Comment on the proposed Covid-status Certification

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Writing as an academic.

Concerns about the evidence base for the use of lateral flow tests as a test to enable as part of the Covid status certification

This statement relates to the proposed use of lateral flow tests to identify individuals who are not infectious and therefore deemed safe to be able to mix with others without social distancing, as is proposed in the use of test results as Covid passports. The evidence on the accuracy of lateral flow tests suggests that this is not a safe way to use these tests.

There are four components to the issue: 1) evidence of the sensitivity of lateral flow test in asymptomatic populations, particularly the tests proposed for use in the UK; 2) evidence of the relationship between viral load and infectiousness; 3) the negative likelihood ratio for lateral tests which indicates their poor diagnostic value in ruling out disease; 4) recommendations from leading organisations.

1) In using a test to rule out disease it is important that the proportion of infected people given false negative test results is low. This property is summarised by the sensitivity of the test. Whilst multiple studies have estimated the sensitivity of the Innova test and other lateral flow tests in people with symptoms, fewer studies have looked at their sensitivity in asymptomatic cases. It is well established that the performance of most diagnostic tests varies between their different intended uses. A use case describes the application of a test in a particular patient group to diagnose a stated condition, namely: the who, where, when, what, how and why a test is applied. In Covid testing, it is key to differentiate testing of symptomatic from apparently healthy people.

   The initial Innova test evaluations reported by the University of Oxford and Public Health England were undertaken in regional test-and-trace centres where recruited participants were expected to be symptomatic, with a sensitivity between 58% when tests were run by test-and-trace centre staff and 78% when test were run by laboratory scientists [1]. From these data it was decided to pilot the use the test for mass screening of asymptomatic people. The sensitivity of other lateral flow test for SARS-CoV-2 in asymptomatic people, as in mass testing, has been noted to have on average a sensitivity between 15% and 20% lower than in symptomatics, thus it should not have been expected that the same performance would be repeated [2]. For example, testing in Wisconsin University Campus, the Sofia antigen test had a sensitivity of 80% when used in symptomatic people, and only 40% when used in asymptomatic people [3]. In the UK the mass testing evaluation in Liverpool showed the same pattern, also reporting 40% sensitivity [4]. Of concern, the test also missed one-third of the cases with higher viral loads which the previous evaluations had indicated it should detect.

Subsequent policy making appears to have been ignoring these findings, and the importance of evaluating the tests for different use cases. For example, implementation in schools has been undertaken without any evaluation of its performance in children.

The higher accuracy in symptomatics likely relates to viral load levels being highest soon after the onset of symptoms, and the PCR test detecting infection at the lower viral levels (and thus missed by lateral flow tests) both before and after they peak in asymptomatics. No completed field studies have been reported for other tests (SureScreen, Orient Gene) which have been mentioned for use in the UK, so we are totally uncertain concerning their performance for this purpose.

The best evidence on the sensitivity for Innova for testing of asymptomatics suggests 40% are detected - thus 60% of infected people are missed.

2) Much discussions has focused on lateral flow tests detecting the most infectious cases, as it will pick up those who have higher viral loads who have been shown to be the most likely to have viable virus and transmit it to others. However, when using a test to say who is not infectious, the same data needs to be considered to look at infectiousness rates in those who are missed by the lateral flow tests. It is not possible to say whether an individual is or is not infectious, so this cannot be done directly. Rather, "proxy" measures of infectiousness have been considered – namely the ability to culture virus (a test of viability) and secondary attack rates (a measure of transmission). Both measures are likely to underestimate infectiousness due to the poor sensitivity of viral culture and the likelihood that those known to be infected are isolating to prevent onward transmission. As no substantial study has directly linked culture and secondary attack rates to results of lateral flow tests, relationships with PCR Ct values are used, considering the lower level of detection of lateral flow tests expressed in Ct values. For the Innova test the University of Oxford/PHE studies have suggested a lower level of detection of Ct=25 [1]. The lack of standardisation of Ct values across different machines, laboratories and times introduces some uncertainty into these comparisons. This further emphasises the lack of clear data upon which conclusions about the ability to correlate lateral flow tests and infectiousness.

