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A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19 tests

Lirong Cao, Shi Zhao, Qi Li, Lowell Ling, William K. K. Wu, Lin Zhang, Jingzhi Lou, Marc K. C. Chong, Zigui Chen, Eliza L. Y. Wong, Benny C. Y. Zee, Matthew T. V. Chan, Paul K. S. Chan and Maggie H. Wang

Article citation details
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Review timeline

Original submission:	18 October 2020
1st revised submission:	4 May 2021
2nd revised submission:	30 August 2021
Final acceptance:	1 September 2021

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSOS-201867.R0 (Original submission)

Review form: Reviewer 1

Is the manuscript scientifically sound in its present form?
No

Are the interpretations and conclusions justified by the results?
No

Is the language acceptable?
Yes

Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
Yes

Recommendation?
Major revision is needed (please make suggestions in comments)

Comments to the Author(s)
Please see uploaded pdf for specific comments (Appendix A).

My key points are:

Firstly, you make a comparison between your method and the use of a single test to make a diagnosis. I do not think this is a fair comparison to make as it confounds two things – firstly the use of multiple tests to make a diagnosis, which even using a completely naïve method would be expected to improve overall diagnostic accuracy, and the benefit of using your method of weighting each test in a probabilistic framework according to its accuracy. What a 'naïve' clinician would usually do would be to look at the outcomes of the multiple tests that they have taken and make a decision based on the proportion of positive tests among those. Again, using a cut-off of 0.5 to determine a positive diagnosis, I think that this would be a much fairer comparison to make with your method to determine its overall benefit.

My second comment is that I think your simulation study is much too restrictive as it is. In the literature, there is usually a great deal of uncertainty as to the exact values of specificity and sensitivity, with ranges of values often given. I think further simulations where you look at the impact of this potential misspecification on your results would make for a better analysis. I think you also need to discuss further the impact of what happens if the underlying disease status of the patient changes across tests. It seems realistic to assume that a patient testing negative on an initial test when not infectious, could then go onto to become infectious by the time of a later test. There is some alluding to this in the discussion but no mention of the impact of this on your results.

I think you also need to justify your comment about conditional independence between tests. Li and Liu (2019) showed this assumption is not valid for tests on the same biological attribute.

I tried to access your online tool, however the page wouldn't load. I would need to be able to see these as it is a significant part of what your paper is proposing as novel.

Many previous studies have conducted Bayesian analysis of multiple tests and I think a greater reference to this literature and how your method is distinct would emphasise its novelty (e.g. Umemneku Chikere et al (2019); Berkvens et al (2006); Dendukuri (2004)). Is there a methodological novelty or is the novelty that you are applying this method to COVID-19?

References:
Berkvens, Dirk*; Speybroeck, Niko*; Praet, Nicolas*; Adel, Amel†; Lesaffre, Emmanuel‡ Estimating Disease Prevalence in a Bayesian Framework Using Probabilistic Constraints, Epidemiology: March 2006 - Volume 17 - Issue 2 - p 145-153
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Review form: Reviewer 2

Is the manuscript scientifically sound in its present form?
No

Are the interpretations and conclusions justified by the results?
No

Is the language acceptable?
No

Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
No

Recommendation?
Major revision is needed (please make suggestions in comments)

Comments to the Author(s)
The authors have used conditional probabilities to estimate the probability that an individual is infected given the results from multiple tests, accounting for the sensitivity and specificity of each test, and the pre-test probability of infection.

The authors have pitched their method as a means to improve diagnostic accuracy to aid with the control of outbreaks, particularly in the context of COVID-19. They suggest that clinicians could use the associated web tool to provide a more accurate estimate of infection status to patients.

There are some disconnects between the theory — which is sound — and how it might be implemented and utilised in practice:

1. The narrative refers to the need for "timely diagnosis" to contain outbreaks, though the example throughout refers to serological testing as one of the three possible tests. The authors themselves note that serological tests provide an accurate indication of prior infection at later stages of infection, which is not consistent with "timely" diagnosis. Particularly for a pathogen such as SARS-CoV-2, where a substantial portion of transmission is pre-symptomatic. Similarly, CT scans are unlikely to be routine for all potential or suspected cases, but rather just for those with more severe disease and/or requiring hospitalisation. As noted further below, the sensitivity and specificity of these tests varies over time, and each would likely be conducted at different times during the infectious profile of an individual (e.g., PCR early, serology later), making them difficult to be combined simply without additional work to determine the sensitivity/specificity specific to the timing of each test. This makes it difficult to see a situation where these different tests are routinely being performed for timely diagnosis of suspected cases, or the outcomes could be simply and reliably combined. Perhaps it would be appropriate to pitch

the narrative along the lines of using multiple rapid diagnostic tests, each of which have lower sensitivity and specificity, but results of which could be combined for a more accurate result.

2. The method requires specification of a pre-test probability to calculate the probability of being infected given the various test results. The authors propose that clinicians specify this probability to calculate the probability the individual is/was infected. While public data is available on daily incidence of cases, it is not immediately clear how the current prevalence would simply inform this probability (e.g., should this be weighted by the generation interval?). Further, these kinds of high-level data cannot account for individual heterogeneities in risk (e.g., healthcare practitioners treating COVID-19 patients would have a higher pre-test probability than another individual in the same population), and thus how much to adjust the pre-test probability in different contexts. Figure 2 in the submitted manuscript highlights the sensitivity of the outcome to this pre-test probability, particularly in the scenarios where it would be most useful — i.e., where the multiple tests give disparate results — and so accurately choosing this probability is key, but difficult. I would propose that were this approach to be implemented in some capacity (e.g., in a diagnostic lab), the authors must provide some more guidance as to how one can reliably estimate this pre-test probability. Perhaps grouping individuals into risk categories, where they have an interval for their pre-test probability (e.g., Pr(D) is 0.0001 – 0.001 for low risk), and results are interpreted in this context, rather than a single estimate, might be useful?

3. Finally, as noted above, the stage of infectiousness will impact the sensitivity and specificity of each different type of test (see for example, Boum et al, Lancet Infectious Diseases 2021). Do the authors propose that the sensitivity and specificity be adjusted for each test according to the time that the test was taken (e.g., relative to symptom onset)? If adjusting the narrative away from combining, for example, PCR and serology, then this point may be less important to address. Alternatively, if subtle changes in the sensitivity/specificity due to phase of infectiousness do not substantially impact the estimated posterior probabilities, it may be useful to show this with a sensitivity analysis so that an end-user can understand how precise they have to be with specifying these values.

Decision letter (RSOS-201867.R0)

We hope you are keeping well at this difficult and unusual time. We continue to value your support of the journal in these challenging circumstances. If Royal Society Open Science can assist you at all, please don't hesitate to let us know at the email address below.

Dear Dr Wang

The Editors assigned to your paper RSOS-201867 "A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19" have now received comments from reviewers and would like you to revise the paper in accordance with the reviewer comments and any comments from the Editors. Please note this decision does not guarantee eventual acceptance.

We invite you to respond to the comments supplied below and revise your manuscript. Below the referees' and Editors' comments (where applicable) we provide additional requirements. Final acceptance of your manuscript is dependent on these requirements being met. We provide guidance below to help you prepare your revision.

We do not generally allow multiple rounds of revision so we urge you to make every effort to fully address all of the comments at this stage. If deemed necessary by the Editors, your

manuscript will be sent back to one or more of the original reviewers for assessment. If the original reviewers are not available, we may invite new reviewers.

Please submit your revised manuscript and required files (see below) no later than 21 days from today's (ie 13-Apr-2021) date. Note: the ScholarOne system will 'lock' if submission of the revision is attempted 21 or more days after the deadline. If you do not think you will be able to meet this deadline please contact the editorial office immediately.

Please note article processing charges apply to papers accepted for publication in Royal Society Open Science (https://royalsocietypublishing.org/rsos/charges). Charges will also apply to papers transferred to the journal from other Royal Society Publishing journals, as well as papers submitted as part of our collaboration with the Royal Society of Chemistry (https://royalsocietypublishing.org/rsos/chemistry). Fee waivers are available but must be requested when you submit your revision (https://royalsocietypublishing.org/rsos/waivers).

