5% (95% CI: 96.5–99.4) . However, 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 populations from developed as well 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], following an official report from the National Reference Center for Respiratory Viruses [*Centre National de Référence Virus des infection respiratoires (dont la grippe)*], Institut Pasteur, Paris, 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

136 in French and English, in A3 format color printing. As an example, the paper-based and video-
137 based instructions for use are depicted as S1 and S2 appendix.
138
139 **Study design and recruitment of participants.** The practicability evaluation
140 of the Exacto® COVID-19 self-test (Biosynex Swiss SA) cross-sectional study, consisting
141 of face-to-face, paper-based, semi-structured, and self-administrated questionnaires. This
142 survey was performed between April and May 2020 by home-based recruitment of adult
143 volunteers using a door-to-door community approach, in 15 neighborhoods of Strasbourg and
144 its suburbs, France. Due to the limited movement during the confinement period in France,
145 especially in the province of Alsace (now "Grand Est") for which Strasbourg is the capital city,
146 the choice of these neighborhoods and its suburbs was based on their easy accessibility and
147 their high prevalence of reported cases of SARS-CoV-2 infection [24].
148 All participants accepted voluntarily to be included. Eligible participants had an age ≥
149 18 years, wanted to know their SRAS-CoV-2 serology status, were capable to speak and read
150 in French, and gave their consent to participate in the study. All trained individuals (physicians,
151 nurses, and biologist) in rapid diagnostic tests were excluded. Informed written consent was
152 signed by all participants. Ethical approval for this study was obtained from the local scientific
153 committee of Parc de l'Innovation, Strasbourg, France.
154
155 **Practicability study outcomes.** The practicability evaluation was divided into four
156 substudies carried out by trained health care professionals, based on previously acquired
157 experience from WHO recommendations for evaluating the practicability of HIV self-tests
158 [17,18,25]. Indeed, the practicability was defined as the correct use of the self-test and the
159 correct interpretation of the result. The correct use of self-test was conditioned by the presence
160 of the control band after 15-min of migration. The correct interpretation of the tests was defined

by the percent agreement between the tests results read and interpret by the participants compared to the expected results coded by the numbers and verified by trained observers. As depicted in the Fig 1, 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 1. 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, provide 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. Note that, all individuals with a positive serological result were referred to the laboratory for diagnostic confirmation and to the hospital for management.

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 provided to the participants for interpretation after random selection of four tests (Fig 2). These standardized tests were coded by numbers to determine the expected results.

Fig 2. Interpretation of self-test results. A. The self-test result was interpreted as negative when a Control line (C) was present and readable and the "IgG" and "IgM" lines were absent. It was positive when a "C" and "IgM" (clearly or poorly readable) (case 1), or "C" and "IgG", or "C", "IgM" (clearly or poorly readable), and "IgG" lines were present. Finally, it was invalid when the "C" line was absent regardless of the presence or absence of the "IgG" and/or "IgM" line. **B.** Panel of 8 Exacto® COVID-19 self-test (Biosynex Swiss SA) cassettes, including 4 positive tests (#2, #3, #6 and #7), 2 negative tests (#4 and #8) and 2 invalid tests (#1 and #5). The #2 and #37 are weakly positive for IgM. Each volunteer randomly 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 [26]. The degree of agreement was determined as ranked by Landlis and Koch [27]. 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), or 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 1). 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.

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

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

Table 2. Analytical results of the evaluation questionnaire concerning the ability of the 167 study participants to understand the instruction for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA) (substudy 1).The questions raising specific issues concerning the manipulation of the kit, the interpretation 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 self-test performance (since the opening of the box until the migration step) was 8.8 (SD: 3.0) minutes. Note that, in this substudy, 11 (13.3%) people had a positive results with the self-test, and they were oriented to laboratory for result confirmation.

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 random selection of four tests from a panel of eight standardized tests. The results are depicted in Fig 3. 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 3. 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 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).

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

[*] Difference and CI were assessed with the Wilson score bounds using data collected in the post-test satisfaction questionnaire paired to those from the pre-test satisfaction questionnaire;

[#] *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 [25]. 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 of high educational attainment, 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 [28]. 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 can be read and understood by all users. Our findings showed that 89.2% of participants correctly answered all 10 questions indicating generally correct understanding of the key messages delivered by the instructions for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA), with an overall rate of good responses of 97.1%. These satisfactory results may be explained in part by the high post-graduate education level of the majority of study participants. Indeed, previous experience from HIV self-testing showed that insufficient educational level constitutes a great challenge in the comprehension of the instructions for use [18,29-31]. Although systematic reviews and meta-analysis have shown that HIV self-testing can be successfully conducted by untrained users without in-person demonstrations [30], our observations emphasize the need to complete the classical paper instructions for use by other

instructional tools such as short video film, which was preferred by 1 of 13 study participants for better instructions for use understanding. These findings are reminiscent to previous WHO recommendations for HIV self-test stating that all self-testers should have the possibility to access or receive assistance over the phone, through the internet, or with additional instructions such as video, animations, or diagrams [15].

Substudy 2. All study participants carried out the COVID-19 self-test and succeeded in obtaining a valid test result with an overall usability index estimated at 98.5%. Some difficulty in the correct use of the pipette to transfer the blood sample was the principal reported concern encountered and was the most common reason for oral help. In previous reports on HIV self-testing, the difficulties in self-lancing and blood transfer to the cassette were also observed by lay users [32]. These features underline the importance of video instructions, when available. Although a small sample size of participants used the video instructions in this series, all of them not needed any help and used the pipette without any difficulty or error. The use of a hotline could also offer direct distant assistance.

Substudy 3. The ability to correctly read and interpret the self-test results is considered as a critical step in self-testing [33]. 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 [34].

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 [35], 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, according to the kinetic profile of the systemic humoral response against SARS-CoV-2 and the lifespan of circulating immunoglobulins, the presence of IgM alone or with IgG means that the contact with the virus was relatively recent [36]. The presence of IgG means that the contact with the virus occurred at least 14 days ago [36]. 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 psychological distress of variable intensity, especially in a person who has not received pre-test counseling [37].

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 to detect a relative difference between groups with high precision. 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.

The role of the COVID-19 self-test in fighting the epidemic, caring for infected people and preventing risk of transmission is not yet known. The possible risk of adverse effects of the COVID-19 self-test should not be underestimated, such as a pseudo-insurance of immunity or non-contagiousness. Furthermore, there is limited understanding of adult public acceptability and usability of rapid diagnostic tests in the home setting, as most are currently designed as professional use to be carried out by healthcare professionals. It will of course be necessary to precisely assess all these potential perverse effects. However, the place of the COVID-19 self-test could simply be a complementary public health tool. Indeed, testing a large number of individuals for serological survey for example would be impractical if a blood sample is required for SARS-CoV-2 serologic testing in a laboratory. The solution to use self-sampling and self-testing with participants reporting their results to the clinicians or epidemiologists has

been recently reported in a nationally representative serosurvey of SARS-CoV-2 in adults in England, demonstrating its full feasibility [38].

