

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

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Appendix Table 1. Novel Types of Assay.	1
Appendix Table 2. Summary of The Real-world Innova Rapid Antigen Lateral Flow Test performance data, in context.....	10
Appendix Table 3. Biochemical Limitations And Logistical, Behavioural And Ethical Challenges To Large Scale Asymptomatic Testing	11
Appendix Table 4. Principal Testing Strategies and Examples of Countries Deploying Them	14

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 RNA per millilitre of transport media.	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	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.

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
			However, LoDs of currently approved assays vary over 10,000-fold. ³	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.	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.
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	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	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

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
			<p>Relative sensitivity of swabs with CT<25 = 100% (CI = 0.96-1.00)</p> <p>Relative sensitivity of swabs with CT<33 = 84.1% (CI 0.76-0.89)</p> <p>Relative specificity = 100.0% (CI = 0.98-1.00)*</p>	<p>swabbed or saliva.</p> <p>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.</p>	<p>detect some residual positives.</p> <p>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.</p>
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	<p>LamPORE</p> <p>SwabSeq</p>	<p>LamPORE⁷</p> <p>Relative sensitivity and specificity on swabs with respiratory symptoms = 100% (n=868 (116 positive)).</p> <p>Relative sensitivity and specificity on swabs from asymptomatic patients = 100% (n=3932 (34 positive)).</p>	<p>2 hours to result (in ideal conditions).</p> <p>High relative sensitivity and specificity.</p> <p>Semi-quantitative.</p> <p>High throughput - Flexible processing of 24–480 samples per run; potential for over 9,000 samples in 24 hours.</p> <p>Additional regulatory submissions to enable the multiplexing of 768</p>	<p>Requires laboratory labour and analysis.</p> <p>Higher throughput (> 480) has not yet been validated or shown to be viable for diagnostics.</p>

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
	per sample, the sample can be classed as positive.		<p>Relative sensitivity on saliva from asymptomatic patients = 98.9% (n=18,136) (299 positive).</p> <p>Relative specificity on saliva from asymptomatic patients = 99.39% (n=18,136) (299 positive).</p>	<p>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 response or local community testing.</p>	
Point of Care (POC) RT-PCR	Like rRT-PCR but requires no significant manual lab work. Sample in, result out.	<p>COVID Nudge</p> <p>Samba II</p>	<p>COVID Nudge⁸ Relative sensitivity (94% (n=71)) Relative specificity (100% (n=315))</p> <p>Samba II^{9**} Relative sensitivity (96.9% (n=32)) Relative specificity (100% (n=117))</p>	<p>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</p>	<p>1 result per instrument per run.</p> <p>Each individual instrument is expensive.</p> <p>Some pilot studies evaluating POC PCR with increased throughput for use in care homes to allow</p>

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
				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%).	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)	<p>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.</p> <p>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.</p>	<p>SD Biosensor Lateral Flow Test (Standard Q COVID-19 Ag kit)</p> <p>SARS-CoV-2 Antigen Rapid Qualitative Test (Innova SARS-Cov-2 Antigen test)</p> <p>PANBIO™ Covid-19 Ag Rapid Test (Abbott)</p>	<p>SD Biosensor STANDARD Q COVID-19 Ag Test FIND Evaluation¹⁰ Relative clinical sensitivity (87.2% (n=344))** Relative clinical specificity (99.1% (n=1844))*** LoD = 5000 plaque forming units per mL.</p> <p>Innova SARS-Cov-2 Antigen test PHE/Oxford Evaluation¹¹ 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</p>	<p>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</p>	<p>Lower sensitivity will result in increased false negatives of infectious individuals.</p> <p>Sensitivity falls when used by untrained staff, or by the public.</p> <p>Not validated for home use.</p> <p>Given lower sensitivity, cluster identification would have to be rapid to avoid false negatives missing infections.</p> <p>Non-quantitative results.</p> <p>Mass testing is a hugely resource intensive intervention. Associated challenges beyond biochemical limitations (logistical, behavioural, and ethical), are given in Appendix 3.</p>

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
			<p>forming units per mL.</p> <p>Innova SARS-Cov-2 Antigen test Liverpool Asymptomatic Evaluation¹² 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.</p> <p>PANBIO Covid-19 Ag Rapid Test (Abbott) FIND Evaluation¹³ Relative clinical sensitivity (85.5% (n=124)) Relative clinical specificity (100%)</p>	<p>particularly effective if combined with rapid antibody tests and/or more sensitive semi-quantitative tests and/or sequencing.</p> <p>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.</p> <p>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.</p>	