Thank you for submitting your manuscript to Royal Society Open Science and we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Kind regards,
Anita Kristiansen
Editorial Coordinator

Royal Society Open Science
openscience@royalsociety.org

on behalf of Professor Joshua Ross (Associate Editor) and Mark Chaplain (Subject Editor)
openscience@royalsociety.org

Reviewer comments to Author:
Reviewer: 1
Comments to the Author(s)
Please see uploaded pdf for specific comments.

My key points are:

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Reviewer: 2
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sensitivity and specificity of these tests varies over time, and each would likely be conducted at different times during the infectious profile of an individual (e.g., PCR early, serology later), making them difficult to be combined simply without additional work to determine the sensitivity/specificity specific to the timing of each test. This makes it difficult to see a situation where these different tests are routinely being performed for timely diagnosis of suspected cases, or the outcomes could be simply and reliably combined. Perhaps it would be appropriate to pitch the narrative along the lines of using multiple rapid diagnostic tests, each of which have lower sensitivity and specificity, but results of which could be combined for a more accurate result.

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3. Finally, as noted above, the stage of infectiousness will impact the sensitivity and specificity of each different type of test (see for example, Boum et al, Lancet Infectious Diseases 2021). Do the authors propose that the sensitivity and specificity be adjusted for each test according to the time that the test was taken (e.g., relative to symptom onset)? If adjusting the narrative away from combining, for example, PCR and serology, then this point may be less important to address. Alternatively, if subtle changes in the sensitivity/specificity due to phase of infectiousness do not substantially impact the estimated posterior probabilities, it may be useful to show this with a sensitivity analysis so that an end-user can understand how precise they have to be with specifying these values.

===PREPARING YOUR MANUSCRIPT===

Your revised paper should include the changes requested by the referees and Editors of your manuscript. You should provide two versions of this manuscript and both versions must be provided in an editable format:
one version identifying all the changes that have been made (for instance, in coloured highlight, in bold text, or tracked changes);
a 'clean' version of the new manuscript that incorporates the changes made, but does not highlight them. This version will be used for typesetting if your manuscript is accepted.
Please ensure that any equations included in the paper are editable text and not embedded images.

Please ensure that you include an acknowledgements' section before your reference list/bibliography. This should acknowledge anyone who assisted with your work, but does not qualify as an author per the guidelines at https://royalsociety.org/journals/ethics-policies/openness/.

While not essential, it will speed up the preparation of your manuscript proof if accepted if you format your references/bibliography in Vancouver style (please see https://royalsociety.org/journals/authors/author-guidelines/#formatting). You should include DOIs for as many of the references as possible.

If you have been asked to revise the written English in your submission as a condition of publication, you must do so, and you are expected to provide evidence that you have received language editing support. The journal would prefer that you use a professional language editing service and provide a certificate of editing, but a signed letter from a colleague who is a native speaker of English is acceptable. Note the journal has arranged a number of discounts for authors using professional language editing services (https://royalsociety.org/journals/authors/benefits/language-editing/).

===PREPARING YOUR REVISION IN SCHOLARONE===

To revise your manuscript, log into https://mc.manuscriptcentral.com/rsos and enter your Author Centre - this may be accessed by clicking on "Author" in the dark toolbar at the top of the page (just below the journal name). You will find your manuscript listed under "Manuscripts with Decisions". Under "Actions", click on "Create a Revision".

Attach your point-by-point response to referees and Editors at Step 1 'View and respond to decision letter'. This document should be uploaded in an editable file type (.doc or .docx are preferred). This is essential.

Please ensure that you include a summary of your paper at Step 2 'Type, Title, & Abstract'. This should be no more than 100 words to explain to a non-scientific audience the key findings of your research. This will be included in a weekly highlights email circulated by the Royal Society press office to national UK, international, and scientific news outlets to promote your work.

At Step 3 'File upload' you should include the following files:
-- Your revised manuscript in editable file format (.doc, .docx, or .tex preferred). You should upload two versions:
1) One version identifying all the changes that have been made (for instance, in coloured highlight, in bold text, or tracked changes);
2) A 'clean' version of the new manuscript that incorporates the changes made, but does not highlight them.
-- An individual file of each figure (EPS or print-quality PDF preferred [either format should be produced directly from original creation package], or original software format).
-- An editable file of each table (.doc, .docx, .xls, .xlsx, or .csv).
-- An editable file of all figure and table captions.
Note: you may upload the figure, table, and caption files in a single Zip folder.
-- Any electronic supplementary material (ESM).
-- If you are requesting a discretionary waiver for the article processing charge, the waiver form must be included at this step.
-- If you are providing image files for potential cover images, please upload these at this step, and inform the editorial office you have done so. You must hold the copyright to any image provided.
-- A copy of your point-by-point response to referees and Editors. This will expedite the preparation of your proof.

At Step 6 'Details & comments', you should review and respond to the queries on the electronic submission form. In particular, we would ask that you do the following:
-- Ensure that your data access statement meets the requirements at https://royalsociety.org/journals/authors/author-guidelines/#data. You should ensure that

you cite the dataset in your reference list. If you have deposited data etc in the Dryad repository, please include both the 'For publication' link and 'For review' link at this stage.
-- If you are requesting an article processing charge waiver, you must select the relevant waiver option (if requesting a discretionary waiver, the form should have been uploaded at Step 3 'File upload' above).
-- If you have uploaded ESM files, please ensure you follow the guidance at https://royalsociety.org/journals/authors/author-guidelines/#supplementary-material to include a suitable title and informative caption. An example of appropriate titling and captioning may be found at https://figshare.com/articles/Table_S2_from_Is_there_a_trade-off_between_peak_performance_and_performance_breadth_across_temperatures_for_aerobic_scope_in_teleost_fishes_/3843624.

At Step 7 'Review & submit', you must view the PDF proof of the manuscript before you will be able to submit the revision. Note: if any parts of the electronic submission form have not been completed, these will be noted by red message boxes.

Author's Response to Decision Letter for (RSOS-201867.R0)

See Appendix B.

RSOS-201867.R1 (Revision)

Review form: Reviewer 1

Is the manuscript scientifically sound in its present form?
Yes

Are the interpretations and conclusions justified by the results?
Yes

Is the language acceptable?
Yes

Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
No

Recommendation?
Accept as is

Comments to the Author(s)
Thank you for addressing my comments fully. I am now happy with the manuscript to be published as it is.

Review form: Reviewer 2

Is the manuscript scientifically sound in its present form?
Yes

Are the interpretations and conclusions justified by the results?
Yes

Is the language acceptable?
Yes

Do you have any ethical concerns with this paper?
No

Have you any concerns about statistical analyses in this paper?
No

Recommendation?
Accept with minor revision (please list in comments)

Comments to the Author(s)
Many thanks for addressing my previous queries. I have only a few minor comments on the current version (line numbers refer to the track changes version):

L181: An individual can test positive when not infectious (e.g., prolonged shedding). This sentence should remove "infectious" so as to not conflate having detectable virus (if the authors are referring to PCR) with being infectious and able to transmit viable virus. For example, the sentence could read: "For example, a patient that tested negative by PCR when first tested shortly after exposure, may not yet have detectable virus, but could later test positive once viral loads are sufficient incubated.", or similar.

L202: I think the word 'suspicious' here should be 'suspected'.

Decision letter (RSOS-201867.R1)

We hope you are keeping well at this difficult and unusual time. We continue to value your support of the journal in these challenging circumstances. If Royal Society Open Science can assist you at all, please don't hesitate to let us know at the email address below.

Dear Dr Wang

On behalf of the Editors, we are pleased to inform you that your Manuscript RSOS-201867.R1 "A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19 tests" has been accepted for publication in Royal Society Open Science subject to minor revision in accordance with the referees' reports. Please find the referees' comments along with any feedback from the Editors below my signature.

We invite you to respond to the comments and revise your manuscript. Below the referees' and Editors' comments (where applicable) we provide additional requirements. Final acceptance of

your manuscript is dependent on these requirements being met. We provide guidance below to help you prepare your revision.

Please submit your revised manuscript and required files (see below) no later than 7 days from today's (ie 17-Aug-2021) date. Note: the ScholarOne system will 'lock' if submission of the revision is attempted 7 or more days after the deadline. If you do not think you will be able to meet this deadline please contact the editorial office immediately.

