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

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Dr Sophie Cook
Editor
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Re: BMJ Analysis Manuscript submission: '*Put to the Test: An evaluation of how new technologies can be deployed to fight COVID-19*'

Dear Dr. Cook,

We wish to submit this manuscript for your consideration for publication in the British Journal of Medicine as a BMJ Analysis piece. This manuscript entitled "*Put to the Test: An evaluation of how new technologies can be deployed to fight COVID-19"* provides new analyses of novel testing technologies and asks how these new technologies can be most appropriately used to support different testing strategies, examining the benefits and risks of each in the context of what we know about transmission of COVID-19.

This is important because interrupting transmission of COVID-19 depends on identifying potential cases early and quickly, which many countries are struggling to achieve with reverse transcriptase PCR tests, leading them to invest considerable resources in developing, validating and piloting novel rapid antigen lateral flow tests (Ag-LFTs). The accuracy and deployment of these assays has received significant scientific, media, and public attention, although much misunderstanding remains. Using a combination of evaluative tables and the main body of text, we address the currently unmet need to analyse the main testing strategies deployed globally, considering the advantages, limitations, challenges, risks, and ethics of each, and summarise the profiles of the main novel assays that have been proposed for large-scale testing, focusing in particular on Ag-LFTs. We also evaluate the use of SMART (Systematic Meaningful Asymptomatic Repeated Testing) policies and mass testing.

This is the only article we are aware of that explains how Ag-LFTs might be used for quick scale-up and decentralised testing by showing how, if used correctly, they might present opportunities for a more innovative and joined-up public health approach to testing. We show how, despite their known limitations, Ag-LFTs could facilitate timely isolation of the most infectious cases and their close contacts, who otherwise may go undetected or transmit infection and outline the benefits and limitations of such an approach. Given this, we evaluate how Ag-LFTs could be deployed to protect the vulnerable (test-to-protect), promote isolation and reduce the time in quarantine (test-to-release), and restart activities vital to the public health, social fabric and the economy (test-to-enable).

We also evaluate the benefits and limitations mass testing as a strategy, before discussing Systematic Meaningful Asymptomatic Repeated Testing) SMART policies, the approach now being piloted in Liverpool. SMART uses public open-access testing but with communications and outreach targeting specific groups who are either vulnerable to COVID-19 directly or to its control measures, particularly the disadvantaged groups hit hardest by the economic effects of the pandemic. SMART takes a dual strategy of targeted reduction in transmission alongside test-to-release and test-to-enable schemes designed to protect key services, rebuild social fabric, and recover the economy.

Yours Sincerely,

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

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Standfirst

Governments across Europe are investing in novel testing technologies at pace, aiming to reduce the health impacts of the pandemic whilst also minimising the restrictions on everyday life and the associated social and economic harms. We ask how new technologies can be most appropriately used to support different testing strategies and examine the benefits and risks of each.

KEY MESSAGES

- As testing capacity increased, strategies to use them diversified, particularly across Europe.
- Although governments invested considerable resources in developing, validating, and piloting novel testing technologies, it is unclear how these tests will be integrated in wider strategies and systems to control transmission and enable smarter release from restrictions.
- We analyse the main testing strategies, considering the benefits and risks of each, and summarise the advantages, limitations, challenges, risks, and ethics of each, and consider the use of SMART (Systematic Meaningful Asymptomatic Repeated Testing) policies over mass testing.

Contributors and sources

The authors have broad experience and direct involvement in COVID-19 responses. Alex Crozier has expertise developing and troubleshooting diagnostic assays and improved COVID-19 testing programmes for sports organisations. Dr Selina Rajan is a Public Health Specialist Registrar who has supported the Public Health England regional response, including managing outbreaks in care homes and educational institutions and has also contributed extensively to the COVID-19 Health Systems Response Monitor produced by the European Observatory on Health Systems and Policies in partnership with the World Health Organisation. Professor Martin McKee is a member of Independent SAGE and has published extensively on the pandemic. Professor Iain Buchan is a Public Health and Informatics / Data Science research leader directly involved in the Liverpool SMART (Systematic Meaningful Asymptomatic Repeated Testing) pilot. Drawing on scientific evidence and our combined real-world experience, we aim to help BMJ readers learn from international testing strategies, and to understand how new testing technologies can be harnessed to improve SARS-CoV-2 transmission control while enabling public return to restricted activities, thereby tackling the mounting public health and economic harms from COVID-19 control measures.

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Patient involvement
No patients were involved in the writing of this manuscript.

Conflicts of Interest
We have read and understood BMJ policy on declaration of interests and have the following interests to declare we have no conflicts of interest

Licence

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

Introduction

Testing is central to international responses to the COVID-19 pandemic and governments have invested enormous resources to scale-up capacity. Real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) was the first, and still the most widely used, test to be adopted. However, delays in ordering a swab kit, transporting it to a laboratory, and analysing it means the result can take several days to be acted on, leaving a window in which infection may spread. In addition, people are often infectious before experiencing symptoms, which drives transmission.[1] Those who never experience symptoms have a similar viral load to those who do and so may also contribute to spread, although the extent of this is unclear.[1,2,3] Given the importance of pre-symptomatic transmission, it is imperative that cases are identified as early in the infection as possible. Therefore, the turnaround time of testing is critical in reducing onward transmission. It is difficult for large-scale rRT-PCR testing to return results quickly enough for effective control of transmission through contact-tracing and quarantine, or for early detection of outbreaks in vulnerable settings.

Rapid antigen lateral flow tests (Ag-LFTs) offer a possible solution because they provide a rapid result, although at the cost of reduced ability to detect infections.[4] Governments are purchasing vast quantities of Ag-LFTs, yet WHO is not yet advising that a single negative Ag-LFT free an individual from quarantine obligations.[4] Repeated Ag-LFTs and their combination with other measures are being studied, for example in Liverpool, where test-to-release (from quarantine) and test-to-enable (cautious return to restricted activities) regimens are being evaluated alongside public open-access to Ag-LFTs. Real-world evaluations of Ag-LFTs, such as in Liverpool, are also needed to better understand the accuracy of the tests, how people behave in response to results and how health systems can embed Ag-LFT in wider measures.

We describe testing strategies used internationally (Figure 1), test characteristics (Figure 2, Appendix 2), and deployment issues (Appendix 3).

Testing Strategies

Testing seeks to interrupt transmission while reducing time spent isolating or quarantining. Countries have adopted different strategies (Figure 1), whose benefits and risks are summarised in Appendix 1. Ag-LFTs offer potential solutions in all these strategies.