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, novel 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. 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 had a past infection (presence of specific IgG, alone or associated with IgM). Thus, COVID-19 self-testing 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 seek confirmatory antibody test by a clinical laboratory and clinical follow-up, which could contribute to accentuating tensions in the healthcare system, in particular during epidemic periods. In any case, the presence of reactivities could constitute an "immunological passport" of protection [46,47], although the general assumption is that the presence of antibodies will provide at least some immunity [49]. However, it should be emphasized that the level of protection of seropositivity for SARS-CoV-2 as well as its duration are not known, and even that the presence of specific antibodies does not mean that the person is not contagious, particularly in onset of infection. It will therefore be important to pass this information on to subjects who self-test so that they continue to take precautions to protect themselves and others. While specific guidelines regarding how "presumptive immunity" will be determined and used do not exist, this potential use has probably generated the interest in the lay public [47]. In any case, an IgG positive COVID-19 self-test result may indicate recovery of a previous SARS-CoV-2 infection, even asymptomatic or mild. Interestingly, serological home testing could be associated with at-home saliva or swab self-sampling for further SARS-CoV-2 molecular diagnosis, and the widespread use of both home approaches is worthy of further study. Those whom the viral test indicates an active SARS-CoV-2 infection (including silent carriers and individuals with early or mild symptoms) will be able to take informed actions, such as self-isolation. Furthermore, the risk exposure of the healthy population will be mitigated by the actions taken by the (informed) infected population, thus slowing the spread of the coronavirus and flattening the curve. Importantly, a confirmed population of "recovered" individuals may facilitate many to return to work, lead to partial lifting of "stay-at-home" or "shelter-in-place" orders, and would help get the economy back to normal, with no loss in protection for the most

vulnerable. Recently, the British government, UK, also making available SARS-CoV-2 antibody home tests for healthcare workers and the general public [50]. Home testing will be voluntary, but there is no doubt more people will test if the tests could be freely available.

Until a cure or a vaccine becomes available, antibody and viral testing for SARS-CoV-2 infection will play a critical role in limiting the pandemic and containing its economic damage to individuals and the country. Our features demonstrate that COVID-19 self-testing for serological immune status assessment is highly feasible with potential for use by at least some groups with high levels of education. If deployed wisely, it may be complementary to other serological screening tools and could facilitate uptake of SARS-CoV-2 serology.

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Supporting information

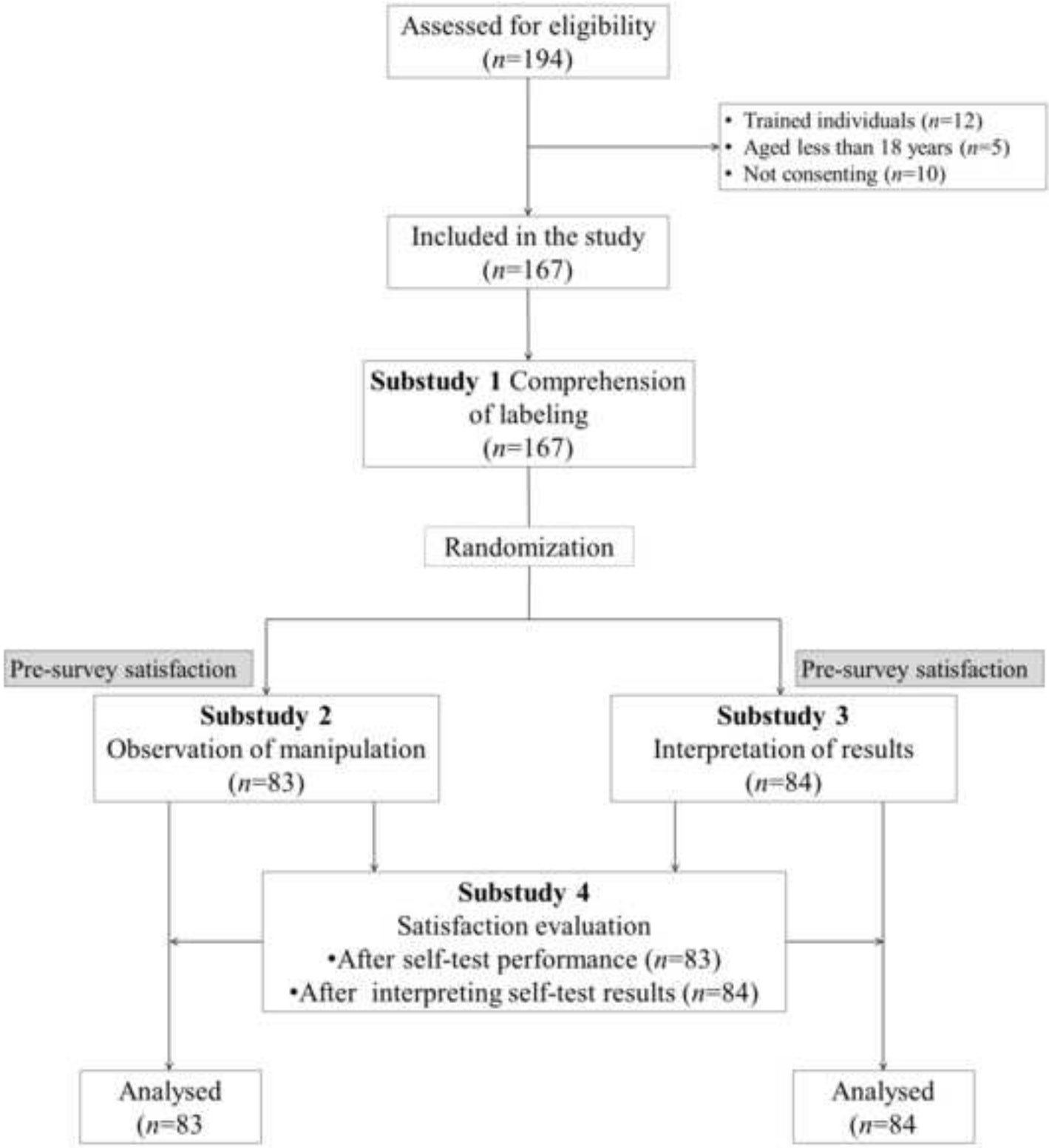
S1 Appendix. Paper-based instruction for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA).

S2 Appendix. video-based instruction for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA).

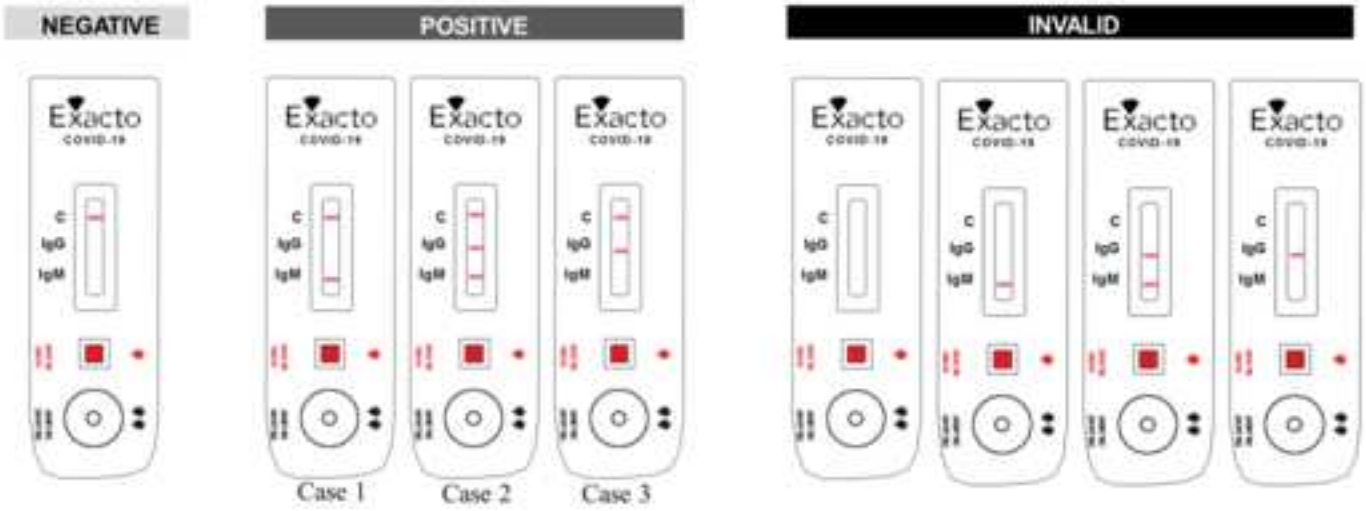
S3 Appendix. Study questionnaires in French (original language).

