

05-Jan-2021

BMJ-2020-063307

Put to the test: An evaluation of how new technologies can be deployed to fight COVID-19

Dear Mr. Crozier,

Thank you for sending us this paper and giving us the chance to consider your work. I must apologise for the delay but after receiving a two reviews quickly we struggled to find a final reviewer which has led to some delay.

The reviewers are supportive of the paper and include some helpful suggestions to further strengthen the piece. We would like to see the paper revised to incorporate some of these suggestions and also the editors' comments with a view to publication.

Editor's comments:

\*This is a very well timed piece which clarifies some elements of mass testing. We agree with Clare Wenham's suggestions to restructure this slightly to make this clearer and more compelling.

\*We also felt the Liverpool example would benefit from being mentioned upfront or integrated into the paper earlier.

\*Table 2 is a very helpful summary of the tests. We think this would be better in the main article rather than as an appendix. We would not have capacity to publish this in print but it would be helpful to have this integrated into the article online.

The reviewers' comments are at the end of this letter.

We hope that you will be willing to revise your manuscript and submit in the next two weeks or as soon as you are able to given the subject matter. When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers. We also ask that you keep the revised manuscript within the word count of 1800-2000 words.

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I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Best wishes,

Dr Sophie Cook  
Head of scholarly comment  
scook@bmj.com

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Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:

Put to the test: An evaluation of how new technologies can be deployed to fight COVID-19 is a very timely description of the English government's testing plans.

There has been a great deal of confusion about new testing technologies their costs and benefits. This evaluation provides a very helpful framework to consider potential benefits and harms in controlling the spread of COVID-19.

The paper covers a range of important areas for consideration including testing strategies, interpretation of test results including those of novel tests.

I strongly support the publication of this paper based on the added value of describing the proposed tests and testing regimes however the paper provides more than this.

It tackles directly the issue of mass testing and describes the recent approach taken in Liverpool. As testing is central to international responses to the COVID-19 pandemic and governments have invested enormous resources to scale-up capacity this paper adds valuable insight into what tests and how they can or could be used. It also challenges the limitations of testing and includes important factors such as ethics and behavioural change. I think the most useful challenge the paper makes is in relation to views that testing can only be effective if it's part of a Holistic Public Health Approach with local contact tracing and support to enable individuals to isolate without financial or other detriments.

This paper also provides some interesting information for Test-to-Protect, Test-to-Release and Test-to-Enable which I have not seen presented in this way before I believe it would be valuable to see this being published. There is also a similar approach to Asymptomatic Testing for International Arrivals which is an area of interest for many and would be useful to have these views published.

What I would have like to have seen in this paper was some cost benefit analysis however this was not what the authors set out to do - stating the large costs the government had already committed - but perhaps could be considered in a future publication.

As indicated above I support the publication of this paper.

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Job Title: President

Institution: Faculty of Public Health

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Reviewer: 2

Recommendation:

Comments:

This is a really important paper and I think analysis of the role of different testing strategies and testing tools is vital as governments across the world negotiate how best to manage detecting COVID within the community and how to start to reopen or keep open as much of the economy as possible. For that reason I support a piece such as this in summarising and analysing the key approaches that can be taken, and I think it can be an important contribution to the literature. However, I think it needs a bit of restructuring before publication.

- I was confused when reading it that you talk of strategies and then talk of tools (ie. PCR or Ag-LFT and then back to strategies. I wonder if it's better to start with one and then the other to make a more logical argument. i.e. that govs have many approaches they can take for their testing strategy, and depending which they choose, and what the policy aim of testing is, then they can choose the relevant test to support that strategy.

- I think this is the over-arching argument you are trying to make in this paper (please correct me if i've misunderstood) but I don't think you make the case compelling enough - I think you might need to start with a blunt statement such as that "governments chose testing for multiple reasons, and this paper analyses those reasons and shows which tools are best for the job" to really make it clear what this paper is about. This can then be reiterated through a restructure and into the conclusion.

In summary, I have less concern about the content (albeit it this is slightly beyond my knowledge base as a social scientist), but think it can be argued more convincingly.

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Please enter your name: Clare Wenham

Job Title: Assistant Professor of Global Health Policy

Institution: London School of Economics and Political Science (LSE)

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Reviewer: 3

Recommendation:

Comments:

Review December 2020 of BMJ manuscript 2020-063307

'Put to the Test: An evaluation of how new technologies can be deployed to fight COVID-19'

by A. Crozier & al.