Test Result Interpretation

Meaningful interpretation of any test requires knowledge of its sensitivity (proportion of infected individuals who test positive), specificity (proportion of non-infected individuals who test negative), and pre-test probability that an individual is infected, which depends on population prevalence and the individual's clinical and epidemiological history.[7]

Although tests have controls to minimise errors, false results can arise from technical problems during sample collection, processing, or reporting. The false positive rate with Ag-LFTs is very low and can be addressed by confirmatory testing with rRT-PCR.[4,8] False negatives are of greater concern. Besides technical errors, false negatives can arise if individuals are tested during the 5-7 days when the virus is incubating and before viral load is sufficient to be detected, usually 1-2 days before symptom onset.[1,2,9] If swabs are taken by untrained individuals,[10,11] test sensitivity falls, generating more false negatives. These can lead to a false sense of security, paradoxically increasing transmission risk.[12] Conversely, rRT-PCR is very sensitive – it detects viral shedding long after the infectious period (approximately 9 days), with individuals continuing to test positive for a mean of 17 days.[2] Although technically true positives, these individuals are not infectious and should not be quarantined.

The public, patients, clinicians, public health teams and policy-makers need to have a clear shared understanding of the uncertainties of these tests.[13] Predictive values can be calculated with specialist tools,[7] but communication of results needs to be effective to appropriately influence behaviour.

Novel Tests

Several novel techniques, such as loop-mediated isothermal amplification, next-generation sequencing, point-of-care PCR, and Ag-LFTs are in different stages of development, validation, and approved implementation (Figure 2, Appendix 2). Each test has advantages and limitations, so which to choose depends on the intended use. Ag-LFTs can be used for quick scale-up and decentralised testing; they are relatively cheap, do not require laboratories, and provide results rapidly. However, they are less sensitive than nucleic acid amplification tests such as rRT-PCR, so will generate more false negatives, and the effect on test performance of swabbing not being supervised by health professionals is uncertain.[4,14]

Given rapidly changing viral loads during the course of COVID-19, the window for using Ag-LFTs to detect infectious cases is narrow.[2,15] Ag-LFTs are most suitable where testing is frequent and the goal is to detect cases with high viral loads in the days immediately before and after symptom onset.[2,4,16] Despite their known limitations, Ag-LFTs could facilitate timely isolation of the most infectious cases and their close contacts,[4,17] who otherwise may go undetected or transmit infection.

The WHO advised that Ag-LFTs should achieve sensitivity >80% and specificity >97% relative to rRT-PCR, with the caveat that the risk of false negatives will increase after 5-7 days.[4] However, while false negatives (largely due to lower viral loads) are a significant concern with Ag-LFTs, the rapid increase in viral load after the incubation period leaves only a short time where there will be a major risk of a difference between first turning positive on a highly sensitive test (rRT-PCR) compared to a lower sensitivity test (Ag-LFT)[18,19] (Figure 3). Importantly, modelling suggests more frequent testing with lower sensitivity tests can achieve the same probability of detecting a case as less frequent testing with higher sensitivity tests.[20,21] Evidence also suggests the limit of detection of Ag-LFTs largely aligns with the viral load typically observed at the end of the first week of symptoms, which marks the end of the infectious period in most patients.[2,15] As detected viral load is a proxy and not a direct indicator of infectiousness, many caveats remain, but it seems the point when Ag-LFT results change from negative to positive and vice versa coincides with the beginning and end of infectiousness of most symptomatic cases[15] and potentially also in asymptomatic cases. Thus, despite their lower sensitivity, Ag-LFTs may be a good identifier of current infectivity, and less likely to detect non-infectious residual shedders.

Test-to-Protect

If implemented carefully, repeated testing in high infection risk settings can protect vulnerable individuals.[22] When evaluating which test to adopt, and how to implement it, the system-wide practicalities must be considered, especially accessibility and acceptability of sampling, turnaround times and re-test intervals. Technically, rRT-PCR's sensitivity is well suited to vulnerable settings. Practically, it is not, because it can take days from requesting a swab to getting the result. Frequent, rapid decentralised Ag-LFT testing may prove more effective. The new policy of bi-weekly testing of front-line NHS staff with Ag-LFTs recognises that frequent testing can compensate for reduced sensitivity. Weekly point-of-care PCR testing is also being evaluated in some UK care homes, both for staff and visitors, but more frequent Ag-LFT may be more (cost) effective. There are additional concerns around the unregulated marketing of tests which may not be appropriate for use in care home settings.

Test-to-Release and Test-to-Enable

Modelling suggests rRT-PCR testing can both shorten the isolation period for exposed contacts (without increasing transmission) and incentivise compliance.[6] Some countries have proposed focussing isolation decisions on infectivity not just evidence of infection or contact, seeing repeated rapid tests as a way to reduce unnecessary isolation/quarantine of non-infectious individuals. However, such a test-to-release policy needs to mitigate the risks of premature return or hazardous behaviours (Appendix 1). Such policies should not detract from the need to provide comprehensive support in tackling low rates of self-isolation, particularly in disadvantaged areas. Any test-to-release policy must be shown to be effective in pilots and account for the incubation period[6] and behavioural challenges.

Test-to-enable policies seek to lift, in a risk responsive way, the current restrictions to social contact that are causing cumulative public health and economic harms. Specific testing strategies enabling social fabric, service

stability or economic recovery may be targeted, for example to care home visiting, emergency services and public transport. Different testing regimens need to be evaluated and should not replace infection control measures, mitigating the risks from false negatives. Targeted regular testing is more logical than single 'tests for entry,' which are unlikely to confer population wide benefits.[12] Context is key; disadvantaged areas with greater mounting harms from COVID-19 control measures could benefit disproportionately from locally-sensitive responses.

Mass Testing

The effectiveness, feasibility, opportunity costs, and ethics of untargeted mass testing are fiercely debated. Some commentaries have likened this to screening programmes like those for cancer, but the pandemic context is quite different. Cancer screening aims to benefit the individual whereas testing for the presence of highly transmissible respiratory infections is to protect others and benefit society.

As the effectiveness of contact tracing depends on speed, modelling suggests mass testing with Ag-LFTs can contribute to significantly reducing transmission;[23] a strategy that has been undertaken in Slovakia. However, mass testing is a tremendous logistical challenge requiring considerable resources and careful planning. To be successful, it would require complex organisation, effective communication of the risk of false negatives, and rapid and effective contact tracing and isolation, with all positive cases supported to isolate immediately while awaiting confirmation. Other considerations include timing. Although mass testing for SARS-CoV-2 may facilitate early identification, tracing, and isolation of infectious cases that may otherwise remain undetected, the window of opportunity is short. Given the importance of pre-symptomatic transmission, mass testing would need to efficiently find cases in the incubation period to have any tangible benefit over existing symptomatic testing.