S4 Appendix. Study questionnaires in English.

Fig 1



A. Interpretation of test results



B. Panel of eight standardized tests

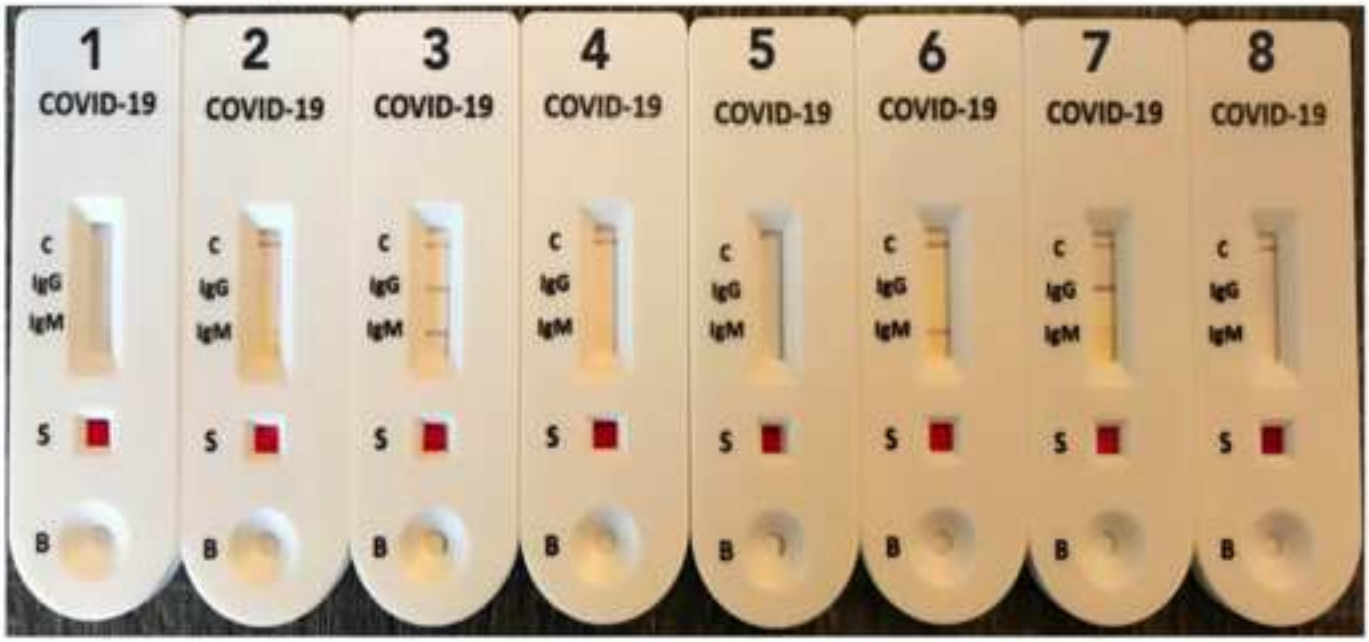


Fig 3

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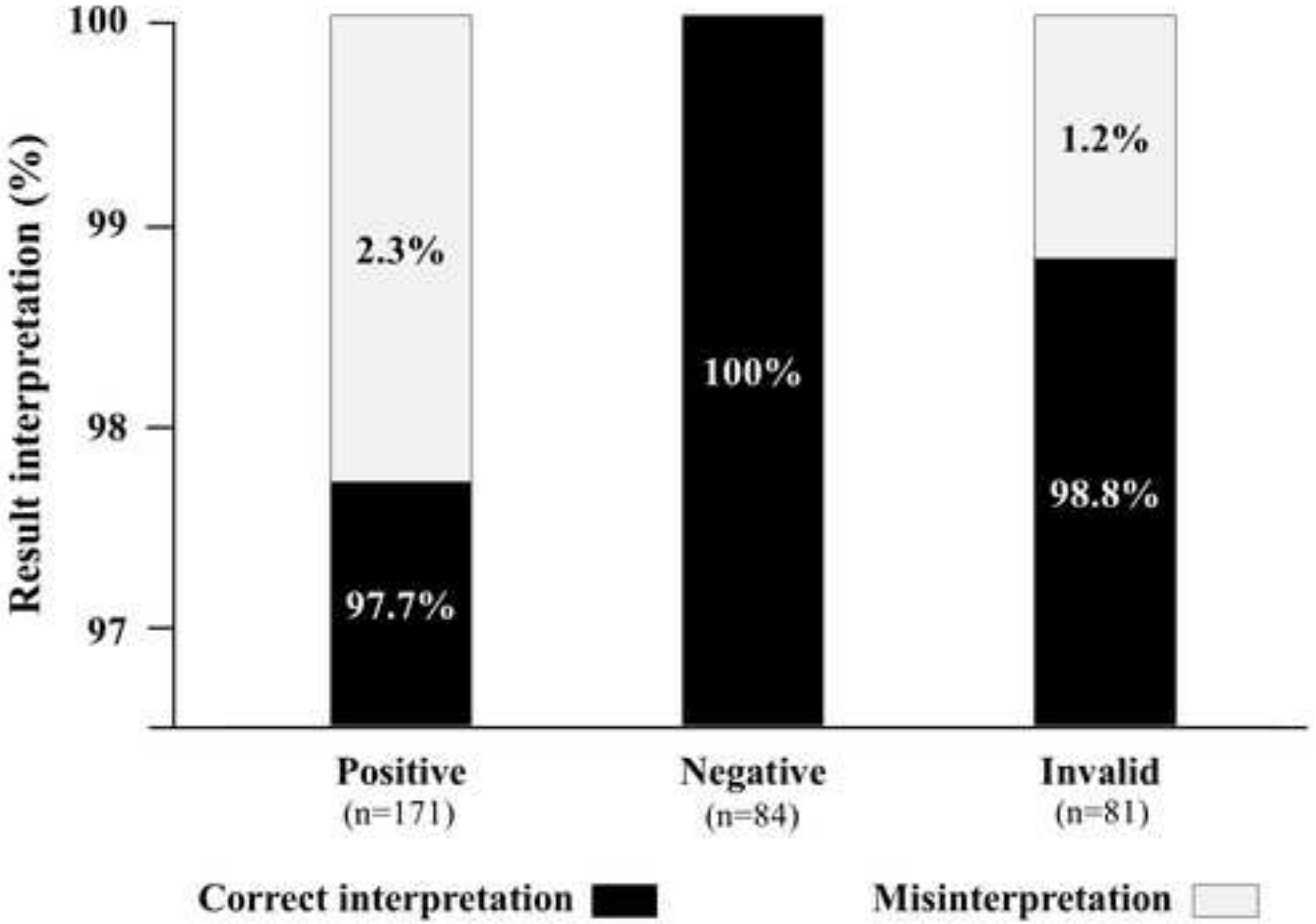


