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

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Complete List of Authors:	Crozier, Alex; University College London, Division of Biosciences Rajan, Selina; London School of Hygiene & Tropical Medicine, Department of Health Services Research and Policy Buchan, Iain; University of Liverpool, Public Health and Policy McKee, Martin; LSHTM, ECOHOST
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Put to the test: An evaluation of how rapid testing technologies can be deployed to fight COVID-19

Alex Crozier[1]
Selina Rajan[2]
Iain Buchan[3]
Martin McKee[2,4]

[1] Division of Biosciences, University College London, London WC1E 6DE, UK
[2] Department of Health Services Research and Policy, The London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
[3] Institute of Population Health, University of Liverpool, Waterhouse Building, Liverpool L69 3DT, UK
[4] European Observatory on Health Systems and Policies, London WC1E 7HT, UK

Correspondence to: Alex Crozier
Full name: Alexander F F Crozier
Mailing address: Division of Biosciences, University College London, London WC1E 6DE, UK
Email: alexander.crozier.20@ucl.ac.uk
Phone: 07412411054

Standfirst

Governments across Europe are investing in deploying 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, assessing the benefits and risks of each, and summarise their individual advantages, limitations, challenges, risks, and ethics and consider how novel tests can be used in SMART (Systematic Meaningful Asymptomatic Repeated Testing) public health policies to improve COVID-19 resilience and recovery.

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 physician and researcher leading evaluation of 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 rapid testing technologies might be harnessed to improve SARS-CoV-2 transmission control while sustaining or reopening activities that are key to the health, social and economic wellbeing of communities.

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Patient involvement

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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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Introduction

Governments have invested enormous resources in scaling up testing capacity in their responses to COVID-19. Real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) was the first, and still the most widely used test. However, there may be delays of several days between requesting a test and getting and acting on a result, leaving a window in which infection may spread. A further problem is that people may transmit infection before recognising symptoms,[1] and this is a key driver of spread. In addition, while some remain asymptomatic, they 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- or pauci-symptomatic transmission in a very short interval,[1] measures that shorten the interval between testing and results are essential for minimising onward transmission. It is difficult to achieve this with large-scale rRT-PCR testing.

Rapid antigen lateral flow tests (Ag-LFTs) offer an alternative. They provide a rapid result but are less able to detect infections.[4] Governments are purchasing them in vast quantities, with some seeing a single test as a way to free an individual from quarantine obligations, a view not supported by WHO.[4] However, repeated Ag-LFTs, in combination with other measures, is being studied, for example in Liverpool,[5] where authorities are examining certain test-to-protect, test-to-release (from quarantine) and test-to-enable (safer return to restricted activities) regimens, alongside outbreak response and public open-access to Ag-LFT testing. Such real-world evaluations of Ag-LFTs are needed to understand how these models work in different populations and settings, how they influence behaviour, and the contribution of Ag-LFT in overall strategies, where they have the potential to interrupt transmission while reducing the harms from restrictions.

We outline the different tests that can facilitate these goals (Appendix 1), and the benefits and risks associated with implementing them (Appendix 2), before asking how novel tests, particularly Ag-LFTs, can support the different testing strategies adopted internationally (Figure 1, Appendix 3) in response to the pandemic.

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, reflecting population prevalence and the individual's circumstances.[6]

Although controls seek to minimise errors, technical problems during sample collection, processing, or reporting can give false results. Ag-LFTs have very few false positives and in a low prevalence setting can be addressed by confirmatory testing with rRT-PCR.[4,7] False negatives are of greater concern. Besides technical errors, they can arise in individuals tested during the 5-7 day incubation period before virus/viral antigen shed in the nose/throat is sufficient to be detected, usually 1-2 days before symptom onset.[1,2,8]. Taking swabs requires skill and lower quality swabs taken by untrained individuals are more likely to yield false negatives.[9,10] False negatives might create a false sense of security, paradoxically increasing transmission risk.[11] Conversely, rRT-PCR is overly 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 rRT-PCR positives, these individuals are not infectious and should not be quarantined. Moreover, any test is just a snapshot of the 'moment' the sample was taken.

Everyone must have a shared understanding of the utility and uncertainties of these tests.[12] Predictive values can be calculated with specialist tools,[6] but effective communication of what results mean is crucial.

Novel Tests

Several novel techniques, such as loop-mediated isothermal amplification, next-generation sequencing (LamPORE), point-of-care PCR, and Ag-LFTs are in different stages of development, validation, approval and implementation (Appendix 1). Each has advantages and limitations, so the choice depends on the intended use. Ag-LFTs (Figure 2) can be scaled-up quickly for 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. The quality of the sample will always be a limiting factor.[4,13]

The window for using Ag-LFTs to detect infectious cases is narrow.[2,14] They are most suitable where testing is frequent and the goal is detection of cases with high viral shedding immediately before and after symptom onset.[2,4] Despite their limitations, Ag-LFTs could thus facilitate timely isolation of the most infectious cases and their close contacts,[4,15] who otherwise may go undetected and transmit infection.