Mass testing in China, Vietnam, and Slovakia mandated population-wide testing and quarantine. The behavioural responses to mass testing are poorly understood at present, particularly the potential increase in hazardous behaviours from a negative test result. Test results should ideally be delivered and acted upon within 12 hours to be effective. Ongoing evaluations will hopefully inform optimal strategies.[24]

SMART (Systematic Meaningful Asymptomatic Repeated Testing)

In Liverpool, UK, there is a current pilot that was initially branded as mass testing but is now intended to be a more targeted approach, which we describe here as SMART. This approach uses public open-access testing but with communications and outreach targeting specific groups who are either vulnerable to COVID-19 directly or to its control measures, particularly the disadvantaged groups hit hardest by the economic effects of the pandemic. SMART takes a dual strategy of targeted reduction in transmission alongside test-to-release and test-to-enable schemes designed to protect key services, rebuild social fabric, and recover the economy. The benefits and risks of the scheme are monitored through public health, healthcare, and administrative data sources, and through continuous qualitative information gathering, in a combined intelligence system. The intelligence is used to make tactical changes to the programme, which is reviewed weekly. Tactics are co-created with relevant community groups. Ag-LFT positive cases are confirmed with rRT-PCR, plus viral genetic sequencing.

Complex public health interventions like SMART must be evaluated regarding their biological, behavioural, and system effects, and the ethical basis on which they are implemented and evolved. Communicating this evidence clearly will be essential to the public trust needed for such testing to meet its aims. Appendix 3 outlines possible solutions and we provide seven principles for testing strategies (Figure 4).

Conclusion

Testing plays a critical role in COVID-19 strategies. Although rapid tests like Ag-LFTs provide new opportunities for general population-scale testing, it remains unclear how to implement such tests to both reduce transmission and alleviate the mounting harms from control measures. Pilots of the SMART approach are due to provide new evidence of large-scale, targeted Ag-LFT uses. Successful approaches need to facilitate earlier and better targeted isolation of the most infectious individuals and their close contacts, while releasing

contacts sooner from unnecessary quarantine and restarting activities vital to the public health, social fabric and the economy. Such strategies must integrate tests into an end-to-end programme, co-created with local leaders and communities, including effective contact-tracing, support for those isolating and credible incentives to be tested. A holistic public health approach, joined up across towns, cities and regions, is key to better resilience to, and recovery from, the COVID-19 pandemic.

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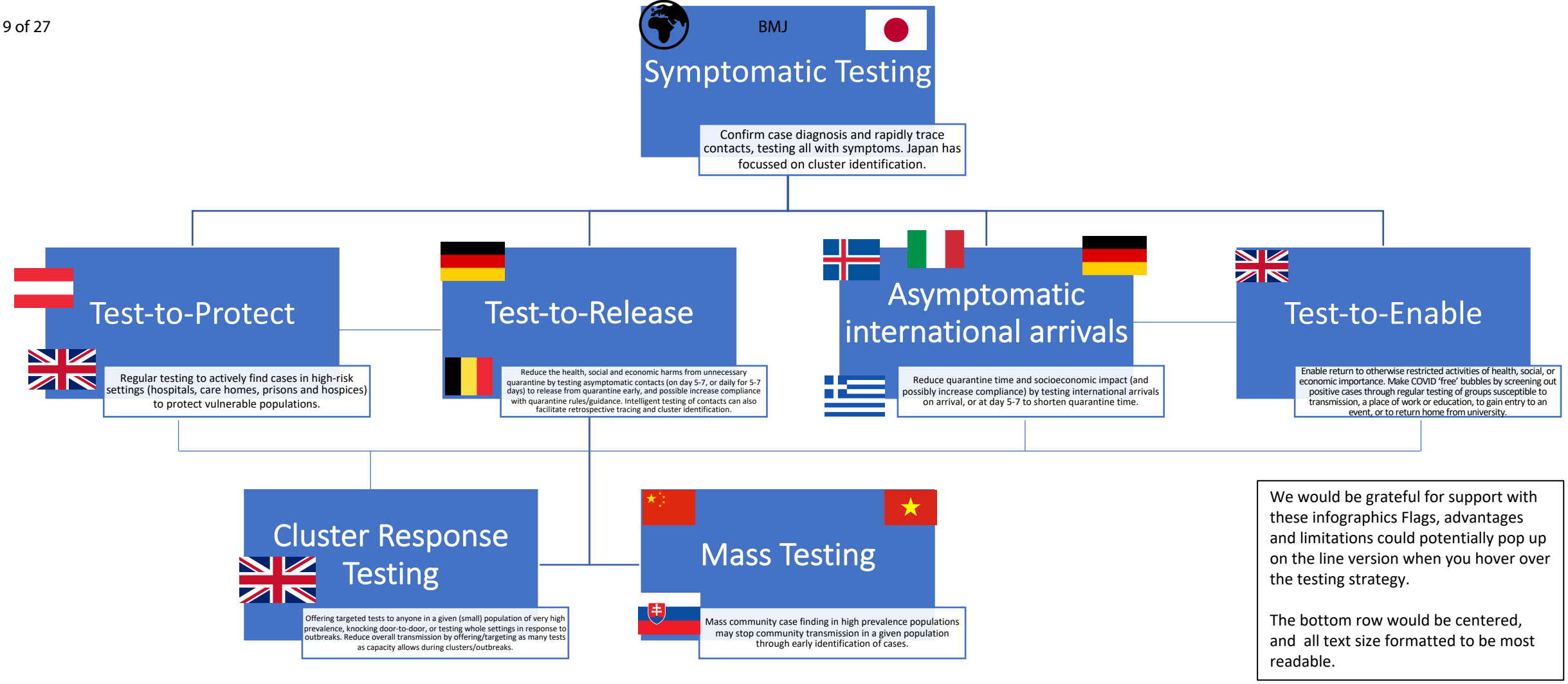

We would be grateful for support with these infographics Flags, advantages and limitations could potentially pop up on the line version when you hover over the testing strategy.

The bottom row would be centered, and all text size formatted to be most readable.

Figure 1. Principle Testing Strategies and Examples of Countries Deploying Them

Countries have deployed differing strategies at different times of the pandemic with varying degrees of success. Some countries, such as Germany and Japan, have focussed on symptomatic testing and investigation of clusters, seeking to identify and intervene with common sources of exposure. This is most likely to be effective in low prevalence because most cases can be traced to a smaller number of events or settings.[5] Many countries have used regular asymptomatic testing in care homes and health facilities. Germany, Iceland, and Italy have tested asymptomatic international arrivals, whilst a similar 'test-to-release' strategy, also briefly adopted in Belgium and France, involves testing asymptomatic contacts on day 5-7, with negative tests enabling release from isolation.[6] Asymptomatic 'test-to-enable' has also been used by elite sports competitions and universities to create COVID-free 'bubble' environments, restricting entry or contact to those testing negative. Whilst many regions have undertaken some form of cluster response testing, some countries, such as China and Slovakia, and regions, such as Liverpool, England, have undertaken mass population testing. Liverpool, UK is taking a different approach of community open access testing supporting linked test-to-protect/release/enable functions.