Instruction for use of the EXACTO COVID-19 SELF-TEST

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 "kit: 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

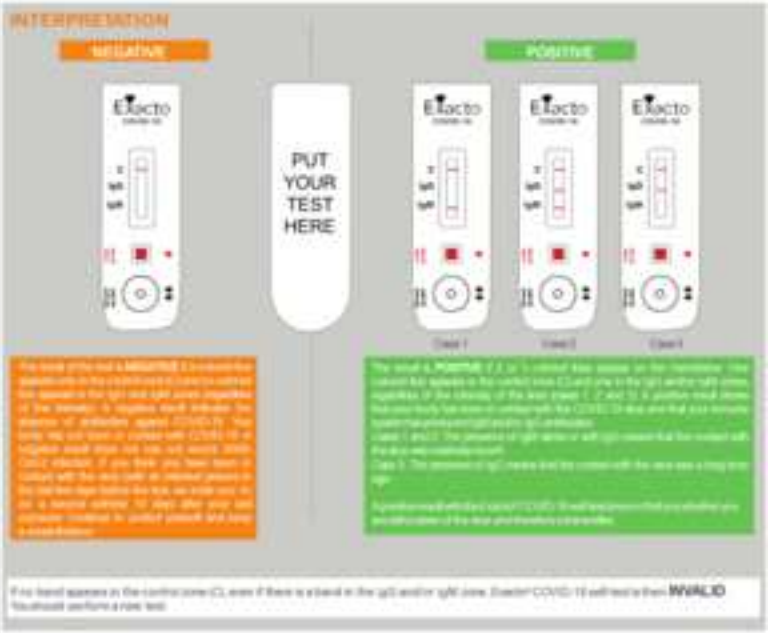
Sensitivity and specificity

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 %	99.0 %
IgM	91.8 %	98.2 %	97.0 %

- 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



- Do not interpret the Exacto® COVID-19 self-test if blood is deposited 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

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Supporting Information
COVID-19 EN V2.mp4

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. Practicability was defined as the correct use of the self-test and the correct interpretation of the result. The correct use of self-test was conditioned by the presence of the control band after 15-min of migration. The correct interpretation of the tests was defined by the percent agreement between the tests results read and interpret by the participants compared to the expected results coded by the numbers and verified by trained observers. 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. The percent agreement between the tests results read and interpret by the participants compared to the expected results was ~~Overall,~~ 98.5% (95% CI: 96.5–99.4) ~~test results were correctly interpreted, while~~. However, 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 ~~profane~~ populations from developed as well 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], following an official report from the National Reference Center for Respiratory Viruses [*Centre National de Référence Virus des infection respiratoires (dont la grippe)*], Institut Pasteur, Paris, 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

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in French and English, in A3 format color printing. As an example, the paper-based and video-based instructions for use are depicted as S1 and S2 appendix~~in Fig 1~~. ~~The online instruction in the video for use was available online from Youtube [24].~~

~~**Fig 1.** 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 manufacturer'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, consisting of face-to-face, paper-based, semi-structured, and self-administrated questionnaires. This survey was performed between April and May 2020 by home-based recruitment of adult volunteers using a door-to-door community approach, in 15 neighborhoods of Strasbourg and its suburbs, France. Due to the limited movement during the confinement period in France, especially in the province of Alsace (now "Grand Est") for which Strasbourg is the capital city, the choice of these neighborhoods and its suburbs was based on their easy accessibility and their high prevalence of reported cases of SARS-CoV-2 infection [24].~~, 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 [17,18,25~~6~~]. Indeed, the practicability was defined as the correct use of the self-test and the correct interpretation of the result. The correct use of self-test was conditioned by the presence of the control band after 15-min of migration. The correct interpretation of the tests was defined by the percent agreement between the tests results read and interpret by the participants compared to the expected results coded by the numbers and verified by trained observers. As depicted in the Fig 1~~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 1~~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~~provide 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. Note that, all individuals with a positive serological result were referred to the laboratory for diagnostic confirmation and to the hospital for management.

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~~ provided to the participants for interpretation after ~~successive~~ random selection of four tests (Fig 2~~3~~). These standardized tests were coded by numbers to determine the expected results.

Fig 2~~3~~. Interpretation of self-test results. A. The self-test result was interpreted as negative when a Control line (C) was present and readable and the "IgG" and "IgM" lines were absent~~s~~. It was positive when a "C" and "IgM" (clearly or poorly readable) (case 1), or "C" and "IgG", or "C", "IgM" (clearly or poorly readable), and "IgG" lines were present~~s~~. ~~And~~Finally, it was invalid when the "C" line was absent regardless of the presence or absence of the "IgG" and/or "IgM" line. **B.** 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~~°~~4~~2~~ and #8n~~°7~~) and 2 invalid tests (#n~~°~~1 and #n~~°~~5). The #n~~°~~2 and #3n~~°~~7 are weakly positive for IgM. Each volunteer randomly~~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.

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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 [26~~7~~]. The degree of agreement was determined as ranked by Landlis and Koch [27~~8~~]. 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~~ or 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 1~~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.

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

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

Table 2. Analytical results of the evaluation questionnaire concerning the ability of the 167 study participants to understand the instruction for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA) (substudy 1).The questions raising specific issues concerning the manipulation of the kit, the interpretation 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 ~~HIV~~ self-test performance (since the opening of the box until the migration step) was 8.8 (SD: 3.0) minutes. Note that, in this substudy, 11 (13.3%) people had a positive results with the self-test, and they were oriented to laboratory for result confirmation.-

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).

	Successful manipulation	**Need**

Usability checklist*			**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 34. 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 34. 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).

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

[*] Difference and CI were assessed with the Wilson score bounds using data collected in the post-test satisfaction questionnaire paired to those from the pre-test satisfaction questionnaire;

[#] *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 [256]. 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 of high educational attainment, 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 [289]. 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

can be read and understood by all users. Our findings showed that 89.2% of participants correctly answered all 10 questions indicating generally correct understanding of the key messages delivered by the instructions for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA), with an overall rate of good responses of 97.1%. These satisfactory results may be explained in part by the high post-graduate education level of the majority of study participants. Indeed, previous experience from HIV self-testing showed that insufficient educational level constitutes a great challenge in the comprehension of the instructions for use [18,2930-312]. Although systematic reviews and meta-analysis have shown that HIV self-testing can be successfully conducted by untrained users without in-person demonstrations [301], our observations emphasize the need to complete the classical paper instructions for use by other instructional tools such as short video film, which was preferred by 1 of 13 study participants for better instructions for use understanding. These findings are reminiscent to previous WHO recommendations for HIV self-test stating that all self-testers should have the possibility to access or receive assistance over the phone, through the internet, or with additional instructions such as video, animations, or diagrams [15].

Substudy 2. All study participants carried out the COVID-19 self-test and succeeded in obtaining a valid test result with an overall usability index estimated at 98.5%. Some difficulty in the correct use of the pipette to transfer the blood sample was the principal reported concern encountered and was the most common reason for oral help. In previous reports on HIV self-testing, the difficulties in self-lancing and blood transfer to the cassette were also observed by lay users [323]. These features underline the importance of video instructions, when available. AIn the present series, lthough a small sample size ofall participants using used the video instructions in this series, all of them did not needed any help and used the pipette without any difficulty or error. The use of a hotline could also offer direct distant assistance.