While recognising the risk of false negatives with Ag-LFTs, in theory the rapid increase in viral shedding after the incubation period leaves only a short period when there will be a substantial difference between first turning positive on a highly sensitive test (rRT-PCR) compared to a lower sensitivity test (Ag-LFT).[16,17] 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 (Figure 3).[18,19] Under laboratory conditions, the limit of detection of Ag-LFTs largely aligns with the viral shedding (quantified as viral load) typically observed at the end of the first week of symptoms, when most patients cease being infectious.[2,14] As detected viral antigen is a proxy and not a direct indicator of infectiousness, caveats remain, but the point when Ag-LFT results change from negative to positive, and vice versa, mostly coincides with the beginning and end of infectiousness of most symptomatic cases,[14] and potentially also in asymptomatic cases. Thus, despite their lower sensitivity, Ag-LFTs may be a useful, albeit imperfect, indicator of current infectivity, and less likely than rRT-PCR to detect post-infectious shedders. However, as explained above, sensitivity is user and operator-dependent[10], and self-swabbing in real-world conditions is likely to miss more infections than swabbing in controlled conditions. In Liverpool, data suggests Ag-LFTs missed around a third of substantially infectious individuals (high detected viral load), although further work is required to more precisely determine how this relates to infectiousness.[5] The test must also be read and laboratory scientists are less likely than others to report false negatives, although this can improve with more robust protocols, additional training, and possibly AI-augmented reading.[5,10] Also, antigen tests and population groups are not all the same so test accuracy must be understood for different groups (e.g. asymptomatic/(pauci-)symptomatic, and by age and background prevalence) before large-scale use.

Testing Strategies

Countries have adopted different testing strategies, many using Ag-LFTs. Their benefits and risks are summarised in Figure 1 and Appendix 3. Each should be evaluated, recognising that testing can only be one part of a comprehensive pandemic response. When deciding which test to adopt, and how to implement it, system-wide practicalities must be considered, especially accessibility and acceptability of sampling, turnaround times and re-test intervals.

Mass Repeat-Testing

The effectiveness, feasibility, opportunity costs, and ethics of large-scale asymptomatic testing are fiercely debated. Some have likened this to cancer screening programmes 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 by breaking transmission chains.

Mass repeat-testing for SARS-CoV-2 has successfully identified cases that would otherwise have gone undetected using rRT-PCR in China, Vietnam and Iceland, while Slovakia used Ag-LFD. However, mass testing poses tremendous logistical challenges, requiring considerable resources and careful planning. In the UK, non-focused mass repeat-testing is unlikely to be feasible or cost-effective.

SMART (Systematic Meaningful Asymptomatic Repeated Testing)

Liverpool, UK has developed a focused approach to mass repeat-testing with Ag-LFD, hereafter termed SMART. Open-access testing of the public is supported by communications and outreach targeting specific groups who are either vulnerable to COVID-19 or its control measures. SMART comprises a dual strategy of focused reduction in transmission alongside outbreak response and specific test-to-protect, test-to-enable and test-to-release schemes (see below), designed to protect key services, reconnect societies, and recover the economy.

The benefits and risks of the scheme are monitored through public health, healthcare, and administrative data and continuous qualitative information gathering. This information is used to adapt the evolving programme in weekly reviews, co-created with community groups. For example, now Liverpool is in national lockdown, testing focused on workplaces, to enable continuity of essential services and to protect against transmission in high mixing environments such as supermarkets. Ag-LFT positive cases are confirmed with rRT-PCR, plus viral genetic sequencing.

Although SMART has significant potential to find asymptomatic or pauci-symptomatic cases early and reduce onwards transmission, large-scale use is resource intensive and requires effective local engagement. Mass testing in China, Vietnam, and Slovakia mandated population-wide testing, with quarantine enforced with consequences for non-adherence. Given the importance of pre- and pauci-symptomatic transmission, SMART must find more cases in the incubation period to improve on symptomatic testing, which in theory it should. Although the behavioural responses to large-scale asymptomatic testing in the community are not fully understood, particularly the potential increase in hazardous behaviours following a negative result, ONS survey data in Liverpool showed most (62%) said a negative result would be unlikely to cause them to change their behaviour.[5] However, some said they were more likely to visit friends (9%) or go to work (7%), emphasising the need to communicate the importance of maintaing COVID-safe behaviours.