These categories of testing strategies are not mutually exclusive, and there is no defined order of progression. Each strategy has unique advantages and limitations, summarised in Appendix Table 1. Changes to strategies have sometimes resulted in the test or trace system being swamped: It must be ensured that as testing capacity increases, any change in testing strategy (addition of a layer) does not impact on the system's ability to find, test, trace, isolate, or support cases identified from a previous 'layer.'

Lateral Flow Test Devices

Rapid antigen lateral flow tests (Ag-LFTs) take fluid from a nasal or saliva swab and detect the viral fragments directly, producing rapid results without the need for scientists or laboratories.

Innova SARS-Cov-2 Antigen test

Limit of detection = 100 plaque forming units per mL

Relative sensitivity	Relative specificity
Laboratory conditions = 79%	Laboratory conditions = 99.94%
Trained HCW = 73%,	In the field = 99.61%
Public = 58%	

Advantages	Limitations
Modelling suggests testing frequency and speed of reporting more important than sensitivity alone for surveillance and controlling transmission	Lower **sensitivity** may lead some infectious individuals to test negative
Does not need laboratory analysis and so can facilitate **frequent** decentralized testing at scale	Sensitivity falls when used by untrained staff or public
Rapid time to results (10 - 30 minutes)	Infectious window is early and short-lived, narrowing the window to find cases before they transmit
Good detector of the most infectious cases and less likely to detect residual positives	Unquantifiable result

Figure 2. Rapid Antigen Lateral Flow Test (Ag-LFT) performance and key advantages and limitations.
Sensitivity and specificity of novel assays are listed as 'relative clinical sensitivity/specificity.' The term relative refers to their performance when compared to the 'gold standard' test, rRT-PCR.
Data for the Innova tests performance is from the preliminary report from the Joint PHE Porton Down & University of Oxford SARS-CoV-2 test development and validation: Rapid evaluation of Lateral Flow Viral Antigen detection devices (LFDs) for mass community testing. (HCW: healthcare worker)

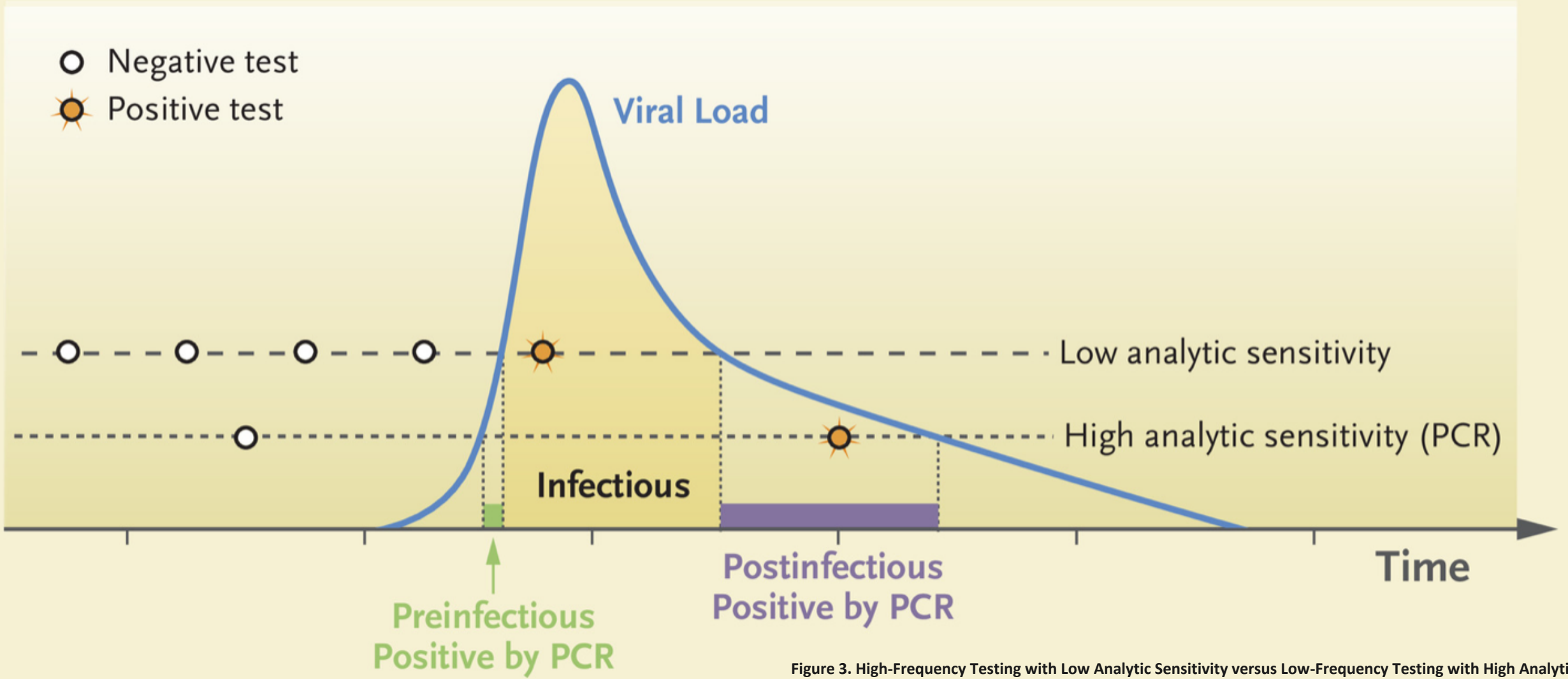

Figure 3. High-Frequency Testing with Low Analytic Sensitivity versus Low-Frequency Testing with High Analytic Sensitivity.
A person's infection trajectory (blue line) is shown in the context of two surveillance regimens (circles) with different analytic sensitivity. The lower sensitivity test (Ag-LFT) is administered frequently and the higher sensitivity test (rRT-PCR) infrequently. Due to its decentralised and rapid nature, higher frequency testing is more likely to test in the infectious window. Therefore, both testing regimens detect the infection (orange circles), but the high-frequency test is more likely to detect it during the transmission window (shading), despite its lower analytic sensitivity, which makes it a more effective filter. The window during which polymerase chain reaction (rRT-PCR) detects infections before infectivity (green) is short, whereas the corresponding postinfectious but PCR-detectable window (purple) is long.