Substudy 3. The ability to correctly read and interpret the self-test results is considered as a ~~delicate~~ critical step in self-testing [3~~4~~]. 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 [3~~4~~5].

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 [3~~5~~6], 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, according to the kinetic profile of the systemic humoral response against SARS-CoV-2 and the lifespan of circulating immunoglobulins, the presence of IgM alone or with IgG means that the contact with the virus was relatively recent [~~-~~3~~6~~7]. The presence of IgG means that the contact with the virus occurred at least 14 days ago [3~~6~~7]. 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

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consequences such as self-medication or psychological distress ~~neuro-psychiatric disorders~~ of variable intensity, especially in a person who has not received pre-test counseling ~~not psychologically prepared~~ [3~~7~~8].

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 to detect a relative difference between groups with high precision. 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.

The role of the COVID-19 self-test in fighting the epidemic, caring for infected people and preventing risk of transmission is not yet known. The possible risk of adverse effects of the

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COVID-19 self-test should not be underestimated, such as a pseudo-insurance of immunity or non-contagiousness. Furthermore, there is limited understanding of adult public acceptability and usability of rapid diagnostic tests in the home setting, as most are currently designed as professional use to be carried out by healthcare professionals. It will of course be necessary to precisely assess all these potential perverse effects. However, the place of the COVID-19 self-test could simply be a complementary public health tool. Indeed, testing a large number of individuals for serological survey for example would be impractical if a blood sample is required for SARS-CoV-2 serologic testing in a laboratory. The solution to use self-sampling and self-testing with participants reporting their results to the clinicians or epidemiologists has been recently reported in a nationally representative serosurvey of SARS-CoV-2 in adults in England, demonstrating its full feasibility [38].

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, ~~original~~ novel 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~~had a past infection (presence of specific IgG, alone or associated with IgM). Thus, COVID-19 self-testing 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 seek confirmatory antibody test by a clinical laboratory and clinical follow-up, which could contribute to accentuating tensions in the healthcare system, in particular during epidemic periods~~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]. However, it should be emphasized that the level of protection of seropositivity for SARS-CoV-2 as well as its duration are not known, and even that the presence of specific antibodies does not mean that the person is not contagious, particularly in onset of infection. It will therefore be important to pass this information on to subjects who self-test so that they continue to take precautions to protect themselves and others. While specific guidelines regarding how “presumptive immunity” will be determined and used do not exist, this potential use has probably generated the interest~~most excitement~~ in the lay

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public [47]. In any case, an IgG positive COVID-19 self-test result may indicate recovery of a previous SARS-CoV-2 infection, even asymptomatic or mild~~, and would allow to take more moderate precautions and also to comfortably interact with other COVID-19 seropositive individuals.~~. Interestingly, serological home testing could be associated with at-home saliva or swab self-sampling for further SARS-CoV-2 molecular diagnosis, and the widespread use of both home approaches is worthy of further study~~would be hugely beneficial to public health~~. Those whom the viral test indicates an active SARS-CoV-2 infection (including silent carriers and ~~patients~~ individuals with early or mild symptoms) will be able to take informed actions, such as self-isolation. Furthermore, the risk exposure of the healthy population will be mitigated by the actions taken by the (informed) infected population, thus slowing the spread of the coronavirus and flattening the curve. Importantly, a confirmed population of "recovered" individuals may facilitate~~would allow~~ many to return to work, lead to partial lifting of "stay-at-home" or "shelter-in-place" orders, and would help get the economy back to normal, with no loss in protection for the most vulnerable. Recently, the British government, UK, are making available SARS-CoV-2 antibody home tests for healthcare workers and the general public [50]. Home testing will be voluntary, but there is no doubt more people will test if the tests could be freely available. ~~are free. Removing financial barriers to self-testing by making publicly-funded tests available free to the entire population will help maximize rapid implementation and help COVID-19-affected country to recover and get back to work.~~

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Until a cure or a vaccine becomes available, antibody and viral testing for SARS-CoV-2 infection will play a critical role in limiting the pandemic and containing its economic damage to individuals and the country. Our features demonstrate that COVID-19 self-testing for serological immune status assessment is highly feasible with potential for use by at least some groups with high levels of education~~the general public~~. If deployed wisely, it ~~will~~ may be complementary to other serological screening tools and could facilitate uptake of SARS-CoV-

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

~~The role of the COVID-19 self-test in fighting the epidemic, caring for infected people and preventing risk of transmission is not yet known. The possible risk of adverse effects of the COVID-19 self-test should not be underestimated, such as a pseudo-insurance of immunity or non-contagiousness. Furthermore, there is limited understanding of adult public acceptability and usability of rapid diagnostic tests in the home setting, as most are currently designed as professional use to be carried out by healthcare professionals. It will of course be necessary to precisely assess all these potential perverse effects. However, the place of the COVID-19 self-test could simply be a complementary public health tool. Indeed, testing a large number of individuals for serological survey for example would be impractical if a blood sample is required for SARS-CoV-2 serologic testing in a laboratory. The solution to use self-sampling and self-testing with participants reporting their results to the clinicians or epidemiologists has been recently reported in a nationally representative serosurvey of SARS-CoV-2 in adults in England, demonstrating its full feasibility [Atchison et al., 2020]," periods.~~

Acknowledgments. The authors are grateful to the volunteers for their willingness to participate in the study. We also thank Biosynex, Strasbourg, France, for providing the Exacto® COVID-19 self-tests for the study.~~ Dr. Serge Tonen-Wolyec was recipient of ERASMUS+ program between the University of Kisangani, Democratic Republic of the Congo, and the University of Liège, Belgium.~~

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Supporting information

S1 Appendix. Paper-based instruction for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA).

S2 Appendix. video-based instruction for use of the Exacto® COVID-19 self-test (Biosynex Swiss SA).

S3 Appendix. Study questionnaires in French (original language).

S4 Appendix. Study questionnaires in English.

~~Atchison C, Pristerà P, Cooper E, Papageorgiou V, Redd R, Piggin M, Flower B, Fontana G, Satkunarajah S, Ashrafian H, Lawrence-Jones A, Naar L, Chigwende J, Gibbard S, Riley S, Darzi A, Elliott P, Ashby D,~~

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Responses to journal requirements and to Reviewers

Journal Requirements:

When submitting your revision, we need you to address these additional requirements.

1. Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming. The PLOS ONE style templates can be found at

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https://clicktime.symantec.com/3J1bpueumkNeCCUwpeXGyX66H2?u=https%3A%2F%2Fjournals.plos.org%2Fplosone%2Fs%2Ffile%3Fid%3Dba62%2FPLOSOne_formatting_sample_title_authors_affiliations.pdf

Our answer: We have checked that the manuscript meets the PLOS ONE'S requirements, including file names and affiliations.

2. Please include additional information regarding the survey or questionnaire used in the study and ensure that you have provided sufficient details that others could replicate the analyses.

For instance, if you developed a questionnaire as part of this study and it is not under a copyright more restrictive than CC-BY, please include a copy, in both the original language and English, as Supporting Information.

Our answer: As requested, the study questionnaires in French (original language) as well as in English have been uploaded in the submission system, as supporting information.