Although 95% of positive cases in the Liverpool pilot self-isolated and informed relevant contacts immediately, not being able to afford the costs of self-isolation was a significant barrier to uptake,[5] highlighting the need for a holistic public health approach including effective communication and comprehensive support to self-isolate. It is essential to recognise that tests alone are not the answer: recent experience of repeat Ag-LFT testing in German care homes highlights the many logistical, economical, and behavioural challenges involved in SMART.[20] Logistic factors are important, such as arrangements for booking and queuing for tests, so the choice of test policy will often be limited by cost and available workforce and capacity of the community to access booking systems and testing sites. The biological, behavioural, ethical and system implications of complex public health interventions like SMART must be evaluated, with findings used to develop rigorous standard operating procedures and protocols that optimise strategies. Communicating this evidence clearly is essential to achieve public and professional trust needed if testing is to succeed. Appendix 2 outlines possible solutions, while Figure 4 shows seven principles for testing strategies.

Improving Cluster Identification and Outbreak Response

It takes approximately 4-5 days for someone infected with SARS-Cov-2 to infect another person so contact tracing must identify and reach contacts as soon as possible[21]. As many people don't request a test until at least 24-48 hours after developing symptoms and rRT-PCR can take more than 24-48 hours to return results (median 38 hours with 14% taking over 72 hours most recently[22]), significant onwards transmission can occur before contacts are reached and clusters of cases can quickly spill over into large outbreaks. Modelling suggests rapid testing can contribute to significantly reducing transmission.[23] In high risk settings for outbreaks (workplaces, care homes, schools, universities, prisons, and hospitals), repeated and frequent Ag-LFTs cut these delays, providing real time results for cases and close exposure contacts, which can identify clusters[24] quickly and limit spread. To mitigate the increased risks of false negatives, symptomatic individuals could be swabbed for Ag-LFT and rRT-PCR in parallel. Robust communication that a negative Ag-LFT does not mean 'not infectious' is essential and symptomatic individuals must continue to isolate.

Cases could also be identified earlier if the clinical case definition were broadened to include symptoms including *disturbance* of taste and smell, headaches and myalgia, which often present earlier than the classical symptoms. Although existing testing capacity might struggle, it would be more consistent with the WHO criteria[25] and should be evaluated. Outbreak response and community testing can also be improved using mobile or pop-up rRT-PCR or LamPORE laboratories (Appendix 1) which can provide relatively high-throughput sensitive testing with a turnaround time of 4-24 hours.

Test-to-Protect

If implemented carefully, repeated testing in high infection risk settings can protect individuals who are either clinically vulnerable or vulnerable to infection (and transmission).[26] 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 recent policy of bi-weekly testing of front-line NHS staff with Ag-LFTs recognises that frequent testing can compensate for reduced sensitivity. Specific testing strategies may also be focused on protecting groups most susceptible to infection and transmission, such as key workers during the current lockdown, enabling essential service continuity, and possibly reducing overall transmission. Whilst such testing can perform an important public health function, communication must be clear that a negative result does not necessarily mean a person is non-infectious. Real-world implementation and practicalities must also be considered and optimised and, crucially, test-to-protect policies will have limited impact unless workers are supported to self-isolate.[27] 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 is also being evaluated and may be more (cost) effective.

Test-to-Release

Test-to-release models use repeated tests to reduce unnecessary isolation/quarantine of non-infectious individuals, focussing isolation decisions on presumed infectivity rather than infection. Various modelling suggests that testing of exposed contacts and international arrivals can shorten the duration of isolation and likely increase compliance, using either delayed rRT-PCR[28,29] or repeat Ag-LFT testing[30]. However, rRT-PCR has a median false negative rate of 38% five days after exposure, and 20% on day 8,[31] and a study which evaluated test to release of household contacts showed 19% false negatives on day 7 after the index case developed symptoms,[32] suggesting this is a highly risky strategy. Any test-to-release policy must account for the incubation period,[30] mitigate the risks of premature return or hazardous behaviours (Appendix 2), and be shown to be cost-effective (which may not be possible). Ultimately no test can replace comprehensive support, both practical (as in this Test-to-Care model[33]) and economical,[27] as a means of tackling low rates of self-isolation, particularly in disadvantaged communities.

Test-to-Enable

Test-to-enable policies seek to lift the current restrictions on social contact that are causing wider public health and economic harms, in a risk responsive way. For example, once current lockdown restrictions are eased, specific test-to-enable strategies may be able to reduce the harms of social isolation by enabling care home visiting, or supporting workplaces in fragile local economies to operate with risk mitigation. Focused regular testing is more logical than single 'tests for entry,' which are unlikely to confer population wide benefits.[11] Context is key; disadvantaged areas with greater mounting harms from COVID-19 control measures could benefit disproportionately from locally-sensitive responses. Again however, real-world implementation, practicalities, and false negatives are of pertinent concern and we must await quality pilot data before any large-scale roll out.