Please note article processing charges apply to papers accepted for publication in Royal Society Open Science (https://royalsocietypublishing.org/rsos/charges). Charges will also apply to papers transferred to the journal from other Royal Society Publishing journals, as well as papers submitted as part of our collaboration with the Royal Society of Chemistry (https://royalsocietypublishing.org/rsos/chemistry). Fee waivers are available but must be requested when you submit your revision (https://royalsocietypublishing.org/rsos/waivers).

Thank you for submitting your manuscript to Royal Society Open Science and we look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Kind regards,
Royal Society Open Science Editorial Office
Royal Society Open Science
openscience@royalsociety.org

on behalf of Professor Joshua Ross (Associate Editor) and Mark Chaplain (Subject Editor)
openscience@royalsociety.org

Reviewer comments to Author:
Reviewer: 1

Comments to the Author(s)
Thank you for addressing my comments fully. I am now happy with the manuscript to be published as it is.

Reviewer: 2
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a 'clean' version of the new manuscript that incorporates the changes made, but does not highlight them. This version will be used for typesetting.
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Please ensure that you include an acknowledgements' section before your reference list/bibliography. This should acknowledge anyone who assisted with your work, but does not qualify as an author per the guidelines at https://royalsociety.org/journals/ethics-policies/openness/.

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===PREPARING YOUR REVISION IN SCHOLARONE===

To revise your manuscript, log into https://mc.manuscriptcentral.com/rsos and enter your Author Centre - this may be accessed by clicking on "Author" in the dark toolbar at the top of the page (just below the journal name). You will find your manuscript listed under "Manuscripts with Decisions". Under "Actions", click on "Create a Revision".

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-- An editable file of each table (.doc, .docx, .xls, .xlsx, or .csv).
-- An editable file of all figure and table captions.
Note: you may upload the figure, table, and caption files in a single Zip folder.

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Author's Response to Decision Letter for (RSOS-201867.R1)

See Appendix C.

Decision letter (RSOS-201867.R2)

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Dear Dr Wang,

I am pleased to inform you that your manuscript entitled "A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19 tests" is now accepted for publication in Royal Society Open Science.

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Appendix A

ROYAL SOCIETY OPEN SCIENCE

A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19

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Manuscript ID	RSOS-201867
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Subject:	Statistics < MATHEMATICS
Keywords:	COVID-19, SARS-CoV-2, RT-PCR, chest CT, serological tests, multiple tests integration
Subject Category:	Mathematics

Author-supplied statements

Relevant information will appear here if provided.

Ethics

Does your article include research that required ethical approval or permits?:
This article does not present research with ethical considerations

Statement (if applicable):
CUST_IF_YES_ETHICS :No data available.

Data

It is a condition of publication that data, code and materials supporting your paper are made publicly available. Does your paper present new data?:
My paper has no data

Statement (if applicable):
CUST_IF_YES_DATA :No data available.

Conflict of interest

I/We declare a competing interest

Statement (if applicable):
MHW is a shareholder of Beth Bioinformatics Co., Ltd. BCYZ is a shareholder of Beth Bioinformatics Co., Ltd and Health View Bioanalytics Ltd. Other authors declared no competing interests.

Authors' contributions

This paper has multiple authors and our individual contributions were as below

Statement (if applicable):
MHW conceived the study. LC conducted the literature review. SZ and MHW carried out the analysis. LC, SZ, QL and MHW discussed the results. LC and SZ drafted the first manuscript. SZ and QL developed the online tool. All authors critically read and revised the manuscript and gave final approval for publication.

Title: A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19

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Abstract

The novel coronavirus disease 2019 (COVID-19) has spread worldwide and threatened human life. Timely diagnosis is needed to contain the spread of SARS-CoV-2 infections. Diagnostic tests for COVID-19 have varying sensitivity and specificity, and the false negative results would have substantial consequences to patient treatment and pandemic control. To detect all suspected infections, multiple testing is widely used. However, it may be difficult to build an assertion when the testing results are inconsistent. Considering the situation when there are more than one diagnostic outcomes for one subject, we proposed a Bayesian probabilistic framework based on the sensitivity and specificity of each diagnostic method to synthesize a posterior probability of being infected by SARS-CoV-2. We demonstrated that the synthesized posterior outcome outperformed each individual testing outcome. A user-friendly web application was developed to implement our analytic framework with free-access via http://39.99.171.158:8080/COVID-19/. The web application enables real-time display of the integrated outcome incorporating two or more tests and calculated based on Bayesian posterior probability. A simulation-based assessment demonstrated higher accuracy and precision of the Bayesian probabilistic model compared to single-test outcome. The online tool developed in this study can assist physicians in making clinical evaluations by effectively integrating multiple COVID-19 tests.

Keywords: COVID-19, SARS-CoV-2, RT-PCR, chest CT, serological tests, multiple tests integration

Background

The ongoing COVID-19 pandemic is causing substantial morbidity and mortality globally [1]. Timely diagnosis is of importance to control outbreaks, especially in the absence of specific treatments or vaccines. To date, the COVID-19 is commonly diagnosed by the detection of unique sequences of SARS-CoV-2 RNA using the Nucleic Acid Amplification Tests (NAAT), e.g., real-time reverse transcription polymerase chain reaction (RT-PCR) [2]. However, suboptimal sample collection, storage and transportation may lead to false negative results. The sensitivity of laboratory-based molecular testing is largely dependent on the types of specimen and the time of collection from onset of illness [3], which also leads to a large range of sensitivity for RT-PCR in previous studies, between 46% and 92% [4-8].

As the RT-PCR test might fall short of testing capacity and timeliness in some regions, recent studies proposed that chest computed tomography (CT) scans could be included as a supplement diagnostic tool if there is clinical symptom, epidemiological characteristic, and imaging characteristics of viral pneumonia that are compatible with COVID-19 infection in epidemic areas [8]. Although the use of chest CT may be useful, the specificity is low due to the absence of pathognomonic CT features, which is even lower than 50% according to earlier research findings [9]. In addition, serological tests are also recommended as a supplement for nucleic acid detection, because the antibody-based methods are relatively cheap, easy to operate and have lower technical requirements [10]. Since the detection of antibodies against SARS-CoV-2 is more accurate in the middle to later stages of COVID-19, antibody tests are primarily used to determine whether a person has been previously infected. In many prior reports, the sensitivity for combined IgM and IgG detection is higher than 71% and the specificity is higher than 90% [11-16].

None of the commonly-used diagnostic test, e.g., RT-PCR, chest CT and serological tests, alone is sufficiently accurate to provide absolute diagnostic certainty [10, 17]. In view of advantages and shortages of each detection method, parallel or serial tests are recommended in the clinic and the results are cross-referenced to improve diagnostic yield [18]. However, clinicians will face immense difficulty diagnosing COVID-19 when the test results are inconsistent. In this study, we provided a statistical method to synthesize multiple diagnostic outcomes and developed an online tool to evaluate the probability of an individual being infected by SARS-CoV-2. The online tool can be applied to assist physicians for diagnosis confirmation of COVID-19.

Methods

Bayesian probabilistic framework With the knowledge of the sensitivity and specificity of each COVID-19 diagnostic test, we constructed a Bayesian probabilistic model to synthesize multiple testing outcomes for individual subject. We calculated the posterior probability of having COVID-19 based on the information and the outcomes of more than one test. Although the outcomes of different tests may be correlated, they are conditionally independent from each other with the disease status fixed (knowingly or unknowingly). Thus, the Bayesian probabilistic framework is applicable to infer the probability of disease status with correlated testing outcomes.

We considered that one individual subject receives M diagnostic tests, where M is an integer and $M > 1$. The testing outcome, i.e., positive or negative, is denoted by T_i for the i-th test. We defined T_i as a binary outcome that is 1 for positive testing outcome and 0 otherwise. We denoted the event that 'the individual subject has COVID-19' by D (stands for 'diagnosed' or 'diseased'). For convenience, we also denoted the complement of event D, i.e., 'the individual subject does

not have COVID-19', by N (stands for 'not diagnosed'). Straightforwardly, the summation of the probabilities (**Pr**) of D and N was 1.

