

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Using digital tools and antigen rapid testing to support household-level SARS-CoV-2 detection by community health workers in Rwanda: an operational pilot study
AUTHORS	Nshimiyimana, Ladislas; Bigirimana, Noella; Ngabonziza, JCS; Rwabihama, Jean-Paul; Rutayisire, Robert; Semakula, Muhammed; RUKUNDO, Gilbert; Mugabo, Hassan; Mutabazi, Josue; Mukamana, Beatrice; Mazarati, Jean-Baptiste; Kadam, Rigveda; Akinwusi, Olukunle; Suleiman, Khairunisa; Muvunyi, Claude; Akugizibwe, Paula

VERSION 1 - REVIEW

REVIEWER NAME	Méndez-Boo, Leonardo
REVIEWER AFFILIATION	Institut Catala De La Salut, Sistemes d'informació (SISAP)
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	26-Feb-2024

GENERAL COMMENTS	I Only have minor comments for the Authors, 1.) Section Methods: Concordance testing: Greater detail must be provided in regarding how many CHW where selected for shadow testing by laboratory technician and how was blindness achieved between the CHW test results and the laboratory technician assessment. 2) Same section, it is not clear if ALL the Ag-RDT testing negative by the laboratory technician where also PCR-tested or just a subset of the Ag-RDT negatives. 3) In section Results: Concordance, it mentions 489 negative cases, but this does not match the number in the table 3 which is 496. 4) Same section: then it is stated "PCR tests... confirmed complete agreement with the Ag-RDT test results" but the number of Ag-RDT negative tests that where PCR re-tested is not reported. 5) Table 3: it is confusing to mix here both the Ag-RDT re-tests by laboratory technicians and the PCR results by NRL, If every negative Ag-RDT result was tested again with PCR and always resulted in a negative confirmation by PCR, then I suggest to remove the mention to PCR in the column group title, and instead use the asterisk call ' * ' in the negative-negative cell number, where the table foot could use wording such as " * Only negative Ag-RDTs for patients with symptoms of COVID-19 where retested by PCR, which confirmed negative results in all cases".
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	6) Table 3: row and column named: Invalid, may be removed from table 3. 7) In Supplementary methods: FGD script, section B: Testing Covid-19 Done By CHWS: item 11: I think it is mistranslated to english, because the item is about the e-ASCOV App in general when in this section B it should be specifically about the Ag-RTD testing by CHWs. 8) in Supplementary Tables and Figures: Supplementary Table 1. the last column mentions "(%)" as if it was intended to present the Number of CHWs selected for the project as a percentage of the CHWs in the district while in the data that proportion is missing except for Gasabo district which informs "(6)". and Finally, 9) Supplementary Figure 1: I suggest to transform the figure into a table.
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REVIEWER NAME	Wagenhäuser , Isabell
REVIEWER AFFILIATION	University Hospital Wurzburg
REVIEWER CONFLICT OF INTEREST	No competing interests to declare
DATE REVIEW RETURNED	24-Mar-2024