3. Thank you for stating the following in the Acknowledgments Section of your manuscript:

'Dr. Serge Tonen-Wolyec was recipient of ERASMUS+ program between the University of Kisangani, Democratic Republic of the Congo, and the University of Liège, Belgium.'

We note that you have provided funding information that is not currently declared in your Funding Statement. However, funding information should not appear in the Acknowledgments section or other areas of your manuscript. We will only publish funding information present in the Funding Statement section of the online submission form.

a. Please remove any funding-related text from the manuscript and let us know how you would like to update your Funding Statement. Currently, your Funding Statement reads as follows:

'The authors received no specific funding for this work.'

Our answer: In order to acknowledge the journal requirement, we have removed any funding-related test from the manuscript and we have updated our Funding Statement as follow: "*This work was partly supported by Biosynex SA. The funders played a role in providing the prototype SARS-CoV-2 test for self-test (Exacto® COVID-19 self-test, Biosynex Swiss SA) and data collection. The study design, analysis, decision to publish, and preparation of the manuscript were not sponsored. Dr. Serge Tonen-Wolyec was recipient of ERASMUS+ program between the University of Kisangani, Democratic Republic of the Congo, and the University of Liège, Belgium.*"

b. Please include your amended statements within your cover letter; we will change the online submission form on your behalf.

Our answer: We have included our amended Funding statement within our cover letter.

4. Thank you for stating the following in the Competing Interests section:

'The authors have declared that no competing interests exist.'

We note that one or more of the authors are employed by a commercial company: BioSynex

a. Please provide an amended Funding Statement declaring this commercial affiliation, as well as a statement regarding the Role of Funders in your study. If the funding organization did not play a role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript and only provided financial support in the form of authors' salaries and/or research materials, please review your statements relating to the author contributions, and ensure you have specifically and accurately indicated the role(s) that these authors had in your study. You can update author roles in the Author Contributions section of the online submission form.

Please also include the following statement within your amended Funding Statement.

"The funder provided support in the form of salaries for authors [insert relevant initials], but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section."

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c. Please include both an updated Funding Statement and Competing Interests Statement in your cover letter. We will change the online submission form on your behalf.

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Our answer: We have declared that no competing interests exist. Dr. Raphael Dupont, who is an employee of Biosynex SA with a salary, had supervised the data collection in Strasbourg,

especially during periods of confinement where the movement of individuals was restricted. This does not alter our adherence to PLOS ONE policies on sharing data and materials. We have added this highlighting in our cover letter and online submission.

5. PLOS requires an ORCID iD for the corresponding author in Editorial Manager on papers submitted after December 6th, 2016. Please ensure that you have an ORCID iD and that it is validated in Editorial Manager. To do this, go to 'Update my Information' (in the upper left-hand corner of the main menu), and click on the Fetch/Validate link next to the ORCID field. This will take you to the ORCID site and allow you to create a new iD or authenticate a pre-existing iD in Editorial Manager. Please see the following video for instructions on linking an ORCID iD to your Editorial Manager account: https://clicktime.symantec.com/3QJAoi3RwJ4rwEt9UViL8wS6H2?u=https%3A%2F%2Fwww.youtube.com%2Fwatch%3Fv%3D_xcclfuvtxQ

Our answer: We have added a validated ORCID iD (https://orcid.org/0000-0002-5001-0405) of the corresponding author in Editorial Manager.

Reviewers' comments:

Reviewer's Responses to Questions

Comments to the Author

1. Is the manuscript technically sound, and do the data support the conclusions?

The manuscript must describe a technically sound piece of scientific research with data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.

Reviewer #1: Partly

Reviewer #2: Partly

Our answer: We thank the reviewers for their nice comments on our work. However, in order to acknowledge the comments raised by referees, we have made corrections thorough the manuscript; therefore, we hope that our revised manuscript is more technically sound.

2. Has the statistical analysis been performed appropriately and rigorously?

Reviewer #1: Yes

Reviewer #2: Yes

Our answer: We thank the reviewers for their nice comments on our work.

3. Have the authors made all data underlying the findings in their manuscript fully available?

The PLOS Data policy requires authors to make all data underlying the findings described in their manuscript fully available without restriction, with rare exception (please refer to the Data Availability Statement in the manuscript PDF file). The data should be provided as part of the manuscript or its supporting information, or deposited to a public repository. For example, in addition to summary statistics, the data points behind means, medians and variance measures should be available. If there are restrictions on publicly sharing data—e.g. participant privacy or use of data from a third party—those must be specified.

Reviewer #1: Yes

Reviewer #2: Yes

Our answer: We thank the reviewers for their nice comments on our work.

4. Is the manuscript presented in an intelligible fashion and written in standard English?

PLOS ONE does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors here.

Reviewer #1: No

Reviewer #2: Yes

Our answer: In order to acknowledge the comments raised by Reviewer # 1, we have corrected words and grammar as suggested by Referee. We hope that our revised manuscript is presented in an intelligible fashion and written in standard American English.

5. Review Comments to the Author

Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)

Answer to reviewer #1

This study is potentially one of several necessary but not sufficient steps towards translation to practice. However, the discussion must be made much more conservative. The extensive speculation on the role of home serology testing could create safety problems and is of major concern.

Our answer: The remark of the reviewer is right. To acknowledge the reviewer's concern, we have completed the Strengths and limitations section by adding the following paragraph: "The role of the COVID-19 self-test in fighting the epidemic, caring for infected people and preventing risk of transmission is not yet known. The possible risk of adverse effects of the COVID-19 self-test should not be underestimated, such as a pseudo-insurance of immunity or non-contagiousness. Furthermore, there is limited understanding of adult public acceptability and usability of rapid diagnostic tests in the home setting, as most are currently designed as professional use to be carried out by healthcare professionals. It will of course be necessary to precisely assess all these potential perverse effects. However, the place of the COVID-19 self-test could simply be a complementary public health tool. Indeed, testing a large number of individuals for serological survey for example would be impractical if a blood sample is required for SARS-CoV-2 serologic testing in a laboratory. The solution to use self-sampling and self-testing with participants reporting their results to the clinicians or epidemiologists has been recently reported in a nationally representative serosurvey of SARS-CoV-2 in adults in England, demonstrating its full feasibility [Atchison et al., 2020]."

Atchison C, Pristerà P, Cooper E, Papageorgiou V, Redd R, Piggin M, Flower B, Fontana G, Satkunarajah S, Ashrafian H, Lawrence-Jones A, Naar L, Chigwende J, Gibbard S, Riley S, Darzi A, Elliott P, Ashby D, Barclay W, Cooke GS, Ward H. Usability and acceptability of home-based self-testing for SARS-CoV-2 antibodies for population surveillance. Clin Infect Dis. 2020 Aug 12:ciaa1178. doi: 10.1093/cid/ciaa1178.

Highlight [page 8]: 98.5% (95% CI: 96.5–99.4) test results were correctly interpreted, while misinterpretation occurred in only…

Note [page 8]: L47. What is the definition of the correct interpretation of the test?

Our answer: Since the expected results were known from the code numbers of the eight standardized tests, the correct interpretation of the tests was defined by the percent agreement between the tests results read and interpreted by the participants compared to the expected results coded by the numbers and verified by observers. Thus, misinterpretation corresponded to the percent disagreement between the test results read and interpret by the participants and the expected results coded by the numbers. We have added these clarifications in the abstract and the body of the text.

Note [page 10]: L88 Change 'as' to 'as well as'

Highlight [page 10]: HIV self-testing has demonstrated high acceptability with very convenient usability in various adolescent and adult profane populations from developed as resources-constrained settings [17-21].