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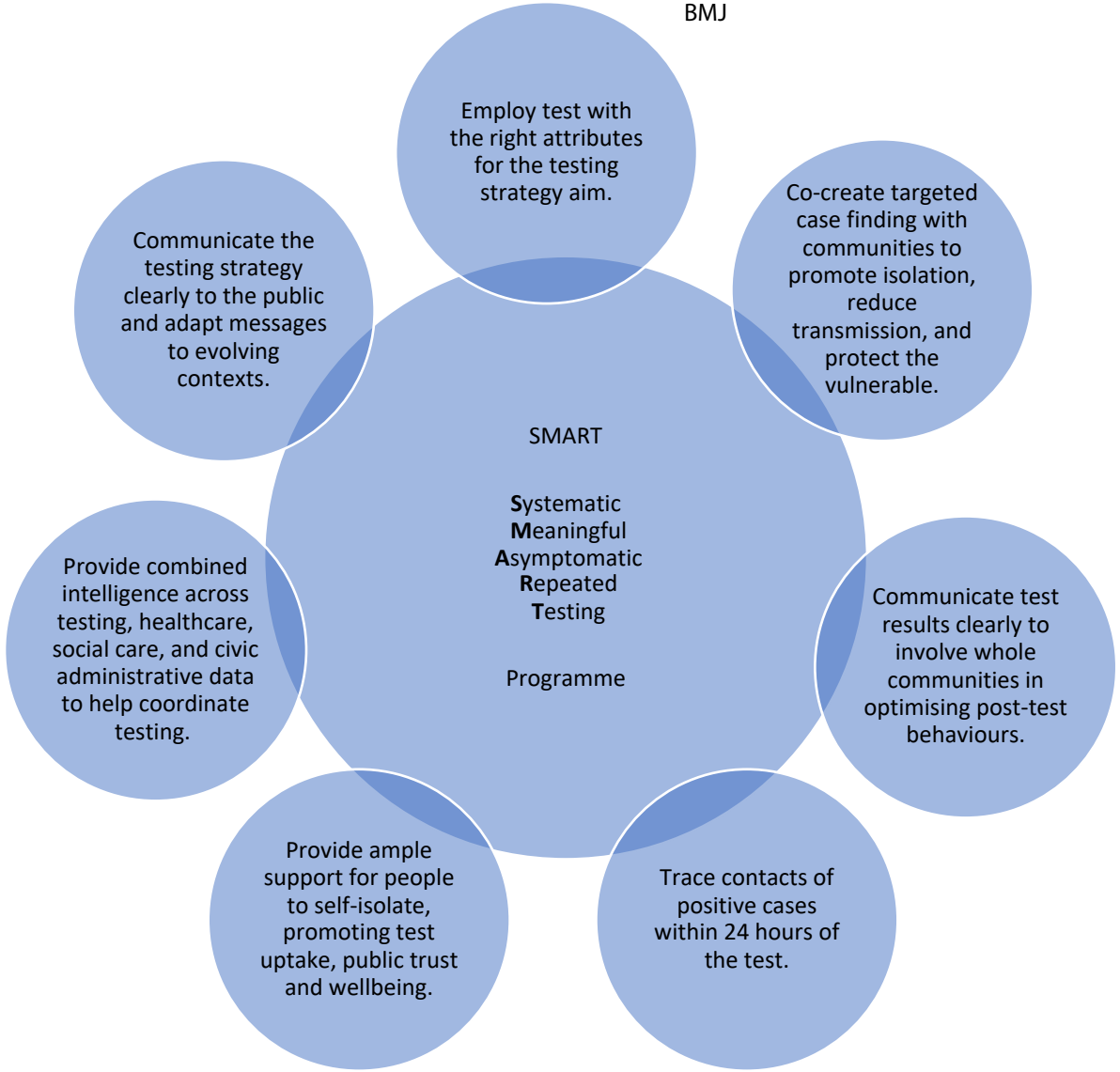

Figure 4. Keys To SMART (Systematic Meaningful Asymptomatic Repeated Testing) Programme

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

Crozier, A., Rajan, S., Buchan, I., and Mckee, M.

Appendix Table 1. Principle Testing Strategies and Examples of Countries Deploying Them

Countries have deployed differing strategies at different times of the pandemic with varying degrees of success. Some countries, such as Germany and Japan, have focussed on symptomatic testing and investigation of clusters, seeking to identify and intervene with common sources of exposure. This is most likely to be effective in low prevalence because most cases can be traced to a smaller number of events or settings. Many countries have used regular asymptomatic testing in care homes and health facilities. Germany, Iceland, and Italy have tested asymptomatic international arrivals, whilst a similar 'test-to-release' strategy, also briefly adopted in Belgium and France, involves testing asymptomatic contacts on day 5-7, with negative tests enabling release from isolation. Asymptomatic 'test-to-enable' has also been used by elite sports competitions and universities to create COVID-free 'bubble' environments, restricting entry or contact to those testing negative. Whilst many regions have undertaken some form of cluster response testing, some countries, such as China and Slovakia, and regions, such as Liverpool, England, have undertaken mass population testing. Liverpool, UK is taking a different approach of community open access testing supporting linked test-to-protect/release/enable functions.

These categories of testing strategies are not mutually exclusive, and there is no defined order of progression. Each strategy has unique advantages and limitations, summarised in Appendix Table 1. Changes to strategies have sometimes resulted in the test or trace system being swamped: It must be ensured that as testing capacity increases, any change in testing strategy (addition of a layer) does not impact on the system's ability to find, test, trace, isolate, or support cases identified from a previous 'layer.'

Testing Strategy 'Layer'	Testing Strategy Overview	Examples where strategy has been used	Benefits	Risks/Limitations
Symptomatic Testing	Confirm case diagnosis and rapidly trace contacts through symptomatic individuals.	Globally	Uses limited testing capacity. High positive predictive value. Can combine with effective forward and retrospective tracing to identify sources of outbreak clusters and interrupt onward transmission to facilitate greater control of transmission (Japan and Germany).	Will miss a significant proportion of infections and won't identify index cases early in infection. Unlikely to keep R < 1 unless low prevalence with very effective forward and backward tracing and high levels of adherence to self-isolation and/or significant social distancing.
Test-to-Protect	Regular testing to actively find cases in high-risk settings (hospitals, care homes, prisons and hospices) to protect vulnerable populations.	UK, Germany and Austria (care homes and hospital pre-admission)	Likely to reduce potential for outbreaks in vulnerable settings and identify vulnerable individuals requiring treatment early.	May falsely quarantine individuals or healthcare and social care workers due to residual positives. Uses significant testing capacity and resources.
Test-to Release	Reduce the health, social and economic harms from unnecessary quarantine by testing asymptomatic contacts (on day 5-7, or daily for 5-7 days) to release from quarantine early, and possibly increase compliance with quarantine rules/guidance. Intelligent testing of contacts can also facilitate retrospective tracing and cluster identification.	France, Germany, Czech Republic, UK (Liverpool pilot ongoing).	Reduces time spent in quarantine/isolation. May incentivise compliance with quarantine rules. Reduces potential for health, social, and economic harms from quarantine.	False negatives may result in some onward transmission and give a false sense of security to infectious cases. Significant stress on testing capacity. Some test-to-release policies may incentivise a premature return to restricted activities.
Asymptomatic International Arrivals	Reduce quarantine time and socioeconomic impact (and possibly increase compliance) by testing international arrivals on arrival, or at day 5-7 to shorten quarantine time.	Hong Kong, Italy, Singapore, Germany, Iceland	Reduces time spent in quarantine/isolation. Promotes free movement between borders and economic recovery.	False negatives give a false sense of security to infectious cases resulting in onward transmission and seeding