Assay Type	How it Works	Example Brands	Sensitivity, Specificity, and Limit of detection	Advantages	Limitations
			<p>(n=411) LoD is to be confirmed.</p> <p>BinaxNOW Rapid Antigen Test (Abbott) CDC Evaluation¹⁴ Relative sensitivity among symptomatic persons (64.2% (n=176)). Relative sensitivity among asymptomatic persons (35.8% (n=123)). Relative specificity (99.8% (n=3419)).</p> <p>Relative sensitivity in specimens from symptomatic individuals with positive viral culture (92.6%).</p> <p>Relative sensitivity in specimens from asymptomatic individuals with positive viral culture (78.6%).</p>		

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 heterogenous, 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).¹⁵ To date, data suggests Ag-LFTs don't perform differently on VOC-2012/01.¹⁶

Appendix Table 1. References

- 1 - <https://www.medrxiv.org/content/10.1101/2020.04.16.20066787v2>
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Appendix Table 2. Summary of The Real-world Innova Rapid Antigen Lateral Flow Test performance data, in context.

Joint PHE Porton Down and University of Oxford evaluation¹⁰ showed The Innova SARS-CoV-2 Antigen tests sensitivity, relative to PCR, was 79% when used in laboratory conditions, 73% when used by healthcare workers, and 58% when used by members of the public. Specificity in the field was 99.61%. The limit of detection (95% detection rate in laboratory conditions) was 100 plaque forming units per mL.

Data from the Liverpool COVID-19 Community Testing Pilot⁵ (sampling performed by supervised self-swab, with results read by trained army/staff) showed that, in an asymptomatic population, the real-world sensitivity, relative to PCR, of the Innova lateral flow test was 40%, and specificity was 99.9%.

However, the sensitivity of PCR and the phase of the epidemic curve means that **over half of the PCR positives identified from asymptomatic testing in Liverpool were likely to be post-infectious residual shedding PCR positives**. Therefore, comparing the lateral flow test results to the PCR results directly does not give the sensitivity results in context.

Authors also noted that understanding of test kits would likely improve use and result interpretation, and therefore accuracy, over time: cumulative sensitivity (relative to PCR) rose to 53% after re-appraisal of data.

Importantly, the majority of true false negatives occurred above Cycle Threshold (CT) 25 (Glasgow Lighthouse Lab PCR assay), with the cumulative sensitivity after re-appraisal being 78% below CT 25 and 89.5% below CT 20. CT values are on an inversely proportional log scale. For the Glasgow Lighthouse Lab Assay, CT 25 to 20 is equivalent to $\approx 10,000$ - 1 million viral copies/mL.

Analysis of case-contact relationships using UK Test and Trace data²¹ showed cases with higher viral loads are more likely to be infectious.

Furthermore, this analysis suggests that 87% of case-contact pairs with a PCR-positive contact, i.e. plausible onward transmission, had CT values of ≤ 24.4 ($\geq 10,000$ RNA copies/mL) and that, under laboratory conditions, the Innova lateral flow test would detect 84% of cases who plausibly subsequently transmitted to a contact, although with implicit uncertainty, dynamics and limitations.

Aside from viral load, culture positivity is another indicator of potential infectiousness. CDC Evaluation of BinaxNOW Rapid Antigen Test showed that relative (to PCR) sensitivity among symptomatic and asymptomatic persons was 64% and 36%, respectively. However, **relative sensitivity in specimens from symptomatic and asymptomatic individuals with a positive viral culture was 93% and 79% respectively**. This highlights how direct comparisons

between lateral flow and PCR test results are not the most optimal way of assessing an assay intended to be used as a public health tool as a test of infectiousness, and not a test of infection.

Lateral flow test-PCR relative sensitivity and viral loads across a population are not a static reference and in reality change with the epidemic phase. Additionally, infectiousness is not binary, and viral load does not always translate directly to infectiousness, and assumptions around infectiousness will not always apply: some cases with a lower detected viral load may well be infectious also, and all tests will produce some false negatives.

We also note that antigen tests and population groups are not all equal, and it is therefore vital that test accuracy is understood for each target population (e.g. asymptomatic/(pauci-)symptomatic, and by age and background prevalence) before large-scale use.

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.

Appendix Table 3. 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	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,

		accurately, to provide locally actionable information.	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	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.

		if governments are to roll out large-scale asymptomatic testing.	
	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.

Appendix Table 4. 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-	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	May falsely quarantine individuals or healthcare and social care workers due to residual positives. Uses significant testing capacity and resources.

Testing Strategy 'Layer'	Testing Strategy Overview	Examples where strategy has been used	Benefits	Risks/Limitations
		weekly NHS staff Ag-LFT testing, and now attempting regular testing of specific key worker groups.	groups, such as NHS and social care staff, or shop workers. This may have positive impacts on reducing overall community transmission.	Potential for false-negatives - Concern of false re-assurance leading to reduction of infection control behaviours.
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. 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.	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

Testing Strategy 'Layer'	Testing Strategy Overview	Examples where strategy has been used	Benefits	Risks/Limitations
		Studies in multiple important but fragile local economy groups (such as restaurants or hairdressers) under way (Liverpool).		'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 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.