Note [page 10]: L88 profane? Don't think you mean this- suggest remove this word.

Our answer: We have corrected the sentence, as suggested.

Highlight [page 11]: 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.

Note [page 11]: L 119: Have these results been peer reviewed and published elsewhere? If so please provide reference? Why not publish the this study and the performance characteristics of the test in the same paper? They ideally need to be assessed together.

Our answer: While the purpose of our study was not to assess the virological analytical performances of the BIOSYNEX® COVID-19 BSS (IgG/IgM) (Biosynex Swiss SA), this rapid diagnostic test has been fully recommended for both SARS-CoV-2-specific IgG and IgM detection by the French Ministry of Health (https://covid-19.sante.gouv.fr/tests. ; last access 25 August 2020), following an official report from the National Reference Center for Respiratory Viruses [*Centre National de Référence Virus des infection respiratoires (dont la grippe)*], Institut Pasteur, Paris. We have added this information in the text.

Highlight [page 11]: The online instruction in the video for use was available online from Youtube [24].

Note [page 11]: When the QR code on Figure 1 is scanned it says the video has been taken down. Please provide the video or QR code. Ideally the video could be permanently attached to this paper by the journal rather than relying on a Youtube video that could be taken down again.

Note [page 12]: 132 See latter suggestions about moving full instructions to supplementary materials and using just top half of interpretation panel as Fig 1. Legend needs to state that this was the exact instructions provided to the subjects in this study in both legends.

Our answer: In order to acknowledge the comments raised by Reviewer # 1, we have moved the full instruction for use to supplementary materials. Furthermore, we have provided the video instruction as its supporting information file.

Note [page 12]: L 134: simplify this phrase

Highlight [page 12]: 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 neighborhoods of Strasbourg and its suburbs,…

Our answer: We have simplified this sentence as suggested.

Note [page 12]: How were these neighborhoods selected? Was there a wide range of socio-economic and eductaional status and was this representative of developed countries in Northern Europe? Will need a discussion on how generalizable are these results likely to be.

Our answer: Due to the limited movement during the lockdown period, the choice of these neighborhoods and its suburbs was based on their easy accessibility and their high prevalence of reported cases of SARS-CoV-2 infection. We have added this sentence in the "Study design and recruitment of participants" section for more highlighting.

Note [page 14]: L189: Change appeal for to provide

Highlight [page 14]: 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.

Our answer: We have changed the words as suggested.

Note [page 14]: L196: change proposed to provided

Highlight [page 14]: 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…

Our answer: We have changed the words as suggested.

Note [page 14]: L196: delete successive
Note [page 14]: L201- 202: suggest change No to #

Highlight [page 14]: 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).

Our answer: We have changed the words as suggested.

Note [page 14]: L202: change successively to randomly

Highlight [page 14]: Each volunteer successively drew 4 tests among a panel of 8 and interpreted them with the help of the reading and interpretation scale.

Our answer: We have changed the words as suggested.

Note [page 15]: L228: change and to or

Highlight [page 15]: excluded because they were trained (n=12), less than 18 years old (n=5), and not consenting (n=10).

Our answer: We have changed the words as suggested.

Note [page 18]: L277: delete HIV

Highlight [page 18]: Overall, the mean time of HIV self-test performance (since the opening of the box until the migration step) was…

Our answer: It was a mistake, we have deleted it.

Note [page 19]: L293: delete successive- not clear what this means

Highlight [page 19]: COVID-19 self-test results after successive random selection of four tests from a panel of eight standardized tests.

Our answer: We have deleted it.

Note [page 20]: L308: would be interesting to know if there were any differences in the results from substudy 4 for those previously in subsidy 2 versus 3.

Highlight [page 20]: Substudy 4.

Our answer: We did not assess such comparisons.

Note [page 22]: L349 Europeans of high educational attainment

Highlight [page 22]: 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.

Our answer: We thank the reviewer for this clarification, which we have added to the text.

Note [page 23]: L 376: ..error, however numbers in this group were small.

Highlight [page 23]: In the present series, all participants using the video instructions did not need any help and used the pipette without any difficulty or error.

Our answer: We have added this precision related to the small sample size in this discussion as follows: “Although a small sample size of participants used the video instructions in this series, all of them did not need any help and used the pipette without any difficulty or error.”

Note [page 24]: L379: Change delicate to critical

Highlight [page 24]: considered as a delicate step in self-testing [34].

Our answer: We have changed the words as suggested.

Note [page 24]: L395 to 396: Is this really established for SARS-CoV-2 infection. Please provide references

Highlight [page 24]: Furthermore, the presence of IgM alone or with IgG means that the contact with the virus was relatively recent.

Our answer: To acknowledge the reviewer’s remarks, we completed as follows: “Furthermore, according to the kinetic profile of the systemic humoral response against SARS-CoV-2 and the lifespan of circulating immunoglobulins, the presence of IgM alone or with IgG means that the contact with the virus was relatively recent [37]”.

Note [page 24]: L401: Change neuropsychiatric disorders to psychological distress and not psychologically prepared to who has not received pre-test counseling.

Highlight [page 24]: This misinterpretation of positive test results can provide unfortunate

consequences such as self-medication or neuro-psychiatric disorders of variable intensity, especially in a person not psychologically prepared [38].

Our answer: We have changed the sentence as suggested.

Note [page 25]: L419: limit the study's power to detect….what?

Highlight [page 25]: Furthermore, the low sample size could reduce the study's power.

Our answer: The low sample size could reduce the study's power to detect a relative difference between groups with high precision.

Note [page 25]: L425: novel rather than original

Highlight [page 25]: During the COVID-19 epidemic, original approaches using individual involvement were proposed in addition to the collective public health approach, and both strategies were furthermore sometimes combined.

Our answer: We have changed the words as suggested.

Note [page 26]: L439: suggest delete ', but this….study"

Highlight [page 26]: 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.

Our answer: We have deleted the sentence as suggested.

Note [page 26]: L442: change has made too had

Highlight [page 26]: 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 (…

Our answer: We have changed the words as suggested.

Note [page 26]: L443: Need to emphasize that it is not yet known if antibodies are protective and if so how durable this protection is and if antibodies guarantee they cannot infect others. Must emphasize the importance of conveying this to the subjects self-testing and of their need to continue to take precautions to protect themselves and others.

Highlight [page 26]: Thus, COVID-19 self-testing 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 epi…

Our answer: To acknowledge these reviewer's remarks, we have added the following sentence: "However, it should be emphasized that the level of protection of seropositivity for SARS-CoV-2 as well as its duration are not known, and even that the presence of specific antibodies does not mean that the person is not contagious, particularly in onset of infection. It will therefore be important to pass this information on to subjects who self-test so that they continue to take precautions to protect themselves and others."

Note [page 26]: L448: "refer.." change to seek confirmatory antibody test by a clinical laboratory and clinical follow-up" Need to comment on the burden this will place on the health care system.

Highlight [page 26]: 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…

Our answer: We have changed the sentence as suggested, and added that "which could contribute to accentuating tensions in the healthcare system, in particular during epidemic periods".

Note [page 26]: L449: change to It should be emphasized that it is not known if a positive antibody test represents protection and the concept of an "immunological passport" cannot be supported at this time.

Highlight [page 26]: 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 antibod…

Our answer: We have deleted the ambiguous sentence: "…..because it is not known if anti-SARS-CoV-2 antibodies are protective at this time…..".