GENERAL COMMENTS	- Line 78: Please add next to the advantages of RDT also the disadvantages including references! Especially in screening use RDTs are far away from the diagnostic reliability of the RT-qPCR which is the diagnostic gold standard. - I would recommend to shorten the introduction to about one page. For example line 112 following can be either moved to the methods or shortened. - Please add the procedure of sample collection for the AG-RDT, was it a nasopharyngeal swab? - It would be an improvement for the manuscript, if the different study sites were presented in a map of Ruanda for a better orientation, the case numbers could be added in this map. - I would prefer to combine Table 1 and Table 2 in one table. - Please always add the absolute figures (group size/total group) if shares of a cohort are given as a relative percentage value - What was the vaccination status of the test subjects and again the status of previous infections? Could it be that in rural areas there were simply more past infections or fewer vaccinations at the time of the test and therefore the symptoms were more pronounced there? Is this data available? This should also be discussed if no data is available. After all, this fact of a different distribution of symptoms could already indicate a different need for care in terms of testing strategy, but possibly also an increased focus on vaccinations / other infection prevention. - Referring the used smartphones: The digital application was suitable for different mobile operation systems, e.g. iOS, Android etc. - How did the application look like? Was it an App? Maybe adding some Screenshot of the design in the Supplements would make the manuscript more realistic. - Supplementary Figure 1: I think this is an important figure which should be presented as Figure in the manuscript. Please add the labeling of the y axes.
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	- I would recommend to better adapt the discussion to the time of publication. The concept is based on the scenario of the COVID-19 pandemic which meanwhile developed to an endemic. The important learning is in my opinion that the concept presented can be used for further outbreaks of pathogens and adapted to these. - Abstract: "PCR and Ag-RDT results were also fully concordant" This is not very well presented in the results section of the manuscript. Further, evidence to data says clearly that PCR is the gold standard for diagnostics. RDTs have reduced sensitivity, depending on the tested cohort (better for symptomatic individuals like in the study presented but not as equal as PCR!) - Please discuss that RDTs are not as reliable as PCR. There is a huge amount of evidence to that, that describes that also including the Panbio RDT (Dinnes et al. https://doi.org/10.1002/14651858.CD013705.pub3; Wagenhäuser et al. https://doi.org/10.1016/j.cmi.2022.08.006; Boujema et al. https://doi.org/10.1016/j.jviromet.2023.114811) The chosen strategy in this study with testing symptomatic individuals decreases the probability of false-negative RDTs but cannot exclude this Minor comments: Please standardise the text formatting with left-aligned and justified changing often. Line 63f: Is there any evidence to cite about the CHWs infrastructure in Rwanda Line 67: Please specify which tests were conducted in which count, PRC or RDT? Or in parallel? Line 69: Is it possible to add a reference to the national incidence data? Line 137: "across eight districts in Rwanda" can be removed as it is repeated again in the following sentence Line 154: Does "described previously" refer to line 112 f. or is there a reference missing? Line 172 (as example) please use only one of the two options "RDT" or "Ag-RDT" throughout the entire manuscript Line 252: "national data security guidelines per the Rwanda Information Security Authority", please add reference Line 395: It is extremely unusual to include quotes from those responsible in a scientific text. In my opinion, this can be used well for a newspaper article outside the scientific publication or in a lecture, but not in a scientific manuscript due to the clear subjectivity. Line 402-404: I would recommend to search for a reference for age-dependency of user skills.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I Only have minor comments for the Authors,

Thank you for your comprehensive review.

1.) Section Methods: Concordance testing: Greater detail must be provided in regarding how many CHW were selected for shadow testing by laboratory technician and how was blindness achieved between the CHW test results and the laboratory technician assessment.

Each CHW tested one patient, who was then retested by the lab technician. We planned to perform 510 concordance tests but due to the decreased incidence of COVID-19 only 499 CHWs were able to get patients and details were added.

We have amended this section to read:

"To assess the concordance of Ag-RDT results between CHW and the laboratory technician, 499 CHWs were randomly selected and shadowed by a laboratory technician for a day, during which Ag-RDTs administered by the CHWs who read and reported the results independently, were repeated by the laboratory technician. The result interpreted by the CHW was blinded to the laboratory technician as an operator. The laboratory technician then repeated the Ag-RDT and reported their result independently. The results from the tests performed by the laboratory technician were considered final and communicated to clients."

2) Same section, it is not clear if ALL the Ag-RDT testing negative by the laboratory technician where also PCR-tested or just a subset of the Ag-RDT negatives.

For PCR, all the RDT testing negative were also retested by PCR. PCR was conducted for 529 clients. However, due to lack of more detailed laboratory and clinical data to interpret the RDT-PCR concordance observed, we have opted to exclude these data from the manuscript, as it was not a key objective of this study.

3) In section Results: Concordance, it mentions 489 negative cases, but this does not match the number in the table 3 which is 496.

Thanks for flagging this typing error, the sentence has been amended to:

"Of these, three positive cases and 496 negative cases were identified by both CHWs and laboratory professionals".

4) Same section: then it is stated "PCR tests... confirmed complete agreement with the Ag-RDT test results" but the number of Ag-RDT negative tests that where PCR re-tested is not reported.

Please see response to question 2.

5) Table 3: it is confusing to mix here both the Ag-RDT re-tests by laboratory technicians and the PCR results by NRL, If every negative Ag-RDT result was tested again with PCR and always resulted in a negative confirmation by PCR, then I suggest to remove the mention to PCR in the column group title, and instead use the asterisk call ' * ' in the negative-negative cell number, where the table foot could

use wording such as " * Only negative Ag-RDTs for patients with symptoms of COVID-19 where retested by PCR, which confirmed negative results in all cases".

Please see response to question 2.

6) Table 3: row and column named: Invalid, may be removed from table 3.

The column "Invalid" was removed from Table 3.

7) In Supplementary methods: FGD script, section B: Testing Covid-19 Done By CHWS: item 11: I think it is mistranslated to english, because the item is about the e-ASCOV App in general when in this section B it should be specifically about the Ag-RTD testing by CHWs.

It was corrected to "How confident are you with COVID-19 testing done by CHWs?" as this is how it was captured during the CHW's experience assessment.