Testing Strategy 'Layer'	Testing Strategy Overview	Examples where strategy has been used	Benefits	Risks/Limitations
			May incentivise compliance to quarantine rules.	between countries. Significant stress on testing capacity.
Test-to-Enable	Enable return to otherwise restricted activities of health, social, or economic importance. Make COVID 'free' bubbles by screening out positive cases through regular testing of groups susceptible to transmission, a place of work or education, to gain entry to an event, or to return home from university.	Elite sports competitions select universities and workplaces. Studies in key workers and multiple groups under way (Liverpool).	May facilitate increase in social and economic activity without significant increases in transmission.	Marginal impact on national R. False negatives may result in some onward transmission and give a false sense of security to infectious cases. Individuals may attempt to 'game' the system to gain entry. Should not be used to replace infection control measures or facilitate release of wider restrictive measures unless testing is very regular.
Cluster Response Testing	Offering tests to anyone in a given (small) population of very high prevalence, knocking door-to-door, or testing whole settings in response to outbreaks. Reduce overall transmission by offering/targeting as many tests as capacity allows during clusters/outbreaks.	UK (Summer), Neighbourhoods within Liverpool (pilot ongoing)	Active case finding of asymptomatic and pre-symptomatic cases can lead to the early identification, isolation, and tracing of the most infectious cases, to reduce onward transmission.	May result in unnecessary quarantine of non-infectious individuals due to residual positives. Significant stress on testing capacity and public health teams, which may slow turnaround.
Mass Testing	Mass community case finding in high prevalence populations (cities or countries)	China, Vietnam, Iceland,	Potential to find and quarantine many cases which may have otherwise gone	Low positive predictive value. Window of opportunity to

Testing Strategy 'Layer'	Testing Strategy Overview	Examples where strategy has been used	Benefits	Risks/Limitations
	may stop community transmission in a given population through early identification of cases.	Slovakia	undetected. Early identification, isolation, and tracing of the most infectious cases to reduce onward transmission. Possible to eliminate the virus from a given population.	find cases before they transmit is short. Logistically very challenging and huge resources required. Ethical concerns.

Appendix Table 2. Novel Types of Assay.

We list the 5 main types of novel assay that are being used for diagnostic testing or in pilot studies of asymptomatic testing.
Sensitivity and specificity of RT-LAMP, Next generation sequencing technologies, POC RT-PCR, and lateral flow antigen assays are relative to qRT-PCR sensitivity and specificity.

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
Real-Time Reverse Transcription-Polymerase Chain Reaction (rRT-PCR)	Combines reverse transcription of RNA into cDNA and amplification of specific DNA targets using gene-specific primers with fluorescently labelled tags over a series of temperature changes. Measures the amount of a specific RNA by monitoring the amplification reaction using fluorescence.	TaqPath COVID-19 CE-IVD RT-PCR Kit GeneXpert Systems	Analytical sensitivity and specificity > 99.9%. Clinical sensitivity 79% - 98%[1] Clinical specificity > 99%[2] Best-in-class rRT-PCR assays demonstrate a limit of detection (LoD) of ~100 copies of viral RNA per millilitre of transport media. However, LoDs of currently approved assays vary over 10,000-fold.[3]	High analytical sensitivity and specificity. Semi-quantitative. Well established molecular diagnostics tool. Total throughput can be increased further by using robot liquid handlers. In certain contexts, throughput of 94 samples per run can be increased 2 - 10 fold by using pooled testing. Can be home swabbed. In ideal conditions, 2 - 4 hours from sample to result. Use of saliva samples can improve sample collection and reduce bottleneck in pooling workflow of RNA extraction.	Requires laboratory labour and analysis, and robots for very high throughput. Uses reagents in high global demand. Time from sample to result normally much longer (24-72 hours) due to delivery and processing times. High sensitivity means likely to detect residual positives. Even though highly sensitive, false negatives will arise due to the incubation period and lower diagnostic sensitivity than analytical sensitivity. Naso-oropharyngeal swab is less reliable when self-swabbed. Saliva testing not yet

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
				Some tests include primers to detect influenzas and other respiratory viruses, useful for clinicians and surveillance.	validated for use on most kits.
Reverse Transcription-Loop Mediated Isothermal Amplification (RT-LAMP)	Like rRT-PCR, LAMP is also nucleic acid amplification, but instead of using a series of temperature changes to produce copies of the viral DNA, LAMP is conducted at a constant temperature of 60-65°C. A positive test result can be seen visually without requiring a machine to read the results.	Color Genomics SARS-CoV-2 RT-LAMP Diagnostic Assay OptiGene's COVID-19 Direct Plus RT-LAMP KIT-500 Direct RT-LAMP test	Color Genomics SARS-CoV-2 RT-LAMP Diagnostic Assay[4,5] Relative sensitivity = 100.0% (n=37) Relative specificity = 100.0% (n=502) LoD = ~500 copies per millilitre of transport media. OptiGene's Covid-19 Direct Plus RT-LAMP test[6] Relative sensitivity of swabs with CT<25 = 100% (CI = 0.96-1.00) Relative sensitivity of swabs with CT<33 = 84.1% (CI 0.76-0.89) Relative specificity = 100.0% (CI = 0.98-1.00)*	High analytical sensitivity and specificity Results in 1 - 2 hours for RNA RT-LAMP and in 10 minutes for single Direct-LAMP strongly positive sample (about 45 minutes for 8 samples). Samples can be swabbed or saliva. RNA RT-LAMP could replace or add to rRT-PCR where there is a need for increased sample throughput (or alternative workflows). Direct RT-LAMP can be a near-patient screening tool to	RNA RT-LAMP requires laboratory labour and analysis. Direct RT-LAMP requires less labour, but still requires laboratory labour and has lower sensitivity - would require increase in resources and opportunity costs should be evaluated. High sensitivity of RT-LAMP means likely to detect some residual positives. Direct RT-LAMP currently has significantly lower sensitivity than normal RT-LAMP or rRT-PCR (but faster time to results).