The posterior probability of D on the conditions of the M testing outcomes is $\mathbf{Pr}(D|T_1, T_2, \ldots, T_M)$. Hence, by using the Bayes theorem, the $\mathbf{Pr}(D|T_1, T_2, \ldots, T_M)$ can be computed by using Equation 1. Based on the intuition of Bayes framework, the test with higher sensitivity or specificity will be assigned with more weights automatically.

$$\mathbf{Pr}(D \mid T_1, T_2, \ldots, T_M) = \frac{\mathbf{Pr}(T_1, T_2, \ldots, T_M|D) \cdot \mathbf{Pr}(D)}{\mathbf{Pr}(T_1, T_2, \ldots, T_M)} = \frac{\mathbf{Pr}(T_1, T_2, \ldots, T_M|D) \cdot \mathbf{Pr}(D)}{\mathbf{Pr}(T_1, T_2, \ldots, T_M \mid D) \cdot \mathbf{Pr}(D) + \mathbf{Pr}(T_1, T_2, \ldots, T_M|N) \cdot \mathbf{Pr}(N)} = \frac{\mathbf{Pr}(D) \cdot \prod \mathbf{Pr}(T_i \mid D)}{\mathbf{Pr}(D) \cdot \prod \mathbf{Pr}(T_i \mid D) + \mathbf{Pr}(N) \cdot \prod \mathbf{Pr}(T_i|N)}. \quad \text{Equation 1.}$$

Here, $\mathbf{Pr}(T_i = 1|D)$ was the sensitivity of the i-th test, and $\mathbf{Pr}(T_i = 0|D)$ was its (1 – sensitivity). The $\mathbf{Pr}(T_i = 0|N)$ was the specificity of the i-th test, and $\mathbf{Pr}(T_i = 1|N)$ was its (1 – specificity). The $\mathbf{Pr}(D)$ indicated the pre-test probability of having COVID-19 for an individual who receives tests. An alternative interpretation of $\mathbf{Pr}(D)$ is the prevalence of the COVID-19 among the testing subjects if there is no contact history or symptom. The prevalence among testing populations is available for each region in "Our World in Data" website [19]. The testing performance of each COVID-19 diagnostic test can be summarized from the existing literatures or obtained from the clinical evaluations of commercial testing kits. Hence, $\mathbf{Pr}(D|T_1, T_2, \ldots, T_M)$ is computable.

COVID-19 Diagnostic Assessment Tool The theoretical framework can be conducted to integrate multiple diagnostic test results for COVID-19. To facilitate public use, we set up an open-access user-friendly online application to our framework by web development languages including HTML, CSS and JavaScript. The application is available at http://39.99.171.158:8080/COVID-19/. The user interface was designed to be intuitive and only

has English version now, see Figure 1. "Setup testing information and outcomes" section offers users to input included tests, sensitivity and specificity, and testing outcome (positive or negative). Test 1, Test 2 and Test 3 can be RT-PCR, chest CT and antibody test, respectively. Or it can be testing results from different samples in serial testing. After typing the pre-test probability for someone with suspected exposure, "Results" section will show the posterior probability of the subject being infected with COVID-19 according to the above settings. A detailed user manual is also available in the web application.

Performance evaluation for the Bayesian method We further simulated disease diagnosis according to the posterior probability. The $\mathbf{Pr}(D|T_1, T_2, \ldots, T_M) > 0.5$ was considered as positive cases for COVID-19. The tested population set in the simulation modelling was one million. The performance of combined method by integrating multiple testing outcomes was compared with that of single test by accuracy and precision. The accuracy and precision can be respectively computed in Equation 2 and Equation 3.

$$\text{Accuracy} = \frac{(\text{TP} + \text{TN})}{(\text{TP} + \text{TN} + \text{FP} + \text{FN})} \quad \text{Equation 2.}$$

$$\text{Precision} = \frac{\text{TP}}{(\text{TP} + \text{FP})} \quad \text{Equation 3.}$$

Here, TP = number of true positive subjects, FP = number of false positive subjects, TN = number of true negative subjects, and FN = number of false negative subjects. All analysis was conducted in **R** statistical software (version 3.5.1) [20].

Results

In Figure 2, we demonstrated the relationship between the probability of having COVID-19 and the prevalence of COVID-19 among testing subjects under a two-test scenario as an example.

The sensitivities were assumed to be at 95% and 80%, and the specificity were assumed to be at 80% and 50%, for test #1 with testing outcome T_1 and test #2 with testing outcome T_2, respectively. Four combinations of the testing outcomes were considered including (T_1 = positive, T_2 = positive) in Fig 1A, (T_1 = positive, T_2 = negative) in Fig 1B, (T_1 = negative, T_2 = positive) in Fig 1C, and (T_1 = negative, T_2 = negative) in Fig 1D. The online tool is also available for three diagnostic tests synthetization and serial testing synthetization (http://39.99.171.158:8080/COVID-19/).

For comparison purposes, we reported the performance of a single test and the Bayesian probabilistic model for multiple tests in COVID-19 diagnosis, given a pre-test probability from 0.001% to 25%, sensitivities and specificities for both T_1 and T_2 from 55% to 100% in Figure 3. T1 and T2 could be two types of tests, or repeated tests for different samples. The mean accuracy for the Bayesian probabilistic model was 88%, which was higher than 81% for T_1 and 74% for T_2. The mean precision was also largest for the Bayesian probabilistic model (51%) compared to T_1 (43%) and T_2 (36%) alone.

Is this a fair comparison?

Is this due to the Bayesian model or because of multiple tests?

Discussion

Rapid and accurate diagnosis of SARS-CoV-2 infections could facilitate timely control of the outbreaks of COVID-19 by early detection. The characteristics of three detection methods, RT-PCR, chest CT and serological tests, against COVID-19 are distinct, which may cause large variation in accuracy when these tests are applicable to different courses of the illness or patients with non-identical symptoms [21]. The testing performance for RT-PCR against different types of specimens varies according to the previous studies. Outcomes obtained from samples of the lower respiratory tract, like sputum specimens, are more accurate than that of the upper tract, e.g., nasal swabs and throat swabs, in COVID-19 diagnosis [22, 23]. Since the exact time of

onset is sometimes unknown, particularly for mild patients, and not all patients with COVID-19 could produce sputum for diagnostic evaluation, parallel or serial testing are widely used in COVID-19 diagnosis. However, clinicians may face uncertainty in the disease diagnosis when one test is positive but the other is negative. We developed a probabilistic model to synthesize the risks of having COVID-19 considering three determining factors that included test sensitivity, specificity, and pre-test probability. Although the test results from the same subject are highly correlated, they are conditionally independent, and thus the correlation will not affect the calculation of the posterior probability. The second advantage for Bayesian model is that suitable weights will be added to the corresponding diagnostic tests according to their sensitivities and specificities, especially when the weight for each test is hard to artificially determined. Multiple tests combined with our diagnostic tool demonstrated improved diagnostic accuracy compared to individual tests.

To contain the outbreak of COVID-19, rapid and accurate diagnostic tests are critical. RT-PCR detects the presence of the specific genetic material with generally high specificity but limited sensitivity. Chest CT method, a valuable tool for the triage of suspected cases, is sensitive but prone to high false-positive. A recent study reported that some patients were test-negative by RT-PCR, but radiological evidence detected lung lesions compatible with COVID-19 [24]. The specificity of chest CT was inconsistent in prior studies [25], which may be caused by the differences in study design of independent studies and the differences in diagnostic experiences of thoracic radiologists. For antibody-based methods, the sensitivity and specificity are higher for combined IgM and IgG detection compared with using any of antibodies alone. However, some studies indicated that antibodies appeared after the onset of symptoms [21]. The presence of IgG is particularly delayed. Therefore, serological tests are more suitable to detect infections in the middle or late stage.

How is this accounted for?

During the surging phase of pandemic, the availability of PT-PCR is often affected by a shortage of laboratory test kits, long waiting time, complex operation, expensive equipment and lack of specialized technicians. Alternative testing methods might be applied to assist the diagnosis of COVID-19. Chest CT as a routine imaging method is often readily accessible in general hospitals. Serological tests, being fast and simple to perform, are also widely accepted in clinical and public health settings. High sensitivity is important for screening and diagnosing COVID-19 considering that asymptomatic cases also have a risk of spreading the virus, while specificity needs to be considered to avoid false treatment or nosocomial infection. Utilizing the Bayesian probabilistic model could fully utilize the outcome of each detection method or testing sample and showed improved performance in COVID-19 diagnosis.

The main limitation for this study is that due to the lack of observational research data, the performance of the Bayesian method can only be evaluated through simulation models and pre-set cut-off values for positive diagnoses. However, the calculation of the posterior probability estimation will not be affected. The only impact caused by this inevitable limitation is that the absolute improvement for the performance of the Bayesian framework will be different in the real world.