Conclusion

Rapid tests like Ag-LFTs provide new opportunities to find and isolate cases and contacts early in the infection. However, implementing such tests in local health systems is complex. There is a need for continued formative evaluation if such testing is to simultaneously reduce transmission and alleviate the mounting harms from control measures. Pilots of the SMART approach provide new evidence of large-scale, targeted Ag-LFT uses. Successful approaches must facilitate earlier and better targeted isolation of the most infectious individuals and their close contacts while, where possible and where the evidence supports, releasing non-infectious contacts sooner from unnecessary quarantine and returning to a more open society and economy. Such strategies must integrate tests into an end-to-end programme, co-created with local leaders and communities, including effective contact-tracing and comprehensive support and credible incentives for those isolating. A holistic public health approach joined up across towns, cities and regions (and coordinated with vaccination programmes), is key to sustainable recovery from the COVID-19 pandemic.

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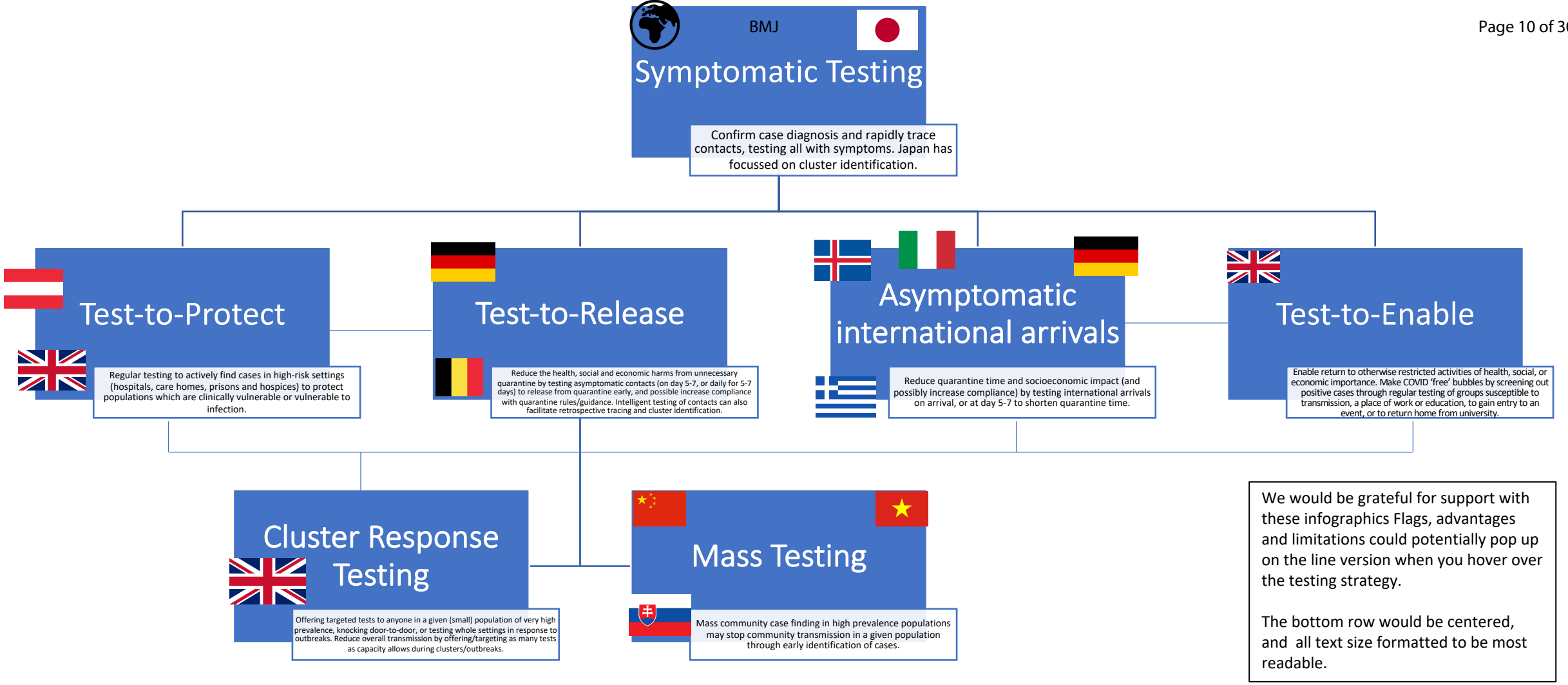


We would be grateful for support with these infographics Flags, advantages and limitations could potentially pop up on the line version when you hover over the testing strategy.

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

Figure 1. Principal 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.'

Antigen Lateral Flow Test Devices

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

Innova SARS-Cov-2 Antigen test

Relative sensitivity[12]
Laboratory conditions = 79%
Trained HCW = 73%,
Public = 58%

Liverpool pilot[5] (supervised self-swab of asymptomatic individuals)
Relative sensitivity = 40% (sensitivity rose to 53% after reappraisal).