   Below are results of four substantial studies [5-8] which indicate that those likely to be missed by lateral flow tests have lower but still substantial risks of having viable virus (34% in the PHE study [5], 24% in the Marseille study [6]) and transmitting the virus to others (13% in those missed compared to 20% in those found in the Catalonia trial [7]; 3.4% compared to 7.4% in the test-and-trace data [8]). Note that these studies are done in groups that are mainly or entirely symptomatic, and the proportions missed by the test will be higher in asymptomatics.

   Clearly these data do not support a conclusion that those cases infected but missed by lateral flow tests are all unlikely to be non-infectious.

RAPID COMMUNICATION

Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020

Anika Singanayagam[1,2], Monika Patel[1,2], Andre Charlett[3], Jamie Lopez Bernal[4], Vanessa Saliba[4], Joanna Ellis[4], Shamez Ladhani[4], Maria Zambon[4], Ruben Gopal[1]
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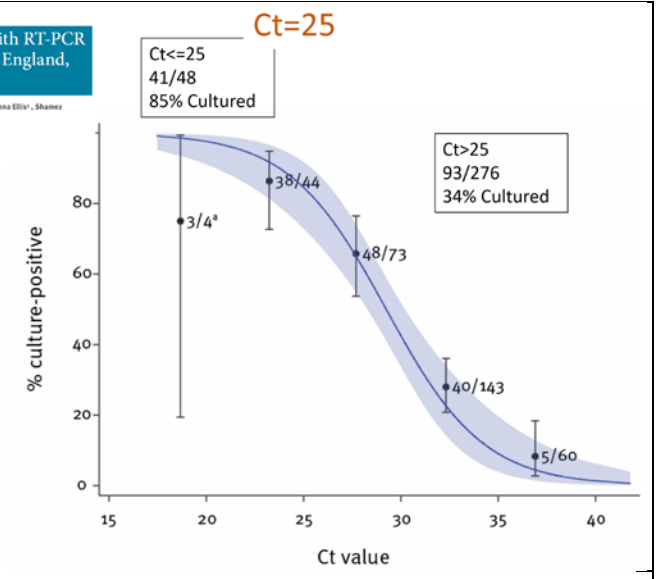
Eurosurveillance

Tests done in Colindale
(symptomatic and asymptomatic)

134 of 324 cultured
(41.4%)

Of those who were cultured
93 of 134 had Ct>25
(70.5%)



Clinical Infectious Diseases
CORRESPONDENCE

Correlation Between 3790 Quantitative Polymerase Chain Reaction–Positives Samples and Positive Cell Cultures, Including 1941 Severe Acute Respiratory Syndrome Coronavirus 2 Isolates

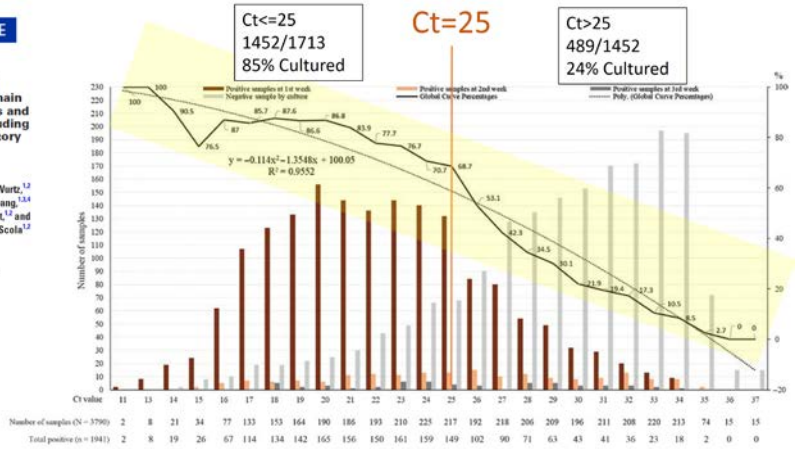
Rita Jaafar,[1,2] Sarah Aherfi,[1,2] Nathalie Wurtz,[1,2] Clio Grimaldier,[1,2] Van Thuan Hoang,[1,3,4] Philippe Colson,[1,2] Didier Raoult,[1,2] and Bernard La Scola[1,2]