8) in Supplementary Tables and Figures: Supplementary Table 1. the last column mentions "(%)" as if it was intended to present the Number of CHWs selected for the project as a percentage of the CHWs in the district while in the data that proportion is missing except for Gasabo district which informs "(6)".

We have added all the percentages in the column.

9) Supplementary Figure 1: I suggest to transform the figure into a table.

Figure 1 was converted to Table 4 in the supplementary material, as suggested.

Reviewer 2

Comments to the Author:

- Line 78: Please add next to the advantages of RDT also the disadvantages including references!

We removed the advantages of RDT to shorten the introduction as advised and explained that the diagnostic gold standard presented access challenges due to limited laboratory infrastructure.

Especially in screening use RDTs are far away from the diagnostic reliability of the RT-qPCR which is the diagnostic gold standard.

In response to question 2 (Reviewer 1): the section of "Concordance testing" was removed, due to lack of more detailed laboratory and clinical data to interpret the RDT-PCR concordance observed and it was not a key objective of this study.

- I would recommend to shorten the introduction to about one page. For example line 112 following can be either moved to the methods or shortened.

Thank you, the introduction section was shortened.

- Please add the procedure of sample collection for the AG-RDT, was it a nasopharyngeal swab?

CHWs collected samples using nasopharyngeal swab, in line 443 the sentence has been modified to:

“The CHW collected nasal samples for the Ag-RDT using nasopharyngeal swabs and were thereafter instructed to start the timer after initiating the test”.

- It would be an improvement for the manuscript, if the different study sites were presented in a map of Ruanda for a better orientation, the case numbers could be added in this map.

We've added a map showing study sites highlighted in circles as supplementary figure 2, in the supplementary material.

- I would prefer to combine Table 1 and Table 2 in one table.

We have combined Table 1 and 2 into “Table 1”

- Please always add the absolute figures (group size/total group) if shares of a cohort are given as a relative percentage value

Thank you, this has been resolved.

- What was the vaccination status of the test subjects and again the status of previous infections? Could it be that in rural areas there were simply more past infections or fewer vaccinations at the time of the test and therefore the symptoms were more pronounced there? Is this data available? This should also be discussed if no data is available. After all, this fact of a different distribution of symptoms could already indicate a different need for care in terms of testing strategy, but possibly also an increased focus on vaccinations / other infection prevention.

The data on the vaccination status and previous infection was not collected during this pilot. We would like to note that we reached the pilot's end when the incidence of COVID-19 reduced and people with related symptoms reduced too. In response to your suggestion line 671 in the discussion section has been amended to:

Community-based testing methods supported by digital tools, as deployed in this study, could be a useful approach to identify earlier identification of high-transmission areas such as these, by facilitating near-patient access to testing. Disaggregated data on vaccination status and previous infection per district was not collected by this study; these would be useful in interpreting the

symptoms and positivity rates seen in the different districts. Towards the end of the study, there was a reduction in COVID-19 incidence and people with COVID-19 symptoms which was also observed nationwide in both urban and rural areas.

- Referring the used smartphones: The digital application was suitable for different mobile operation systems, e.g. iOS, Android etc.

All the smartphone used were Androids (Maraphone made in Rwanda), this is indicated in the strength and limitations section as below:

“The study used only Android smartphones; challenges related to different phones were not assessed. However, the application met the requirement for installation and use in all smartphone versions.”

- How did the application look like? Was it an App? Maybe adding some Screenshot of the design in the Supplements would make the manuscript more realistic.

Screenshots of the app were added to the supplementary materials as supplementary Figure 1.

- Supplementary Figure 1: I think this is an important figure which should be presented as Figure in the manuscript. Please add the labeling of the y axes.

In line with Reviewer 1, Supplementary Figure 1 was removed and results are presented in supplementary Table 4

- I would recommend to better adapt the discussion to the time of publication. The concept is based on the COVID-19 pandemic scenario which developed to an endemic. The important learning is in my opinion that the concept presented can be used for further outbreaks of pathogens and adapted to these.

Thank you, we agree that updating the discussion to the current time of publication. However, the epidemiology of COVID-19 has changed a lot. The time we conducted this pilot, it was an urgent solution to maximize the early detection of COVID-19 case and control. Importantly we found out that the tool has a potential to be adapted for other diseases and institutionalize it for early outbreak warning in the community but also to respond to the need for digital health. We have amended the discussion to include the following statement:

“Although this study was conducted during the COVID-19 pandemic, when Rwanda needed urgent solutions to maximize early detection and control of the disease and COVID-19 is currently endemic, the lessons from this study can also be adapted for early warning of outbreaks and surveillance of other diseases. As an example, the digital approaches used in this study have subsequently been applied in the development of a national community health information system, by designing digital symptom screening and decision support integrated across the full package of services delivered by CHWs. This system has been piloted in Rwanda since 2023.”