Limit of detection = 100 plaque forming units per mL[12]

Relative specificity[12]
Laboratory conditions = 99.94%
In the field = 99.61%

Liverpool pilot[5] showed a specificity of 99.9% (n=5434)

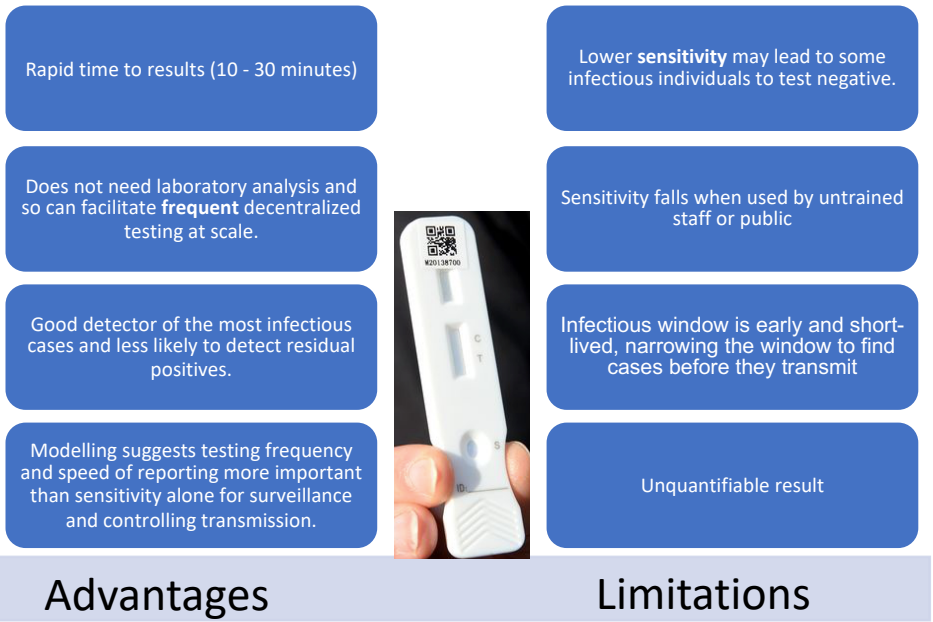
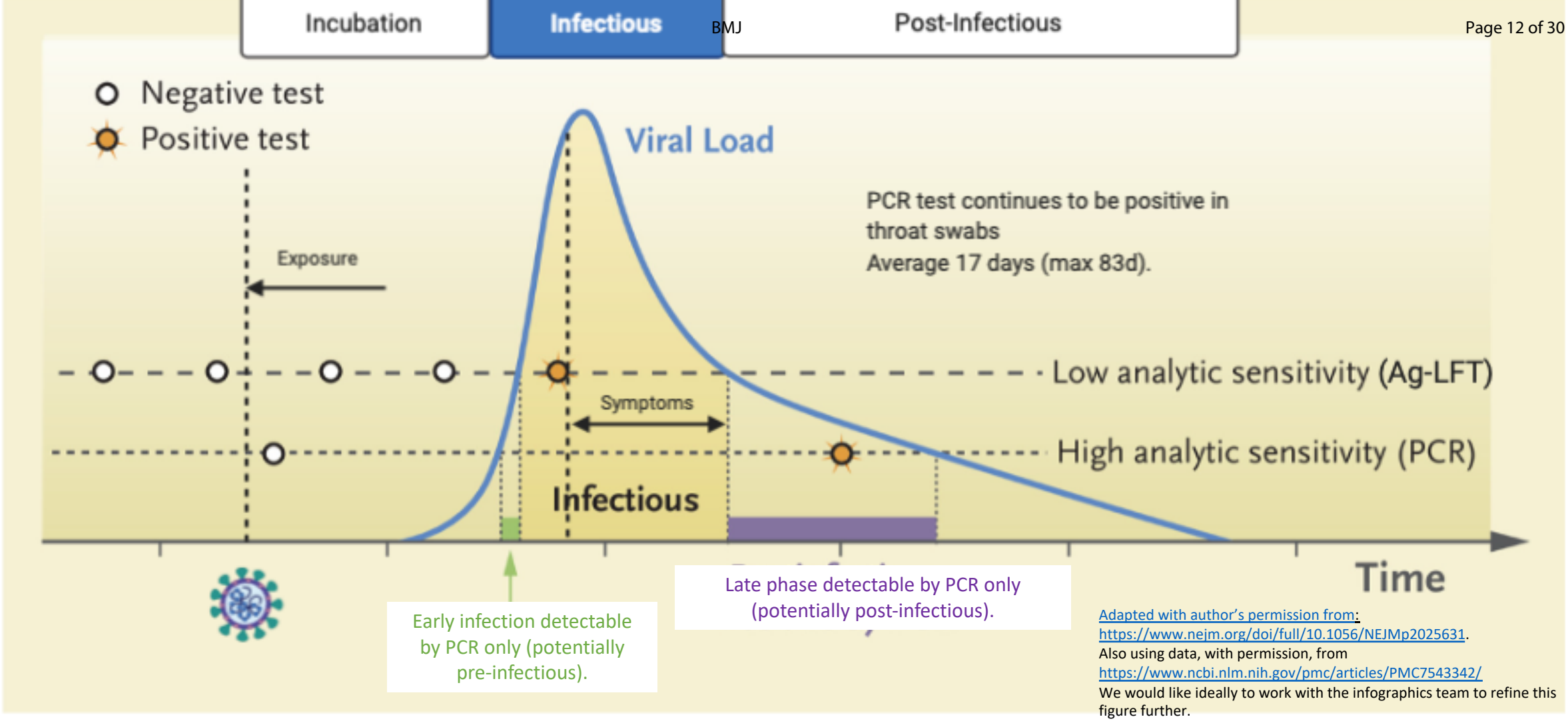