Tests done in Marseille
(ref lab for SE France)

Likely symptomatic

1941 of 3790 cultured
(51.2%)

Of those cultured
489 of 1941 had Ct>25
(25.2%)



Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study

Michael Marks, Pere Millat-Martinez, Dan Ouchi, Chrissy h Roberts, Andrea Alemany, Marc Corbacho-Monné, Maria Ubals, Aurelio Tobias, Cristian Tebé, Ester Ballana, Quique Bassat, Barbara Bora, Martí Vall-Mayans, Camila G-Beiras, Nuria Prat, Jordi Ara, Bonaventura Clotet, Oriol Mitjà

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Contacts of cases tested at enrolment and at day 14
In RCT

125 of 753 contacts infected
(16.6%)

Of those who were infected
36 of 125 had Ct>25
(29.9%)

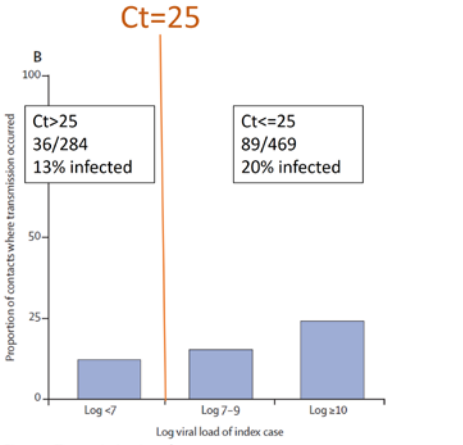
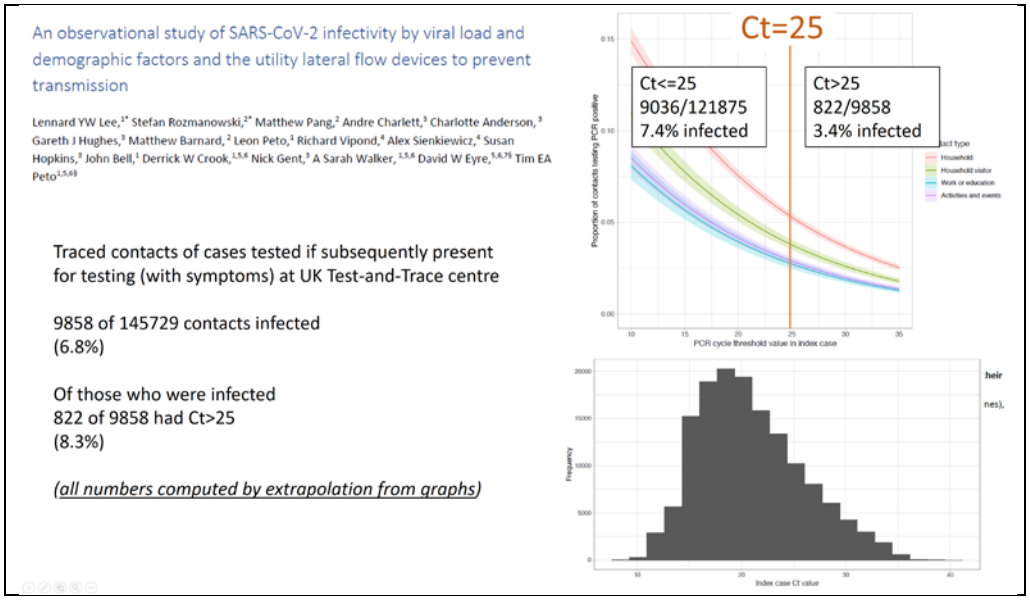


Figure 1: **Transmission in a cluster**
(A) Number of secondary cases per cluster. (B) Relationship between viral load of the index case and the proportion of contacts developing COVID-19: 36 of 284 contacts in group <1 × 110[7] copies per mL, 72 of 398 in group 1 × 110[7] to <1 × 110[10], and 17 of 71 in group ≥1 × 10[10].