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
				rapidly identify highly contagious individuals within emergency departments and care homes during times of increased disease prevalence.	Saliva sample decreases sensitivity further.
Next Generation Sequencing (NGS) Technology	Combines target specific amplification (LAMP or RT-PCR) and real-time sequencing and analysis. During amplification and sample preparation, unique molecular barcodes are added to each individual sample, enabling large numbers of samples to be combined and analysed simultaneously. When sequencing reads aligning to the SARS-CoV-2 genome and control target reach a threshold number per sample, the sample can be classed as positive.	LamPORE SwabSeq	LamPORE[7] Relative sensitivity = 99.1% (n=228) Relative specificity = 99.6% (n=279))	2 hours to result (in ideal conditions). High relative sensitivity and specificity. Semi-quantitative. High throughput - Flexible processing of 24–480 samples per run; potential for over 9,000 samples in 24 hours. Additional regulatory submissions to enable the multiplexing of 768 samples per flow cell are in preparation, offering the potential to increase sample	Requires laboratory labour and analysis. Higher throughput (> 480) has not yet been validated or shown to be viable for diagnostics.

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
				throughput >20,000 samples in 24 hours. LamPORE also detects common winter respiratory viruses including Influenza A and B and RSV, useful for both clinicians and for surveillance.	
Point of Care (POC) RT-PCR	Like rRT-PCR but requires no significant manual lab work. Sample in, result out.	COVID Nudge Samba II	COVID Nudge[8] Relative sensitivity (94.4% (n=71)) Relative specificity (100% (n=315)) Samba II[9] Relative sensitivity (96.9% (n=32)) Relative specificity (100% (n=117))	1.5 - 3 hours to result. Sample in - result out. Sensitive and specific point of care test. Clinical validation and implementation study showed SAMBA II time to result 2.6 h for POC versus 26.4 h for standard lab RT- PCR, reduces median time-to-bed placement by 6 h, and improves indices of hospital functioning and patient care. SAMBA II suitable for use in warmer temperatures (10 - 38°C and relative humidities (80%).	1 result per instrument per run. Each individual instrument is expensive. Some pilot studies evaluating POC PCR with increased throughput for use in care homes to allow visits. Promising in theory, although real-world feasibility questionable, and opportunity costs and risks of false negatives must be evaluated.

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
Antigen rapid lateral flow test (Ag-LFT)	Lateral flow tests operate on the same principles as the enzyme-linked immunosorbent assays (ELISA). They are simple devices intended to detect the presence of a target substance in a liquid sample without the need for specialized and costly equipment. In essence, these tests run the liquid sample along the surface of a pad with reactive molecules that show a visual positive or negative result. The pads are based on a series of capillary beds, such as pieces of porous paper, micro structured polymer, or sintered polymer. Each of these pads has the capacity to transport fluid (swab buffer or saliva) spontaneously.	SD Biosensor Lateral Flow Test (Standard Q COVID-19 Ag kit) SARS-CoV-2 Antigen Rapid Qualitative Test (Innova SARS-Cov-2 Antigen test) PANBIO™ Covid-19 Ag Rapid Test (Abbott)	SD Biosensor STANDARD Q COVID-19 Ag Test FIND Evaluation[10] Relative clinical sensitivity (87.2% (n=344))** Relative clinical specificity (99.1.% (n=1844))** LoD = 5000 plaque forming units per mL. Innova SARS-Cov-2 Antigen test DHSC/PHE/Oxford Evaluation[11] Relative diagnostic sensitivity when used in laboratory conditions (79.2% (n=197)), by trained HCW (73.0% (n=126)), and self-trained members of public given a protocol (57.5%(372)). Relative specificity when used in laboratory conditions (99.94% (n=1655)) and 99.61% (n=5312) in the field. LoD = 100 plaque	Rapid time to results (10 - 30 minutes). Lower sensitivity means good detector of infectious cases and less likely to detect residual positives. False positives can be mitigated by using confirmatory testing. False negatives can be somewhat mitigated by repeat testing after 5-7 days. May facilitate decentralised mass testing. Some tests use saliva samples - improves throughput. Decentralised nature and rapid time to results means tests can be used to quickly identify sources of outbreak clusters, facilitating greater control of the pandemic - Backwards tracing may be particularly effective if combined with rapid	Lower sensitivity will result in increased false negatives of infectious individuals. Sensitivity falls when used by untrained staff, or by the public. Not validated for home use. Given lower sensitivity, cluster identification would have to be rapid to avoid false negatives missing infections. Non-quantitative results. Mass testing is a hugely resource intensive intervention. Associated challenges beyond biochemical limitations (logistical, behavioural, and ethical), are given in Appendix 3.

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
			forming units per mL PANBIO Covid-19 Ag Rapid Test (Abbott) FIND Evaluation[12] Relative clinical sensitivity (85.5% (n=124) Relative clinical specificity (100% (n=411) LoD is to be confirmed	antibody tests and/or more sensitive semi-quantitative tests and/or sequencing. Fast upswing in viral titres shows only small time difference between when people turn rRT-PCR positive and when they turn rapid antigen positive. Modelling suggests testing frequency and turnaround time more important than sensitivity for surveillance. The sensitivity range of most Ag-LFTs overlaps with the infectious period in the majority of patients. Although many caveats remain, Ag-LFT positives may broadly indicate the time at which infectivity begins and then resolves.	

The term 'clinical sensitivity/specificity' refers to the real-world identification of infections, rather than the analytical properties under laboratory conditions.
The term 'relative sensitivity/specificity' refers to their performance when compared to the 'gold standard' test, rRT-PCR.
* Note that this is information taken from the OptiGene COVID-19 Direct Plus RT-LAMP KIT-500 Direct RT-LAMP test manual. These tests have been piloted in selected UK hospitals by DHSC and there is more recent real-world data for this assay, but it is as yet unpublished.

** Mean of FIND evaluations from Brazil, Germany, and Switzerland.
It should be noted that data for the Innova Antigen test from the DHSC/PHE/Oxford evaluations includes some testing of asymptomatic, which is likely to impact on reported sensitivity, compared to the evaluation of the PANBIO Covid-19 Ag Rapid Test which was on symptomatic individuals only.