Figure 2. Rapid Antigen Lateral Flow Test (Ag-LFT) performance and key advantages and limitations.
Sensitivity and specificity of novel assays are listed as 'relative clinical sensitivity/specificity.' The term relative refers to their performance when compared to the 'gold standard' test, rRT-PCR.
Data 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. This study evaluated Ag-LFT performance when used by laboratory scientists, healthcare workers, and members of the public (after watching a training video).



Adapted with author's permission from: https://www.nejm.org/doi/full/10.1056/NEJMp2025631.
Also using data, with permission, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7543342/
We would like ideally to work with the infographics team to refine this figure further.

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. Due to its decentralised and rapid nature, the lower sensitivity test (Ag-LFT) can be administered frequently and the higher sensitivity test (rRT-PCR) infrequently. Higher frequency testing is more likely to test in the infectious window. Therefore, although both testing regimens detect the infection (orange circles), the high-frequency test is more likely to detect it during the transmission window (shading), despite its lower analytic sensitivity. This means, even with reduced sensitivity, Ag-LFTs can be more effective for early case identification and transmission control, particularly as they give results almost immediately and so contact tracing can be made more effective. The window during which polymerase chain reaction (rRT-PCR) detects infections before possibly before infectivity (green) is short, whereas the corresponding post-infectious but PCR-detectable window (purple) is long. It is important to note that, whilst this figure is intended to present the theoretical value of frequent testing with lower sensitivity tests, it should not be interpreted as an accurate representation of exactly when a positive test is likely to signify that a case is infectious, as this is still uncertain, and individual differences are expected.
The average incubation period is 5-6 days (2-21 days), with the infectious period beginning (on average) 2 days before symptom onset.[1,2,3] Although patients with severe illness may shed infectious virus up to day 14, the most infectious period is in the days directly before and after symptom onset, normally lasting up to 10 days.[1,2,3]
Figure adapted from Mina, Parker, Larremore (2020)[18] and Cevik et al., (2020).