This contribution keeps loyally to the BMJ Analysis format (the Standfirst is found on p. 2 (of 27) of the pdf proof, the manus beginning on p. 4). It presents the key elements of what is known or assumed concerning the course of the covid infection and its 'interaction' with important tests in present use, leading to a survey of the natural roads of attack: Test-to-Protect the weak, -to-Release from quarantine/isolation and -to-Enable resumption of duties – as components of the strategies of 'simple' mass-repeat testing vs. intelligently individualized (SMART) mass testing. Each of these labels is understood to be combined with appropriate isolation policies, etc.

Central in this discussion are the strengths and limitations of molecular (PCR) vs. 'quick' (antigen-based, Ag-LFT) tests. The text convincingly advocates the use of the SMART-quick/PCR combination as introduced in Liverpool.

The authors take pains to present advantages, limitations, challenges and risks of each approach (briefly in the main text, with details in appendices for web presentation).

I am not in a position to criticize the contents or the division of the material between the short main text and the appendices. The points that follow may be useful anyhow.

Substance

A1) A number of issues receive little attention, obviously because of the wordcount limit of 2000 words. Anyhow I would have liked to see them mentioned, if only as 'bypassed for reasons of space.' I am thinking of following collateral concerns: cost and logistics; booking, delays and queuing (waiting time is a problem when people queue under the winter sky); epidemiological monitoring (including quantification of immunity and vaccination effects); problems at frontiers; and global coordination. Later also coordination with vaccination policies and the successive phases of a vaccination programme.

A2) Medical autonomy vs. concerns for 'thy neighbour' in the face of (non-wartime) global threats: the authors touch upon this but clearly do not commit themselves to a war analogy. Personally, I would vote for certain restrictions of autonomy.

A3) Many of the pros and cons involved in the choice of test policy depend on cost and manpower comparisons. The paper holds almost no quantitative information in that regard.

Sensitivity, disease phases, etc.

B1) As regards the 'relative sensitivity,' i.e., that of the 'quick' test when the PCR result is treated as the truth, please warn newcomers that it can only be interpreted as done here (and in the media) if the relative specificity is very very high. Hypothetical example in which the 'quick' test is possibly the better test despite a low relative sensitivity ( $n = 10,000$ ): Both positive: 80, only PCR positive: 20, only 'quick' test positive: 21 (!), both negative: 9,879; here, relative sens = 0.80, relative spec =  $9879/9900 = 0.998$ , very high but not very very high (for comparison, the reverse relative sens =  $80/101 = 0.792 < 0.80$ ).

B2) P5/32-33 and elsewhere: the words 'residual' and 'shedding' require a precise definition: 'residual' = 'post-symptomatic but possibly still infectious' or 'no longer infectious'? 'Shedding' = 'of any viral material' or 'of innocuous material only'? The literature is ambiguous, isn't it?

B3) The authors have borrowed Figure 3 from another source. Unfortunately, the texts under the horizontal axis are logically wrong. As shown by the crossings of the dotted lines, the green phase should be called 'Early infection detectable by PCR only (possibly still in part pre-infectious),' and the purple phase: 'Late phase detectable by PCR only (possibly in part already non-infectious).' There are two biological transitions of interest: from pre-infectiousness to infectiousness, and from there to a non-infectious post-phase. Whether they coincide with the vertical dotted lines is an empirical matter; the dotted lines as drawn here reflect test response only, not necessarily the biological epochs. [To depict the two transitions two separate vertical lines would be needed, and they may, one may imagine, fall before, within or after the green phase (and similarly with the purple phase). Better still, one might draw two hump-shaped curves, one, marked 'Infectious virus load,' within the other, marked 'Total virus load'; horizontal dotted lines (representing hypothetical levels of biochemical sensitivity) may then cut, or not cut, the humps in several ways, leading to diverse conclusions.]

#### Presentation

C1) The term mass screening is really mass-repeat screening in the covid context. Readers (journalists!) may misunderstand the term.

C2) Similarly, the wording on p. 5(bottom)-6(top) is academically precise and elegant, but hardly to be understood by junior media people or by the parties affected (nursing home leaders, public transport managers, ...). Writing a contribution of this kind for the BMJ means writing for health policy people in Belgrad and Bogotá. Plain words, please.