Note [page 27]: L454 Change most excitement to interest

Highlight [page 27]: "presumptive immunity" will be determined and used do not exist, this potential use has probably generated the most excitement in the lay public [47].

Our answer: We have changed the words as suggested.

Note [page 27]: L456-457: delete: …and would…individuals" No evidence to support his statement.

Highlight [page 27]: In any case, an IgG positive COVID-19 self-test result may indicate recovery of a previous SARS-CoV-2 infection, even asymptomatic or mild, and would allow to take more moderate precautions and also to comfortably interact with other COVID-19-seropositive individuals.

Our answer: We have deleted it as suggested.

Note [page 27]: L459: delete would be hugely beneficial to public health. The is conjecture. Suggest 'is worthy of further study'

Highlight [page 27]: Interestingly, serological home testing could be associated with at-home saliva or swab self-sampling for further SARS- CoV-2 molecular diagnosis, and the widespread use of both home approaches would be hugely beneficial to public health.

Our answer: We have corrected the sentence as suggested.

Note [page 27]: L461: should consider themselves potentially infected and self-isolate until the results of clinical testing for the virus is known.

Highlight [page 27]: Those whom the viral test indicates an active SARS-CoV-2 infection (including silent carriers and patients with early or mild symptoms) will be able to take informed actions, such as self-isolation.

Our answer: We agree with the reviewer. We have changed "patients" by "individuals".

Note [page 27]: L465: Change 'would allow' to 'may facilitate'. All of this discussion is too much conjecture and should be toned down.

Highlight [page 27]: Importantly, a confirmed population of "recovered" individuals would allow many to return to work, lead to partial lifting of "stay

Our answer: We have corrected the sentence as suggested.

Note [page 27]: L451: change will to may and indicate how this could be study to support such policies. Discuss how cost-effectiveness would have to be studies.

Highlight [page 27]: Removing financial barriers to self-testing by making publicly-funded tests available free to the entire population will help maximize rapid implementation and help COVID-19-affected country to recover and get back to work.

Our answer: We have deleted this ambiguous sentence.

Note [page 27]: L476: change the general public to 'by at least some groups with high levels of education.

Highlight [page 27]: Our features demonstrate that COVID-19 self-testing for serological immune status assessment is highly feasible with potential for use by the general public.

Our answer: We have changed the sentence as suggested.

Note [page 27]: L477: change will to may

Highlight [page 27]: If deployed wisely, it will be complementary to other serological screening tools and
Our answer: We have changed the word as suggested.

Note [page 28]: L478: change 'offer an immediate and easy solution for' to facilitate uptake of SARS-CoV-2 serology and delete rest of sentence.

Highlight [page 28]: could offer an immediate and easy solution for SARS-CoV-2 serology, especially during recovery or de-confinement periods.

Our answer: We have changed the sentence as suggested.

Note [page 33]: Figure 1. Impractical to include the entire instruction in the main body of the paper. It should be moved to supplementary materials. The top half of the interpretation panel with an appropriate legend would be more appropriate. Given this is the peer reviewed study examining the issue of interpretation the comment under performance about the 98.5% correct interpretation should be removed. Also the reference to support the performance characteristics of the test shown above that statement needs to be provided.

Highlight [page 34]: Click here to access/download;Figure;Fig…
None of these links worked on this version.

Our answer: As answered above, we have moved the full instruction for use to supplementary materials. And we have provided the video instruction as its supporting information file. However, we have added a Section A to the former Figure 3 (considered as a Section B) to present the interpretation of the results. Thus, this new figure is entitled Fig 2 in the revised version of our manuscript with legend written as follows: "**Fig 2. Interpretation of self-test results. A.** The self-test result was interpreted as negative when a Control line (C) was present and readable and the "IgG" and "IgM" lines were absent. It was positive when a "C" and "IgM" (clearly or poorly readable) (case 1), or "C" and "IgG", or "C", "IgM" (clearly or poorly readable), and "IgG" lines were present. Finally, it was invalid when the "C" line was absent regardless of the presence or absence of the "IgG" and/or "IgM" line. **B.** Panel of 8 Exacto® COVID-19 self-test (Biosynex Swiss SA) cassettes, including 4 positive tests (#2, #3, #6 and #7), 2 negative tests (#4 and #8) and 2 invalid tests (#1 and #5). The #2 and #37 are weakly positive for IgM. Each volunteer randomly 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".

Concerning the interpretation of results, since the expected results were known from the code numbers of the eight standardized tests, the correct interpretation of the tests was defined by the percent agreement between the tests results read and interpret by the participants compared to the expected results coded by the numbers and verified by observers. Thus, misinterpretation corresponded to the percent disagreement between the test results read and interpret by the participants and the expected results coded by the numbers. We have added these clarifications in the abstract and the body of the text.

Finally, the virological analytical performances characteristic of the evaluated self-test are provided in the Material and methods section, in the Prototype SARS-CoV-2 test for self-testing.

Answer to reviewer #2

The authors report on 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. They performed their evaluation of this test using a cross sectional, general adult population study between April and May 2020 in Strasbourg, France. The study design consisted of face-to-face, paper-based, semi-structured, and self administrated questionnaires. The study enrolled 167 participants of which 82% had a post-graduate level of education. The study evaluated the participants ability to use the test in a number of different testing settings. The authors conclude that 100% of the participants found that performing the self test was easy and 98% found that the interpretation of the self-test results are easy.

Our answer: We thank the reviewer for this perfect summary of our study.

While this study is very interesting and brings forward an important POC / self- administered SARS-COv-2 serological assay the authors failed to bench mark the antibody status to a gold standard lab based assay. The absence of this weakens their initial pilot findings. Does it bring value if people can follow directions and get a result if the test does not corelate highly to what would be considered a typical bench mark to an assay performed in the laboratory under a clinical standard? The absence of comparative data is a major flaw in the study design.

Our answer: We thank the reviewer for this pertinent remark. However, the objective of this survey was to assess the ability of lay persons to perform or interpret a serological test for SARS-CoV-2 immunochromatography. It was not intended to conduct a self-test performance study as such a study would require a large enough sample size of positive individuals to properly estimate the sensitivity of the self-test. Although this survey was carried out during the epidemic period in France, it should be noted that at that time, only confirmatory molecular testing using RT-PCR was recommended for suspect cases according to the recommendations of the French government to avoid wastage of reagents. Reference serological testing for IgG antibodies to SARS-CoV-2 was only progressively implemented in France during the study period, to be only available at the end of May, after the beginning of the deconfinement. While the purpose of our study was not to assess the virological analytical performances of the BIOSYNEX® COVID-19 BSS (IgG/IgM) (Biosynex Swiss SA), this rapid diagnostic test has been fully recommended for both SARS-CoV-2-specific IgG and IgM detection by the French Ministry of Health (https://covid-19.sante.gouv.fr/tests. ; last access 25 August 2020), following an official report from the National Reference Center for Respiratory Viruses [Centre National de Référence Virus des infection respiratoires (dont la grippe)], Institut Pasteur, Paris. We have added this information in the text.

Furthermore, in order to comply with the requirements of the ethical committee, all persons with a positive serological result were referred to the laboratory for diagnostic confirmation and to the hospital for management. In this study, 11 (13.3%) people had a positive result with the self-test and they were oriented to laboratory for result confirmation. We

have added these details in the “substudy 2” sections of Methods and results in the revised manuscript.