- Abstract: "PCR and Ag-RDT results were also fully concordant" This is not very well presented in the results section of the manuscript. Further, evidence to data says clearly that PCR is the gold standard for diagnostics. RDTs have reduced sensitivity, depending on the tested cohort (better for symptomatic individuals like in the study presented but not as equal as PCR!)

- Please discuss that RDTs are not as reliable as PCR. There is a huge amount of evidence to that, that describes that also including the Panbio RDT (Dinnes et al. <https://doi.org/10.1002/14651858.CD013705.pub3>; Wagenhäuser et al. <https://doi.org/10.1016/j.cmi.2022.08.006>; Boujema et al. <https://doi.org/10.1016/j.jviromet.2023.114811>) The chosen strategy in this study with testing symptomatic individuals decreases the probability of false-negative RDTs but cannot exclude this

Please see response to question 2 (Reviewer 1): due to absence of more detailed data to interpret the concordance findings, we have opted to exclude this exploratory objective.

Minor comments:

Please standardise the text formatting with left-aligned and justified changing often.

Thank you, the formatting has been updated.

Line 63f: Is there any evidence to cite about the CHWs infrastructure in Rwanda

We have deleted line 63, when shortening the introduction

Line 67: Please specify which tests were conducted in which count, PRC or RDT? Or in parallel?

Of the 4.5 million tests, 73.3% were antigen-based rapid diagnostic tests (Ag-RDTs), while 26.7% were polymerase chain reaction (PCR) tests. We have added a line to the introduction to note this.

Line 69: Is it possible to add a reference to the national incidence data?

The reference is the same as Reference 1 and has been added. It was an online dynamic dashboard updated on a daily basis.

Line 137: "across eight districts in Rwanda" can be removed as it is repeated again in the following sentence

This has been corrected.

Line 154: Does "described previously" refer to line 112 f. or is there a reference missing?

A reference has been added.

Line 172 (as example) please use only one of the two options “RDT” or “Ag-RDT” throughout the entire manuscript

This has been corrected to “Ag-RDT”.

Line 252: “national data security guidelines per the Rwanda Information Security Authority”, please add reference

We have added a reference.

Line 395: It is extremely unusual to include quotes from those responsible in a scientific text. In my opinion, this can be used well for a newspaper article outside the scientific publication or in a lecture, but not in a scientific manuscript due to the clear subjectivity.

Thank you, we have paraphrased respondents’ input and updated the discussion.

Line 402-404: I would recommend searching for a reference for age-dependency of user skills.

Thank you, we have added a reference.

VERSION 2 – REVIEW

REVIEWER NAME	Wagenhäuser , Isabell
REVIEWER AFFILIATION	University Hospital Würzburg
REVIEWER CONFLICT OF INTEREST	No competing interests to declare.
DATE REVIEW RETURNED	16-Jul-2024

GENERAL COMMENTS	Thank you very much for carefully revising the manuscript! - Please remove the dot in line 16. - Supplemenatary Figure 2: Pleas cite the source of the map like the other resources and add the last date of access. - please add a reference for line 64/65 -Supplementary Figure 1: Please label the y axes
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Isabell Wagenhäuser, University Hospital Würzburg

Comments to the Author:

Thank you very much for carefully revising the manuscript!

Response: Thank you for the feedback.

- Please remove the dot in line 16.

Response: We have checked and the dot is not visible in the clean version in which we have provided the amends.

- Supplementary Figure 2: Please cite the source of the map like the other resources and add the last date of access.

Response: We have updated the source for the map and provided the date of access below the figure. In terms of citing the source of the map like other resources, we have understood this to mean adding the source as a reference. As such, we have also added the source for the map into a reference list in the Supplementary materials (page 11 in the supplement).

- please add a reference for line 64/65

Response: We have added an additional reference to line 64/65 (copied below) as requested. We have cited a World Health Organization document on the importance of testing to support the part of the sentence about the importance of widespread testing to enable to rapid detection of SARS-CoV-2 and contain its transmission.

"Most COVID-19 cases were reported during three major waves in which rapid surges of infection took place in a short period of time,¹ underscoring the importance of widespread testing to enable the rapid detection of SARS-CoV-2 and contain its transmission.²"

New reference: World Health Organization. Why testing is important? 2022 [Available from: <https://www.who.int/multi-media/details/why-testing-is-important> accessed 14 August 2024.

-Supplementary Figure 1: Please label the y axes

Response: Supplementary Figure 1 is an image of the e-ASCov application and as such, there is no Y axis.

Reviewer: 2

Competing interests of Reviewer: No competing interests to declare.