There are many other issues with real data.

Yes, which is why I think more simulations are necessary.

The decision analytical model found that the probability of having COVID-19 calculated based on multiple testing varied with pre-test probabilities, which would be an important factor to consider, particularly in regions with increasing disease prevalence. Pre-test probability, an estimate of a person's chance of being infected before testing, mainly depends on local positive rate of COVID-19 among testing samples, SARS-CoV-2 exposure history and clinical signs [26]. Someone who is feeling unwell after close contact with suspected patients may have a higher risk of COVID-19 compared to local prevalence. The online tool developed in this study can assist physicians in performing a quick diagnosis onsite. The statistic underpinning of the proposed method is generic and can be applied to other infectious diseases.

Conclusions

Diagnostic tests for COVID-19 currently in use have varying sensitivity and specificity. As parallel and serial testing are widely used in the clinic to avoid missed diagnosis or misdiagnosis, we presented a Bayesian probabilistic framework that takes advantage of the outcome of multiple detection methods or testing samples for the COVID-19. We also developed a convenient online tool to display the posterior probability of being infected by SARS-CoV-2 by effectively integrating multiple COVID-19 tests. The online tool adds value to existing detection methods and can aid physicians in making clinical evaluations.

Abbreviations

Not applicable.

Declarations

Ethics

Neither ethical approval nor individual consent is applicable.

Data accessibility

No real-world data is used in this study. The code supporting this article have been uploaded as part of the supplementary material.

Authors' Contributions

MHW conceived the study. LC conducted the literature review. SZ and MHW carried out the analysis. LC, SZ, QL and MHW discussed the results. LC and SZ drafted the first manuscript. SZ and QL developed the online tool. All authors critically read and revised the manuscript and gave final approval for publication.

Competing interests

MHW is a shareholder of Beth Bioinformatics Co., Ltd. BCYZ is a shareholder of Beth Bioinformatics Co., Ltd and Health View Bioanalytics Ltd. Other authors declared no competing interests.

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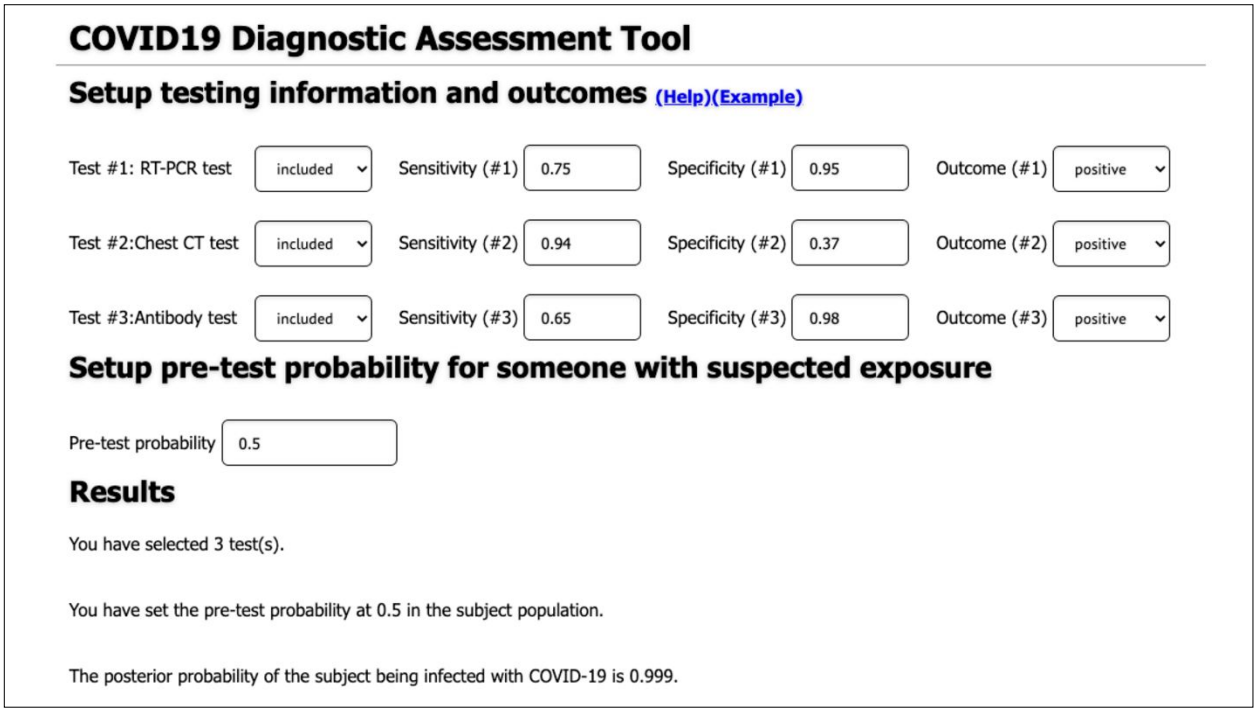


Figure 1. User interface for COVID-19 Diagnostic Assessment Tool.

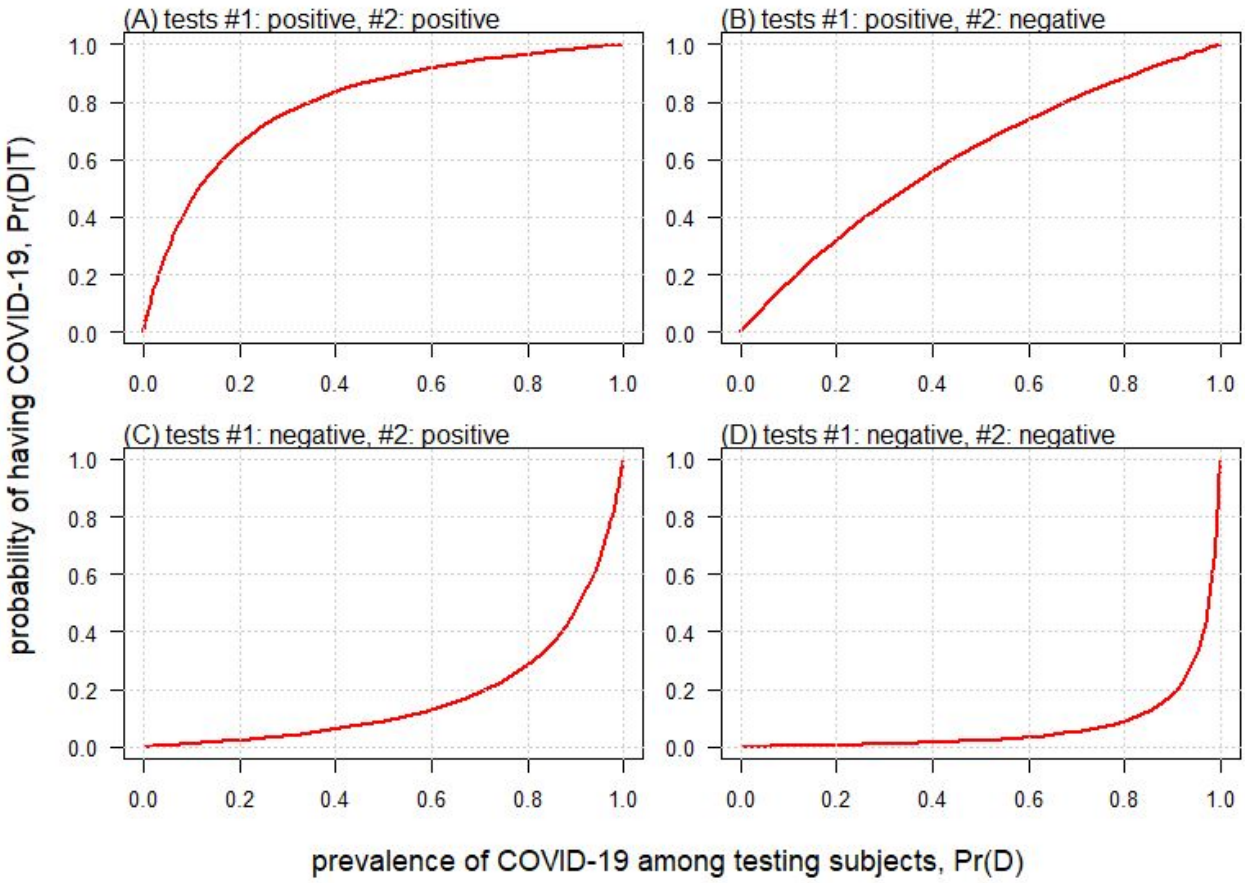


Figure 2. The relationship between **Pr**(D) and **Pr**($D|T_1$, T_2). The sensitivities are assumed at 95% and 80%, and the specificity are assumed at 80% and 50%, for test #1 and test #2 respectively.