3) The ability of positive and negative results to rule in and rule infection is best considered using likelihood ratios, which can then be applied via Bayes' theorem to predict infection rates in those who are test positive and test negative. Bayes' theorem is based on odds of disease, but these can be approximated to probabilities where events are rare (such as with Covid infection rates).

   Likelihood ratios are computed from estimates of sensitivity and specificity, and state how many times higher the odds of disease is in somebody who tests positive compared to somebody who is untested, and how many times lower the odds of disease is in somebody who tests negative compared to somebody who is yet to be tested.

   The assessment of Innova in asymptomatic testing in Liverpool have estimates of sensitivity of 40% and specificity of 99.9% [4]. Simple computation of the positive likelihood confirms that a positive test result greatly increases the chances of disease (LR+ = sens/(1-spec) = 0.4/0.001 = 400) such that the odds of disease are increased 400-fold in those positive compared to those yet to be tested. Recent data suggesting the specificity may be higher increases this value. There is no doubt that positive results from these tests are strongly linked to Covid infection.

   However, a negative result makes little difference to the chances of an individual not having Covid (LR- = (1-sens)/spec = 0.6/0.999 = 0.6) as it reduces the odds that an individual has Covid by only 40% (which can be interpreted as the probability being reduced by 40%).

   Thus we would predict that of 100 people with Covid-19 infection being tested, only 40 would be found, the remaining 60 being admitted to the venue. Combining with point 2 – which showed that those missed by lateral flow tests have roughly half the risk of transmitting the virus compared to those detected, would suggest that the number of "infectious" people allowed in the venue would be between 40 and 50%. Thus testing negative on a lateral flow test does not indicate that the risk of infection and associated risks of transmission have been safely reduced.

   In summary, negative tests do not indicate that an individual has substantially lower risk of having the virus at levels which can infect others.

4) The failure of the Innova test and many other lateral flow tests to accurately identify cases has led to experts, systematic reviews, regulations and guidelines clearly recommending against their use in “test-to-enable” scenarios.

   Leading medical journals have carried peer reviewed articles comment on this issue, such as the BMJ [9].

   The Cochrane review of rapid tests concluded: “Due to the variable sensitivity of antigen tests, people who test negative may still be infected. Evidence for testing in asymptomatic cohorts was limited. Test accuracy studies cannot adequately assess the ability of antigen tests to differentiate those who are infectious and require isolation from those who pose no risk, as there is no reference standard for infectiousness”[2].

   The MHRA have approved Innova only for use to identify cases, not for use to green light purposes such as test-to-release and test-to-enable [10].

   The WHO do not recommend use of tests in low prevalence situations [11].

   The manufacturers of Innova themselves state “Negative results do not rule out SARS-CoV-2 infection and should not be used as the sole basis for treatment or patient management decisions, including infection control decisions” [12].

In summary – there is evidence that negative results from lateral flow tests, notably the Innova test, in asymptomatic people will not substantially reduce the risk of infection or infectious Covid in those who test negative. There is no scientific basis for its use in a test-to-enable purpose such as for Covid-status certification, and concern that it will facilitate spread of infection.

Illustrative example

If attendees at an event number 5000, with the current prevalence of Covid-19 infection of 0.17%, 9 out of 5000 would be expect to have Covid-19. Assuming 2 out of 3 cases have symptoms, 6 infected participants would be expected not to attend because of symptoms, leaving 3 to be found by lateral flow testing. Using a test which detects 40% of infections in cases would find on average 1 of the 3. Thus testing would reduce the number with Covid infection from 3 in 5000 to 2 in 5000.