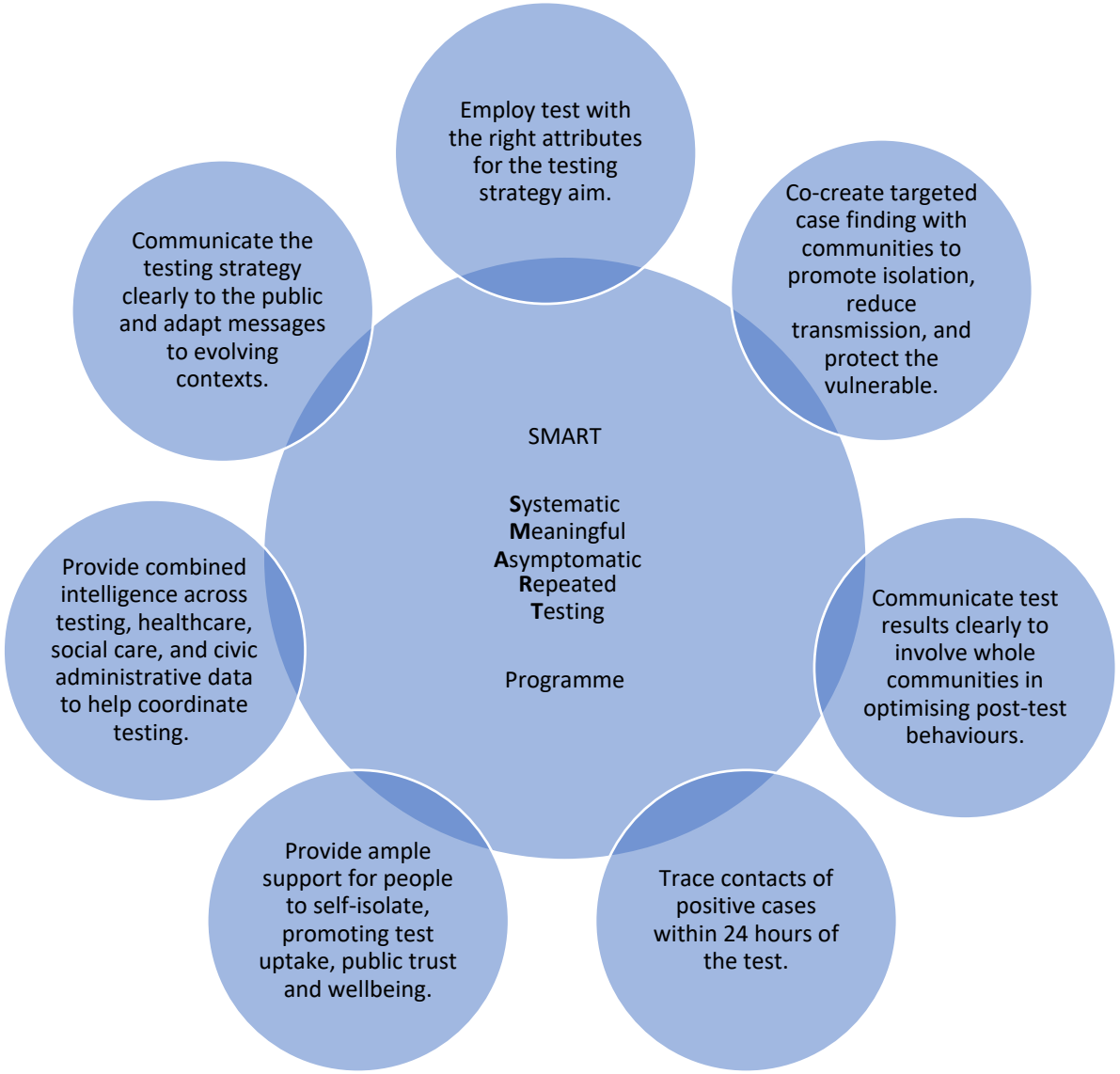


Figure 4. Keys To SMART (Systematic Meaningful Asymptomatic Repeated Testing) Programme

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

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

Appendix Table 1. 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	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	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

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
			RNA per millilitre of transport media. However, LoDs of currently approved assays vary over 10,000-fold.[3]	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. Some tests include primers to detect influenzas and other respiratory viruses, useful for clinicians and surveillance.	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 validated for use on most kits.

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
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 rapidly identify highly contagious individuals within emergency departments and care homes during times of increased disease prevalence.	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). Saliva sample decreases sensitivity further.

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
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 and specificity on swabs with respiratory symptoms = 100% (n=868 (116 positive)). Relative sensitivity and specificity on swabs from asymptomatic patients = 100% (n=3932 (34 positive)). Relative sensitivity on saliva from asymptomatic patients = 98.9% (n=18,136) (299 positive). Relative specificity on saliva from asymptomatic patients = 99.39% (n=18,136) (299 positive).	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 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. Potential for deployment in mobile/pop-up laboratories for high-throughput outbreak	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
				response or local community testing.	
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% (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 (does not require laboratory handling or sample pre-processing). 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	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
				suitable for use in warmer temperatures (10 - 38°C and relative humidities (80%).	

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 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%(n=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 - can improve throughput and acceptability (although may reduce accuracy). 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	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. **Innova SARS-Cov-2 Antigen test Liverpool Asymptomatic Evaluation[12]** Relative sensitivity (40.0% (n=70 (28 positive)). Relative specificity (99.9% (n=5434). Relative sensitivity after re-appraisal of dataset (53.4% (n=74)). Cumulative sensitivity of re-appraised data at <CT 25 was 78.3% (n=43) and at <CT 20 was 89.5% (n=19). CT 25 and CT 20 are in the range of ≈10,000 – 1 million viral copies/mL. **PANBIO Covid-19 Ag Rapid Test (Abbott) FIND Evaluation[13]** Relative clinical sensitivity (85.5% (n=124) Relative clinical specificity (100%	particularly effective if combined with rapid 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.	

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
			(n=411) LoD is to be confirmed		

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 test performance when compared to the ‘gold standard’ test, rRT-PCR. These estimates of accuracy for alternative tests can only be interpreted in the context of the performance of the ‘gold standard’ test, rRT-PCR. It is also important to note that diagnostic false negatives can occur due to the incubation period or poor swabbing technique, and true false negatives can also occur, even with highly sensitive rRT-PCR. All tests can only give a ‘snapshot’ indicator of possible infection.