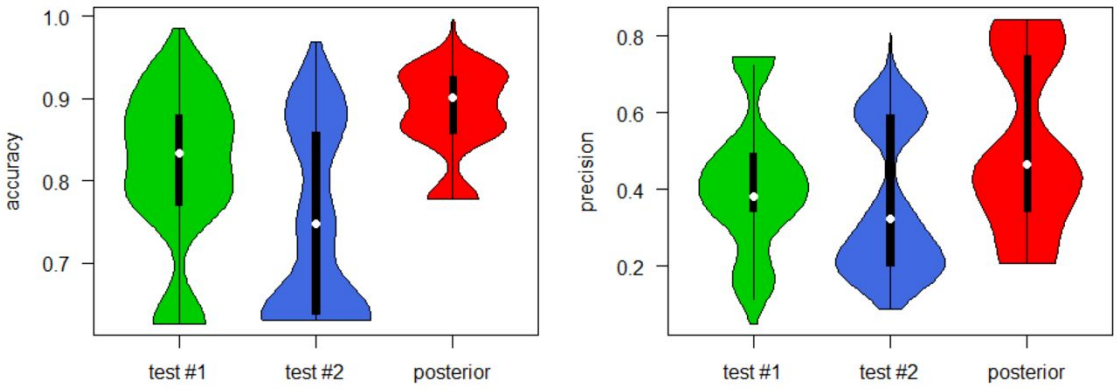


Figure 3. Violin plot of the accuracy and precision for test #1, test #2 and the Bayesian probabilistic model. The pre-test probability is assumed from 0.001% to 25%, and sensitivities and specificities for both T1 and T2 are assumed from 55% - 100% in Figure 3.

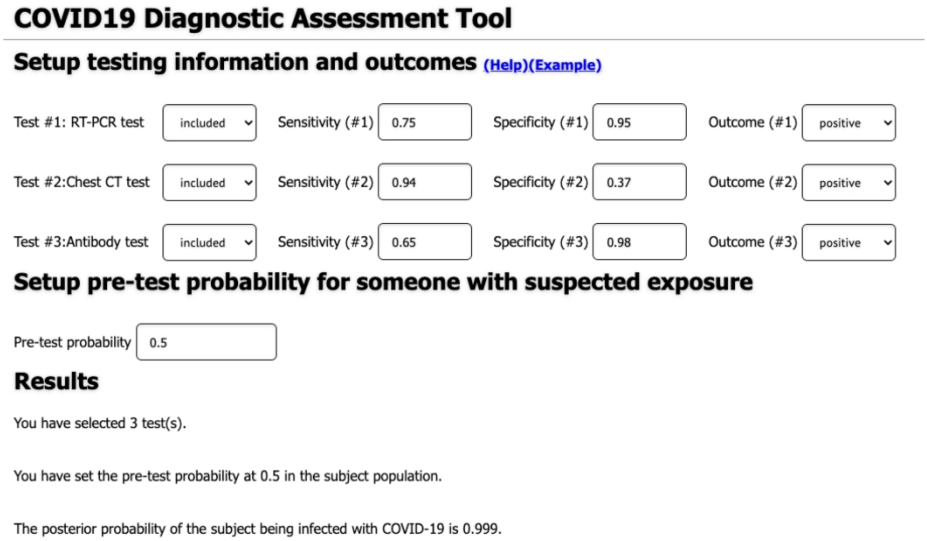


Figure 1. User interface for COVID-19 Diagnostic Assessment Tool.

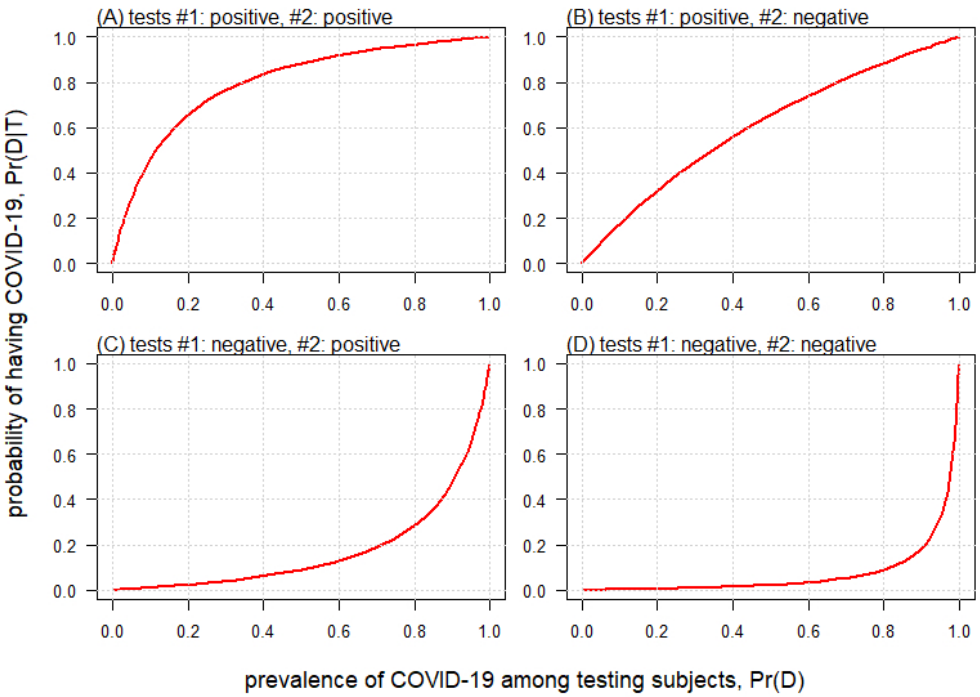
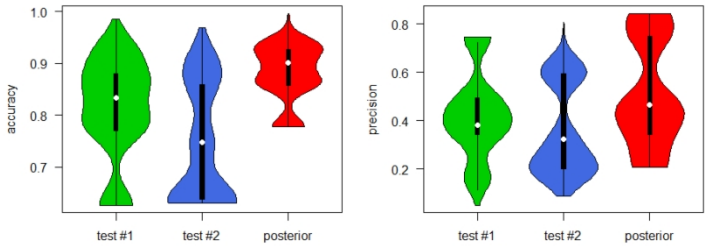


Figure 2. The relationship between Pr(D) and Pr(D|T1, T2). The sensitivities are assumed at 95% and 80%, and the specificity are assumed at 80% and 50%, for test #1 and test #2 respectively.

205x146mm (96 x 96 DPI)



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Appendix B

Dear Editor,

Thanks for handling our manuscript entitled "***A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19***" (MS ID: **RSOS-201867**). We appreciate your positive decisions and comments from the reviewers. Please find our point-by-point response below.

Regards,

Maggie H Wang, PhD (corresponding author)

Reviewer #1:

(1) *Specific comments in the uploaded pdf.*

Response: Thank you very much for your valuable comments. We have extensively revised and improved the manuscript as suggested.

(2) *The last sentence in the background part would benefit from more details.*

Response: Thanks for your suggestions. We have improved it with more details.

Line 86: "In this study, we provide a Bayesian method to synthesize multiple diagnostic outcomes and develop an online tool to evaluate the probability of an individual being infected by SARS-CoV-2."

(3) *"Knowingly or unknowingly" in the Bayesian probabilistic framework of the method section needs justification.*

Response: Thank you for your comments. To avoid confusion, we have removed 'Knowingly or unknowingly' in the revised manuscript.

(4) *In the Performance evaluation for the Bayesian method part, "Pr(D|T1, T2, …, TM) > 0.5" and "one million" need justification.*

Response: Thank you for your comments. The cut-off 0.5 is adopted because 0.5 gives a fair 'guess' for binary variables. If one event has a probability larger than 0.5 against its counter side, this event is more likely to occur probabilistically. The 'one million' is to mimic the city-level population size. Other numbers, e.g., 10M, 100M or 0.1M, will not alter the main results.