Appendix Table 2. References

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Appendix Table 3. Biochemical Limitations And Logistical, Behavioural And Ethical Challenges To Mass Asymptomatic Testing

Large scale asymptomatic testing has the potential to enable the early identification, isolation, and tracing of many more cases that would otherwise be unlikely to be detected. As such, it may be appealing, but there are many and considerable biochemical limitations and logistical, behavioural, and ethical challenges to mass testing. Although analytical sensitivity and specificity in symptomatic individuals of most tests are both believed to be over 95%, the diagnostic (real world) sensitivity and specificity depends on operational conditions (e.g. timing of test, sampling technique, specimen packaging and transport) and are thus more difficult to quantify. When testing at low pre-test probability (low prevalence), result interpretation becomes more complex: False positives, residual positives, and false negatives can all occur, and provide several challenges to mass testing. There are also major logistical, behavioural, and ethical challenges of testing at such scale. The main challenges, and some possible solutions, are summarised here.

Type of Limitation or Challenge	Limitations and Challenges of Mass testing	Additional Information	Possible Solutions
Biochemical Limitations	Although **false positive** rate is relatively low (<1%), they become highly relevant when testing at low prevalence where pre-test probability is low.	False positives are of concern as they can result in individuals self-isolating unnecessarily to the detriment of their socioeconomic wellbeing or health by, for example, missing elective surgery.	False positives can be largely mitigated by using confirmatory testing, where the pre-test probability is low.
	Diagnostic **false negative** rate of rRT-PCR is estimated to be between 2 - 29%. Rapid tests have a lower sensitivity than rRT-PCR, so false negatives will be more frequent.	**False negatives may provide false reassurance to infectious individuals**, leading to laxity of infection control measures and increased transmission to people with whom they are in contact.	Swab or saliva sampling by trained staff can increase the reliability and sensitivity of sampling but would likely decrease the efficiency and throughput of mass testing. **Effective public health communication** may reduce unwarranted behaviour change following a negative test result.
	Residual non-infectious positives, which arise due to prolonged viral shedding of recovered infections, may result in unnecessary quarantine of non-infectious individuals if detected during testing.	**Shedding duration can be significantly longer than the duration of infectiousness**: Such cases are often detected in asymptomatic care home testing and healthcare worker screening, resulting in some care homes being 'locked down' and healthcare workers having to isolate even though they may not be infectious.	Current Public Health England guidance states that individuals are ineligible for testing within 90 days of a positive test, reducing the repeated unnecessary isolation of non-infectious care home staff that occurred earlier in the pandemic. Ag-LFTs, which are less sensitive than rRT-PCR, are less likely to detect these prolonged shedders.
	SARS-CoV-2 virus can normally only initially be detected in upper respiratory samples 1–2 days prior to symptom onset. This means **the window of opportunity for active**	**Pre-symptomatic transmission is a key driver of spread**. To be most effective, community active case finding must be	Fast upswing in viral titres shows only small-time difference between when people turn positive on highly sensitive tests such as rRT-PCR and

	case finding to identify infectious cases before they transmit is short.	coupled with effective contact tracing and cluster identification.	when they turn positive on less sensitive tests such as Ag-LFTs.
Logistical Challenges	**Mass testing is extremely resource intensive. Cost effectiveness** of mass testing must be evaluated from both health systems and societal perspectives. **Bottlenecks** exist at many stages of the process, including procurement, supply, integration with health systems, contact tracing and access to support.	**Testing strategies need a systems approach**, and to thoroughly consider sample collection and delivery, sample extraction, how results would feed into the contact tracing system, how to analyse such a large volume of integrated data securely, promptly, and accurately, to provide locally actionable information.	Novel rapid assays, such as Ag-LFTs, which require no instrumentation or laboratory processing or analysis can in theory overcome some bottlenecks such as sample collection, delivery and extraction time, and laboratory labour. Local integrated healthcare, social care, public health, and administrative data/intelligence systems, where available, can be employed to coordinate and target testing.
Behavioural Challenges	**False negatives** test results may encourage a reduction in infection control behaviours, and lead to increases in transmission.	Some have argued tests can be used to incentivise compliance and reduce quarantine time, but false negatives are a concern here. People may also attempt to 'game the system' to get a negative result.	Although reporting testing results with the inherent risk and nuanced details may reduce some of these risks, there is, as yet, no strong evidence that this is a substantial problem.
Ethical Challenges	**The benefits of screening for COVID-19 accrue not to the patient but to wider society.**	Even though the harms, such as the discomfort of swabbing and a short period of isolation may be relatively trivial, they will always outweigh the benefits at an individual level. This may limit uptake, especially in the general population. Most whole population testing programmes to date have enforced testing and isolation, and so it remains to be seen how feasible it is for voluntary mass testing to effectively reduce transmission.	Effective communication and **engagement with communities** can explain how testing programmes can be of significant benefit to the common good and how effective testing strategies can facilitate a return to increased economic and social activities.

	The effectiveness of testing relies on routine reporting of person-level information to public health authorities for contact tracing, and large-scale testing raises the importance of **privacy protection**. Fears have been reported in the media of test and trace data being misused, with police being given access to testing data and able to issue large fines for those failing to comply.	There are also challenges to the principle of autonomy for those who refuse or are unable to consent to testing, and for those whose consent may be obtained under the threat of coercion by employer or state. Additionally, the history of stigma associated with positive results that arise from screening for transmissible disease, such as with HIV, suggests this is a concern requiring urgent evaluation if governments are to roll out large-scale asymptomatic testing.	Aim to keep test and trace data within the relevant health authorities, under the information governance and data protections that are usually applied to healthcare and social care records.
	Some have argued that participation in mass testing programmes can be encouraged because of the freedoms it may afford, where recent evidence of a negative test can not only release contacts from quarantine, but also open access to otherwise restricted activities such as restaurants, bars, large events, and other public venues. The scientific feasibility, ethics, and logistics of this need further investigation and careful scenario planning for whole health systems. The argument for this approach in tackling harms from COVID-19 control measures is different but must be considered in option appraisals.	Such policies will likely have minimal impact on reducing the national reproduction number. The health, economic and social impacts of conditional release from reduced social contact need assessing at whole system level. Similarly to immunity passports based on antibody tests, tests for infection face substantial technical, legal, and ethical challenges.	Prioritise testing strategies on protecting vulnerable groups and for reducing overall transmission. Carefully appraise the options at whole health system level for tackling the health, social, and economic harms of COVID-19 restrictions.
	Although mass testing may stop community transmission through early self-identification of infectiousness, moving into an era where everyone is tested regularly changes the public relationship with, and trust in, health authorities and must be considered carefully before large-scale deployment.	Mass testing is vulnerable to profiteering and abuse, and regulation of the diagnostics industry is not currently equipped for the protections needed.	The fundamental aims of any mass testing must be clearly described, and the focus must be to improve public health, and not for commercial or political gains. Fundamentally, testing must be reoriented in a comprehensive, holistic and intelligence-led public health strategy of pandemic management.