Should those with symptoms try to attend, the test is likely to detect 4 and miss 2 with symptoms (assuming 60% sensitivity in symptomatic people), so 4 in 5000 would enter the event with Covid infection.

At the same time, assuming the test has 99.9% specificity, 1 in 1000 would get a false positive result, so 5 out of 5000 would be expected to be given false positive results.

References

[1] Tim Peto, UK COVID-19 Lateral Flow Oversight Team. COVID-19: Rapid Antigen detection for SARS-CoV-2 by lateral flow assay: a national systematic evaluation for mass-testing. medRxiv 2021.01.13.21249563; doi: https://doi.org/10.1101/2021.01.13.21249563

[2] Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Domen J, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, Hooft L, Leeflang MMG, McInnes MDF, Spijker R, Van den Bruel A. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database of Systematic Reviews 2021, Issue 3. Art. No.: CD013705. DOI: 10.1002/14651858.CD013705.pub2. Accessed 29 March 2021.

[3] Pray IW, Ford L, Cole D, et al. Performance of an Antigen-Based Test for Asymptomatic and Symptomatic SARS-CoV-2 Testing at Two University Campuses — Wisconsin, September–October 2020. MMWR Morb Mortal Wkly Rep 2021;69:1642–1647.
DOI: http://dx.doi.org/10.15585/mmwr.mm695152a3external icon.

[4] Liverpool Covid-19 Community Testing Pilot - Interim Evaluation Report. https://www.liverpool.ac.uk/media/livacuk/coronavirus/Liverpool,Community,Testing,Pilot,Interim, Evaluation.pdf

[5] Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill2020;25:2001483. doi:10.2807/1560-7917.ES.2020.25.32.2001483 pmid:32794447

[6] Rita Jaafar, Sarah Aherfi, Nathalie Wurtz, Clio Grimaldier, Thuan Van Hoang, Philippe Colson, Didier Raoult, Bernard La Scola, Correlation Between 3790 Quantitative Polymerase Chain Reaction–Positives Samples and Positive Cell Cultures, Including 1941 Severe Acute Respiratory Syndrome Coronavirus 2 Isolates, Clinical Infectious Diseases, 2020;, ciaa1491, https://doi.org/10.1093/cid/ciaa1491.

[7] Marks, M., et al. "Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study." The Lancet Infectious Diseases. https://doi.org/10.1016/S1473-3099(20)30985-3.

[8] Lennard YW Lee, Stefan Rozmanowski, Matthew Pang, Andre Charlett, Charlotte Anderson, Gareth J Hughes, Matthew Barnard, Leon Peto, Richard Vipond,Alex Sienkiewicz, Susan Hopkins, John Bell, Derrick W Crook, Nick Gent, A Sarah Walker, David W Eyre, Tim EA Peto. An observational study of SARS-CoV-2 infectivity by viral load and demographic factors and the utility lateral flow devices to prevent transmission. http://modmedmicro.nsms.ox.ac.uk/wp-content/uploads/2021/01/infectivity_manuscript_20210119_merged.pdf

[9] Deeks J J, Raffle A E. Lateral flow tests cannot rule out SARS-CoV-2 infection BMJ 2020; 371 :m4787 doi:10.1136/bmj.m4787

[10] WHO. SARS-CoV-2 antigen-detecting rapid diagnostic tests – an implementation guide. December 2020. file://mds/user/A-F/deeksj/Desktop/9789240017740-eng%20(1).pdf

[11] Medicine and Healthcare Products Regulatory Agency. MHRA issues exceptional use authorisation for NHS Test and Trace COVID-19 Self-Test device. 23 Dec 2020.

https://www.gov.uk/government/news/mhra-issues-exceptional-use-authorisation-for-nhs-test-and-trace-covid-19-self-testdevice.

[12] Innova Medical Group. SARS-CoV-2 antigen rapid qualitative test. Instructions for use. Version A/02 2020-07-01. https://cdn.website-editor.net/6f54caea7c6f4adfba8399428f3c0b0c/files/uploaded/Innova-SARS-Cov-2-Antigen-test-IFU.pd