(5) *Is there a fair comparison for comparison of a single test and the Bayesian probabilistic model for multiple tests. Is this due to Bayesian model or because of multiple tests?*

Response: This is a very good question. The common approaches to combine multiple tests are based on calculating a summary statistic from the weighted Z-statistics or p-values (Fisher's method). Such integration is based on the level of significance but cannot account for "effect size" in the summary statistics. The Bayesian approach combines the tests outcomes based on individual tests predicted disease probabilities. Furthermore, the Bayesian method incorporates prior information of disease prevalence, which is very important consideration for infectious disease diagnosis. Because of these differences, it is also hard to have a fair comparison of the Bayesian model against the Fisher's method either, as they are completely different in nature. In clinical setting, Fisher's test is not appropriate to apply to make diagnosis decisions, therefore we present the comparison against the single test in application.

(6) *How is this, "middle or late stage" in the discussion section account for?*

Response: Thank you for the comment. We have revised "middle or late stage" to "after 7 days of symptom onset" in the sentence, as follows:

Line 200: "Therefore, serological tests are more sensitive to detect infections after 7 days of symptom onset (Honacker et al 2020). A negative serological test conducted in the early stage of disease onset may not be sufficient to rule out suspicious cases. Comprehensive reference to multiple testing results, especially results from the rapid diagnostic tests with lower sensitivity and specificity, can provide a more accurate result."

Reference: Van Honacker, E., Coorevits, L., Boelens, J., Verhasselt, B., Van Braeckel, E., Bauters, F., De Bus, L., Schelstraete, P., Willems, J., Vandendriessche, S., *et al.* 2020 Sensitivity and specificity of 14 SARS-CoV-2 serological assays and their diagnostic potential in RT-PCR negative COVID-19 infections. *Acta Clin Belg*. 1-6.

(7) *"However, the calculation of the posterior probability estimation will not be affected." Yes, which is why I think more simulations are necessary. There are many other issues with real data.*

Response: Yes, we agree that the real situations are indeed more complicated. We have conducted more simulations and added the results in the revised manuscript, see Figure S1. The pre-test probability is assumed from 0.001% to 5%; sensitivities and specificities for T1 are assumed from 70% - 100% and 80% - 100%, respectively; sensitivities and specificities for T2 are assumed from 90% - 100% and 50% - 100%, respectively. It is obvious that the performance of the Bayesian probabilistic model is much better than any single test. It is very hard to make specific assumptions in the complex scenarios that might affect the performance. Nevertheless, these different issues would only influence the level of improvement of the performance by the Bayesian framework. With our free-access online tool, users can adjust the parameters according to the real situations and obtain the posterior probability estimation conveniently.

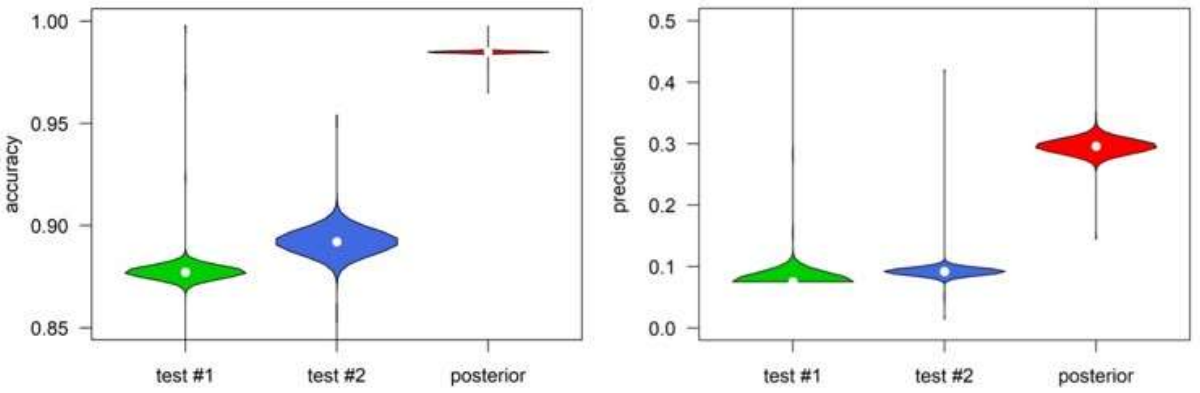

Figure S1. Violin plot of the accuracy and precision for test #1, test #2 and the Bayesian probabilistic model.

(8) *You make a comparison between your method and the use of a single test to make a diagnosis. I do not think this is a fair comparison to make as it confounds two things – firstly the use of multiple tests to make a diagnosis, which even using a completely naïve method would be expected to improve overall diagnostic accuracy, and the benefit of using your method of weighting each test in a probabilistic framework according to its accuracy. What a 'naïve' clinician would usually do would be to look at the outcomes of the multiple tests that they have taken and make a decision based on the proportion of positive tests among those. Again, using a cut-off of 0.5 to determine a positive diagnosis, I think that this would be a much fairer comparison to make with your method to determine its overall benefit.*

Response: Thanks for the comments. Here is an example to illustrate the difference between the naïve approach and Bayesian framework. Suppose there are only two tests involved and they gave opposite test results, one positive and the other is negative. In this case, using the majority vote method will result in a random assignment – with no additional information added to the "combined" multiple tests, either statistically or biologically. The classical way of meta-analysis integrates multiple tests either based on a test-statistic value or the p-value while both are based on the level of evidence rather than effect size, and this approach is not ideal to handle the situation of opposite test outcomes. Probability method would provide an appropriate handling by utilizing the predicted probabilities. The Bayesian framework further considers the quality of the individual tests in terms of sensitivity and specificity, which provides a holistic estimation of the test outcome considering the test power (sensitivity and specificity) of individual tests.

(9) *I think your simulation study is much too restrictive as it is. In the literature, there is usually a great deal of uncertainty as to the exact values of specificity and sensitivity, with ranges of values often given. I think further simulations where you look at the impact of this potential misspecification on your results would make for a better analysis. I think you also need to discuss further the impact of what happens if the underlying disease status of the*

patient changes across tests. It seems realistic to assume that a patient testing negative on an initial test when not infectious, could then go onto to become infectious by the time of a later test. There is some alluding to this in the discussion but no mention of the impact of this on your results.

Response: Thank you for your comments. Yes, we agree that the sensitivity and specificity might vary. Therefore, in our simulation, the sensitivity and specificity are not exact values but are assumed from 55% - 100%, see last paragraph in Result section. We have also performed more simulations and added the information in the new manuscript, please see comment (7). The results show that multiple tests combined with our diagnostic tool demonstrated improved diagnostic accuracy and precision compared to individual tests. Furthermore, the underlying disease status of the patient may indeed change across tests. We have added the following content about the impact of underlying disease status in the discussion as suggested.

Line 178: "In serial diagnostic tests applied on a same subject, inconsistent testing results might be observed as a result of the change of underlying disease status rather than the power of the tests themselves. For example, a patient tested negative on an initial test when not infectious could then go onto infectious by the time of a later test. In application, clinicians would also need to consider factors such as exposure risk before and between tests to interpret results."

(10) *I think you also need to justify your comment about conditional independence between tests. Li and Liu (2019) showed this assumption is not valid for tests on the same biological attribute.*

Response: Thanks for pointing it out. We agree with the reviewer as well as the paper mentioned here. We have revised this part as "*Although the outcomes of different tests may be correlated, they are assumed conditionally independent with the disease status fixed when these tests are based on the different biological attributes.*"

(11) *I tried to access your online tool, however the page wouldn't load. I would need to be able to see these as it is a significant part of what your paper is proposing as novel.*

Response: Thanks for the comment. The online tool is available at http://www2.ccrb.cuhk.edu.hk/statgene/COVID_19/. We have revised the link in the new manuscript.

(12) *Many previous studies have conducted Bayesian analysis of multiple tests and I think a greater reference to this literature and how your method is distinct would emphasise its novelty (e.g. Umemneku Chikere et al (2019); Berkvens et al (2006); Dendukuri (2004)). Is there a methodological novelty or is the novelty that you are applying this method to COVID-19?*

Response: Thank you for your comments. We have added the references in the revised manuscript. Based on the classic Bayesian framework, we applied it in the COVID-19 diagnostic scenario and developed a new web application for flexible use. This online tool enables convenient implementation of synthesized testing, especially for countries or regions currently in the COVID-19 pandemic but lack sufficient medical resources. The online tool can help clinicians calculate the risk of suspected cases with COVID-19.