* Note that this is information taken from the OptiGene COVID-19 Direct Plus RT-LAMP KIT-500 Direct RT-LAMP test instructions for use. These tests have been piloted in selected UK hospitals by DHSC and there is more recent real-world data for this assay published by DHSC, but it combines spiked and clinical samples. We therefore deemed it more appropriate to publish the IFU data which is for clinical samples only.
**Reported SAMBA II results are after discrepant analysis (i.e re-testing) of initially false positive and false negative results and therefore likely to inflate accuracy measures.
*** Mean of FIND evaluations from Brazil, Germany, and Switzerland.
Although peak viral load between symptomatic and asymptomatic individuals is comparable,[11] clearance rates are likely to differ - It should be noted that data for the Innova Antigen test from the PHE/Oxford evaluations includes some testing of asymptomatic individuals, which is likely to impact on reported relative sensitivity, compared to the evaluation of the PANBIO Covid-19 Ag Rapid Test which was on almost all symptomatic individuals within the first few days of symptom onset, and SD Biosensor which was on mostly symptomatic individuals. It is also important to note that antigen tests and population groups are not all equal, and it is therefore vital that test accuracy is understood in each population it is used in (for example asymptomatic/pauci/symptomatic, and by age and background prevalence) before any large-scale roll-out.
All results here should be treated with caution – Manufacturer's instruction for use may over-estimate accuracy compared to real-world test use. Although data here is, where possible, from real-world pilot evaluations, results may not be directly applicable to specific real-world scenarios.
Caution must also be given to new variants such as B.1.1.7 (VOC-2012/01), which may affect test accuracy. Whilst some S gene PCR assays, including the Thermo Fisher assay used in the UK Lighthouse Laboratories, are affected, many assays target for multiple genes and should still be able to identify cases. S gene target failure (SGTF) in Lighthouse Laboratories is in fact being used as a proxy to indicate carriage of VOC-2012/01).[14] To date, data suggests Ag-LFTs don't perform differently on VOC-2012/01.[15]

Appendix Table 1. References

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2 – Office for National Statistics COVID-19 Infection Survey (Pilot): methods and further information
3 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7302192/
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5 - https://www.fda.gov/media/138249/download
6 - http://www.optigene.co.uk/wp-content/uploads/2020/12/IFU_DirectPlus_v1.1-1.pdf
7 - https://www.medrxiv.org/content/10.1101/2020.12.15.20247031v1.full.pdf
8 - https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30121-X/fulltext
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10 - https://www.finddx.org/wp-content/uploads/2020/09/SDQ-Ag-Public-Report_20200918.pdf
11 - https://www.ox.ac.uk/sites/files/oxford/media_wysiwyg/UK%20evaluation_PHE%20Porton%20Down%20%20University%20of%20Oxford_final.pdf
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Appendix Table 2. Biochemical Limitations And Logistical, Behavioural And Ethical Challenges To Large Scale 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 case finding to identify infectious cases before they transmit is short.**	**Pre-symptomatic transmission is a key driver of spread**. To be most effective, community active case finding must be coupled with effective contact tracing and cluster identification.	Fast upswing in viral titres shows only small-time difference between when people turn positive on highly sensitive tests such as rRT-PCR and 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	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	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.

	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.	on antibody tests, tests for infection face substantial technical, legal, and ethical challenges.	
	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.

Appendix Table 3. Principal 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, Slovakia, and Iceland, 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 populations which are clinically vulnerable or vulnerable to infection.	UK, Germany and Austria (care homes and hospital pre-admission). UK recently introduced bi-weekly NHS staff Ag-LFT testing, and now attempting regular testing of specific key worker groups.	Likely to reduce potential for outbreaks in vulnerable settings and identify vulnerable individuals requiring treatment early. Likely to mitigate risks of infection and transmission of key worker groups, such as NHS and social care staff, or shop workers. This may have positive impacts on reducing overall community transmission.	May falsely quarantine individuals or healthcare and social care workers due to residual positives. Uses significant testing capacity and resources. Potential for false-negatives - Concern of false re-assurance leading to reduction of infection control behaviours.
Test-to	Reduce the health, social and economic	France,	Reduces time spent in	False negatives may result in

Testing Strategy 'Layer'	Testing Strategy Overview	Examples where strategy has been used	Benefits	Risks/Limitations
Release	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.	Germany, Czech Republic, UK (Liverpool pilot ongoing).	quarantine/isolation. May incentivise compliance with quarantine rules. Reduces potential for health, social, and economic harms from quarantine.	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. May incentivise compliance to quarantine rules.	False negatives give a false sense of security to infectious cases resulting in onward transmission and seeding 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 multiple important but fragile local economy groups (such as restaurants or hairdressers) under way	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.

Testing Strategy 'Layer'	Testing Strategy Overview	Examples where strategy has been used	Benefits	Risks/Limitations
		(Liverpool).		
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 outbreaks or clusters.	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) may stop community transmission in a given population through early identification of cases.	China, Vietnam, Iceland, Slovakia	Potential to find and quarantine many cases which may have otherwise gone undetected. Early identification, isolation, and tracing of the most infectious cases to reduce onward transmission. Possible to eliminate the virus from a given population.	Low positive predictive value. Window of opportunity to find cases before they transmit is short. Logistically very challenging and huge resources required. Ethical concerns.