C3) If the tables and figures of the appendices present themselves as they do with my browser on my home (!) PC, they are hard to read. Some of the text needs enlargement, other parts a reduction. As the authors recognize, a professional hand is needed.

C4) References 14 and 16 are identical. Different paper may be meant.

C5) Appendices, Figure 1 and Appendix Table 1: both legends start with 'Principle,' a noun. It should be the adjective 'Principal.'

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Please enter your name: Jørgen Hilden

Job Title: emer. assoc. prof.

Institution: Univ. of Copenhagen

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Reviewer: 4

Recommendation:

Comments:

This Analysis paper provides a really nice characterisation of potential testing strategies that could be deployed to reduce transmission of covid-19 infection in the community with a particular focus on use of rapid antigen tests for testing asymptomatic individuals. The paper is highly relevant and well thought



through and will certainly be of interest to a general readership. I have a few comments on specifics of the paper that the authors might want to consider.

Pg 4 line – the title does not reflect the paper's focus on antigen tests nor their use for asymptomatic testing strategies.

Pg 4 line 24-26 - The authors make the point that real world evaluations of rapid tests are needed in order to better understand accuracy and how tests might be used more widely, however this misses a crucial step in the evaluation process, which is to first establish accuracy in the populations in which these tests are intended to be deployed. Appendix 2 gives examples of the accuracy of 3 different Ag tests established in independent test evaluations but fails to mention that these were established predominantly in symptomatic individuals within the first few days of symptom onset and cannot be assumed to apply in asymptomatic cohorts. Antigen tests are not all equal, and it is vital that test accuracy is well understood before tests are selected for implementation in large scale evaluations such as we have seen in Liverpool.

Pg 4 line 46-50 – There is an implication here that false negatives on Ag tests only occur at lower viral loads, however false negatives on Ag tests also arise at higher viral loads (e.g.  $\leq 25$  Ct) although at a lower rate. As Ag tests are increasingly being promoted as tests of so called 'infectiousness', it is important that we do not lose sight of the fact that they are not perfect even at high viral load.

Pg 4 line 46-50 – It is not just swab collection that incurs false negatives but test interpretation even by health care workers has been shown to incur more false negatives compared to interpretation by laboratory scientists.

Pg 4 line 55-58 - The communication to the public in regard what a negative test result means, especially a negative Ag test, is fundamentally important to any testing strategy that involves asymptomatic individuals. The point that Ag tests are a test of the 'moment', and only reduce risk of infection at the time of the test, could perhaps be made more strongly here.

Pg 5-6 – As mentioned above, the exposition of possible testing strategies is really well done. The SMART approach looks highly sensible if implemented correctly and with the right test. Given emerging evidence for exceptionally poor performance of Innova in mass testing scenarios, it will be interesting to see how effective a SMART approach can actually be (assuming Innova is the test of choice here). More detail in regard to frequency of testing, how test results and ongoing 'risk' are communicated, and what sort of 'tactical changes' might be implemented would be nice to see.

Appendix Table 2 – could be much clearer about the sources of accuracy data here which range from a systematic review (RT-PCR), to manufacturer instructions for use (Rt-LAMP and NGS) which are notorious for over-estimating accuracy compared to real world test use, to independent test evaluations of Ag tests. All quoted sensitivities and specificities are from symptomatic populations and will not be directly applicable to the scenarios presented in the paper.

Pg 8 – line 26-30 – the reported SAMBA II results are after discrepant analysis (i.e. re-testing) of initially FP and FN results and therefore likely to inflate accuracy measures.

Pg 9 line 24-27 – Some tests do use saliva samples but I do not think that accuracy has yet been shown to be the same as for nasopharyngeal swabs.

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Please enter your name: Jac Dinnes

Job Title: Senior Test Evaluation Methodologist

Institution: University of Birmingham

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 5

Recommendation:

Comments:

This is a timely paper that is of considerable immediate interest and it fully deserves publication. The importance of the paper arises not only from the assessment of the value of testing methodologies deployed in respect of COVID-19 but also from the way in which the authors make the connection between the science behind the testing methodologies and the ways in which the testing methods should be deployed. It is particularly valuable to those making decisions on the approach to test that should be used at a local level and within institutions.

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Please enter your name: Gabriel Scally

Job Title: Visiting Professor of Public Health

Institution: University of Bristol

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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