Reviewer #2:

(1) *The narrative refers to the need for "timely diagnosis" to contain outbreaks, though the example throughout refers to serological testing as one of the three possible tests. The authors themselves note that serological tests provide an accurate indication of prior infection at later stages of infection, which is not consistent with "timely" diagnosis. Particularly for a pathogen such as SARS-CoV-2, where a substantial portion of transmission is pre-symptomatic. Similarly, CT scans are unlikely to be routine for all potential or suspected cases, but rather just for those with more severe disease and/or requiring hospitalisation. As noted further below, the sensitivity and specificity of these tests varies over time, and each would likely be conducted at different times during the infectious profile of an individual (e.g., PCR early, serology later), making them difficult to be combined simply without additional work to determine the sensitivity/specificity specific to the timing of each test. This makes it difficult to see a situation where these different tests are routinely being performed for timely diagnosis of suspected cases, or the outcomes could be simply and reliably combined. Perhaps it would be appropriate to pitch the narrative along the lines of using multiple rapid diagnostic tests, each of which have lower sensitivity and specificity, but results of which could be combined for a more accurate result.*

Response: Thank you very much for your valuable comments. We have revised the manuscript as suggested. We removed the word "Timely" before "Diagnosis" to make the application more general. We also added reviewer's suggestion addressing the potential use in multiple rapid diagnostic tests with lower sensitivity and specificity.

Line 202: "Comprehensive integration of multiple testing results, especially results from the rapid diagnostic tests with lower sensitivity and specificity, can provide a more accurate result."

(2) *The method requires specification of a pre-test probability to calculate the probability of being infected given the various test results. The authors propose that clinicians specify this probability to calculate the probability the individual is/was infected. While public data is available on daily incidence of cases, it is not immediately clear how the current prevalence would simply inform this probability (e.g., should this be weighted by the generation interval?). Further, these kinds of high-level data cannot account for individual heterogeneities in risk (e.g., healthcare practitioners treating COVID-19 patients would have a higher pre-test probability than another individual in the same population), and thus how much to adjust the pre-test probability in different contexts.*

Figure 2 in the submitted manuscript highlights the sensitivity of the outcome to this pre-test probability, particularly in the scenarios where it would be most useful — i.e., where the multiple tests give disparate results — and so accurately choosing this probability is key, but difficult. I would propose that were this approach to be implemented in some capacity (e.g., in a diagnostic lab), the authors must provide some more guidance as to how one can reliably estimate this pre-test probability. Perhaps grouping individuals into risk categories, where they have an interval for their pre-test probability (e.g., Pr(D) is 0.0001 – 0.001 for

low risk), and results are interpreted in this context, rather than a single estimate, might be useful?

Response: We are grateful for the valuable comment. Yes, we agree that it is very useful to have an interval for the pre-test probability, but it is difficult for us to provide this interval. We have added the following guidance in the revised manuscript.

Line 118: "Additionally, if the testing subjects are at higher exposure risk, like healthcare practitioners or customs officers, the pre-test probability should be adjusted to a higher range and vice versa.

We have also assumed a lower pre-test probability (Pr(D) is 0.001% to 5%) and conducted further simulations to check the performance of the Bayesian model in low-risk populations. The results are included in the revised manuscript, please see Figure S1. The results are consistent with the previous results that the accuracy and precision of the Bayesian model are better than individual tests.

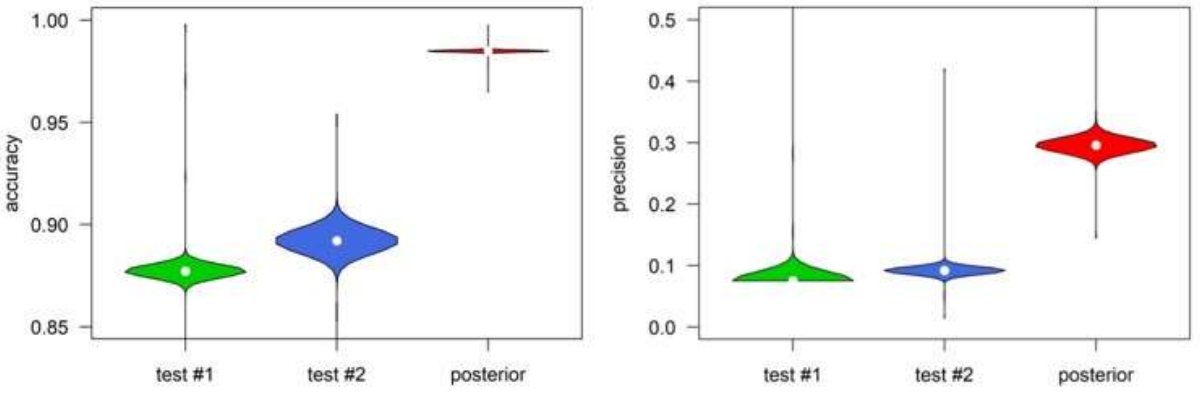

Figure S1. Violin plot of the accuracy and precision for test #1, test #2 and the Bayesian probabilistic model.

(3) *Finally, as noted above, the stage of infectiousness will impact the sensitivity and specificity of each different type of test (see for example, Boum et al, Lancet Infectious Diseases 2021). Do the authors propose that the sensitivity and specificity be adjusted for each test according to the time that the test was taken (e.g., relative to symptom onset)? If adjusting the narrative away from combining, for example, PCR and serology, then this point may be less important to address. Alternatively, if subtle changes in the sensitivity/specificity due to phase of infectiousness do not substantially impact the estimated posterior probabilities, it may be useful to show this with a sensitivity analysis so that an end-user can understand how precise they have to be with specifying these values.*

Response: We are grateful for the valuable comment. We have added the following content in the methods as the reviewer suggested.

Line 130: "Many factors, such as variation of incubation period, severity of disease, and sample quality, might impact the sensitivity and specificity of diagnostic tests (Boum et al). Users are suggested to adjust these parameters accordingly."

We appreciate the comments from both reviewers. In this manuscript, we developed a web-based analysis tool using Bayesian method to integrate multiple diagnostic tests, the study is motivated and presented in the scenario of COVID-19 diagnosis. In the online calculator, users can input their desired parameters including pre-test probability, sensitivity and specificity and obtain an integrated test outcome. The specific parameters are subject to a number of other variables such as sampling location, tissue, DNA concentration, stage of disease, severity of diseases, manufacturer claimed test power, and many others, and thus, could only be a rough estimate influenced by these observed or unobserved factors.

Reference: Boum, Y., Fai, K. N., Nicolay, B., Mboringong, A. B., Bebell, L. M., Ndifon, M., Abbah, A., Essaka, R., Eteki, L., Luquero, F., *et al.* 2021 Performance and operational feasibility of antigen and antibody rapid diagnostic tests for COVID-19 in symptomatic and asymptomatic patients in Cameroon: a clinical, prospective, diagnostic accuracy study. *Lancet Infect Dis*.

Appendix C

Dear Editor,

Thank you for considering our manuscript entitled "***A Bayesian method for synthesizing multiple diagnostic outcomes of COVID-19 tests***" (MS ID: **RSOS-201867.R2**) for publication in Royal Society Open Science. We are grateful to you and the reviewers for the valuable suggestions provided. Please find our point-by-point response below.

Regards,

Maggie H Wang, PhD (corresponding author)

Reviewer #1:

(1) *Thank you for addressing my comments fully. I am now happy with the manuscript to be published as it is.*

Response: Thank you for the positive comment. We highly appreciate your professional review work on our manuscript.

Reviewer #2:

(1) *L181: An individual can test positive when not infectious (e.g., prolonged shedding). This sentence should remove "infectious" so as to not conflate having detectable virus (if the authors are referring to PCR) with being infectious and able to transmit viable virus. For example, the sentence could read: "For example, a patient that tested negative by PCR when first tested shortly after exposure, may not yet have detectable virus, but could later test positive once viral loads are sufficient incubated.", or similar.*

Response: Thank you very much for your valuable comments. We have revised the manuscript as suggested.

(2) *L202: I think the word 'suspicious' here should be 'suspected'.*

Response: We are grateful for the correction. We have revised 'suspicious' to 'suspected' in the sentence.