

Safe Sustainable Re-opening: The Role of Rapid SARS-CoV-2 Testing

Report of the COVID-19 Rapid Testing Group

19th March 2021

1. Recommendations	2
2. Group Membership.....	8
3. Terms of Reference.....	8
4. Introduction	9
5. Rapid Tests that could be used in different settings	19
6. Availability and Validation of Rapid Tests.....	22
7. Testing for Asymptomatic Infection.....	27
8. Rapid Testing in Community Settings	30
9. Settings where Ireland should prioritise rapid testing	35
10. To suggest how Ireland could implement any recommendations	43
11. Acknowledgements.....	51
12. Appendix 1 - Details of testing approaches	52

1. Recommendations

We group our recommendations under the four Terms of Reference. The rationale, evidence, and discussion around each of these is in the body of the report.

A. To recommend rapid test(s) that could be used in different settings, especially asymptomatic community populations.

- A 1.1 Rapid tests, such as lateral flow antigen tests (LFAT) and loop-mediated isothermal amplification (LAMP) tests, should complement existing national HSE Public Health polymerase chain reaction (PCR) testing programmes. Individuals with COVID-19 symptoms should continue to be tested within the existing public health testing framework. The evidence base for deployment of rapid tests designed for use in asymptomatic populations is growing as are the numbers and types of commercially available rapid tests. It is important that Ireland is positioned to take advantage of these developments.
- A 1.2 Rapid tests should deploy easy self-administered sampling - currently either nasal swab or saliva. Much progress has been made with such sampling, which have much higher compliance rates and much lower costs than nasopharyngeal swabs.
- A 1.3 Ireland should deploy rapid tests (currently lateral flow antigen tests), which meet a specified and regularly updated set of criteria, including CE mark, appropriate specificity and sensitivity especially in situations of low viral load and low prevalence of virus, reproducible results (i.e. minimal batch variation), detect nucleocapsid (N) not spike (S) antigens and be able to detect all current SARS-CoV-2 variants, easy to use with nasal swabs or saliva sampling, provide good self-administration instructions, training and reading (e.g. through bar code or smart phone) allowing people to take control over their health.
- A 1.4 In order to maintain quality and benefit from collective procurement, Ireland should select commercial tests from the list of validated tests within the European Commission Joint Research Centre (JRC), which are mutually recognised as validated tests. Additionally, Ireland should consider utilising commercial tests that have been validated, with published results in other non-EU countries, e.g., UK, USA (CDC) etc. This may be important if there are procurement challenges or if a non-EU country has validated a particularly good new commercial test first or if Ireland requires criteria additional to those required by the EU, e.g., barcoding of individual devices. As this is a rapidly developing field, Ireland should also investigate, and where appropriate validate selected newly released tests (which have the potential to be more accurate, easier to use, cheaper etc.) and thereby contribute to the collective European validation programme.
- A 1.5 Tests which are easier to perform with high throughput, generate rapid results and require less specialised equipment/reagents/personnel than PCR, e.g., LAMP, but which can easily be established with minimal additional infrastructure / personnel, e.g., in a university, large company, community, sporting organisation should be established to supplement current PCR testing and recommended widespread self-testing. This could include establishing some mobile testing facilities, which could be rapidly deployed to future outbreaks, clusters or high- risk areas.

B. To suggest settings where Ireland should prioritise rapid testing

- B 1.6 Establish quickly a number of major pilot / feasibility programmes focused on testing in priority target areas, that collect core, common outcome data sets including data on sampling, compliance, retention, accuracy, cost, acceptability and behavioural change, which will rapidly inform future widespread deployment of rapid testing.
- B 1.7 Consideration should be given to establishing a number of testing pilots / feasibility studies by different Government Departments and Agencies as well as key stakeholders: Employers, Community Groups, Schools, Colleges, Sporting organisations and the public. Additional testing capacity, e.g., in Higher Education Institutions and Companies, should be maximally leveraged. Particular focus should be paid to young people who will be the last to be vaccinated, who are more likely to be asymptomatic, have been identified as key, early drivers of new waves of SARS-CoV-2 infection, have the lowest risk of severe disease and the greatest desire to socialise responsibly. These programmes should include clear aims and outcome measures, such that they can be quickly evaluated and if positive, then widely implemented, incorporating the learnings from the pilot / feasibility studies.
- B 1.8 Immediate focus should be placed on establishing the agile rapid test knowledge group – Recommendation D 1.15. This will mean that information on validated tests, sampling, training videos etc. can be widely and easily shared so that there is a national standard for rapid testing (which can increase and evolve over time). This in turn will facilitate employers, sports clubs, Universities, etc. to establish their own effective and efficient rapid testing programmes. In parallel, the HSE should focus initially on assisting in the establishment of rapid testing in healthcare settings, schools and in other areas of the public sector.
- B 1.9 Specifically we recommend that the following programmes are established:
- (a) The HSE should:
 - (i) Establish programmes in long term residential care facilities (LTRCF) where the majority of the residents have been vaccinated, whereby visitors to the residents would be permitted face-to-face visits if they did not test positive on a rapid lateral flow antigen test, taken at the time of arrival at the LTRCF. Operation of such a programme would be informed by public health risk assessment and may cease when the prevalence of the virus is low.
 - (ii) In collaboration with regional public health units, establish programmes to explore the use of rapid LFAT as a companion diagnostic to PCR testing in SARS-CoV-2 outbreaks to rapidly identify and isolate infectious cases at the time of identification of an index case.
 - (iii) Establish programmes in any other areas where reducing the risk to workers and patients would be beneficial, e.g., point of entry screening of casual workers or contractors visiting healthcare settings containing vulnerable populations (such as LTRCF and rehabilitation facilities), Accident & Emergency waiting rooms,

Ambulance Crews, dialysis patients etc. Pilots are already ongoing in some of these.

- (iv) Pilot testing and evaluation in state run institutions, e.g., prisons or situations where the state provides social care, e.g., homeless shelters, direct provision centres.
- (v) Assist, where possible and necessary, other Government Departments and Agencies to establish their programmes.

(b) The Department of Enterprise, Trade and Employment, and individual employers should establish:

- (i) Programmes (including feasibility pilots) of rapid testing in selected workplaces, in collaboration with employers and employees in different sectors, e.g., , construction, hospitality, office, warehouse, manufacturing etc. Priority should be given to individuals who have significant face-to-face interaction with members of the public, e.g., retail staff, to those whose role necessitates in-person attendance in the workplace, e.g., essential workers in factories, supply chains etc. and to critical industries / infrastructure. These programmes may be co-funded with the State, or completely funded by the private sector or the State could fund a feasibility pilot which, if successful, is taken over for implementation by the private sector.
- (ii) Programmes of repeated rapid testing of essential workers who travel into the country.

(c) The Department of Further and Higher Education, Research, Innovation and Science should establish:

- (i) Widespread rapid testing in Universities, Colleges, IoTs and further education establishments with either rapid lateral flow antigen tests, or rapid platform-based testing (e.g., LAMP) This would be voluntary serial testing of students and all staff at least twice per week. Particular attention should be focused on students living in shared Halls of Residence. Many Universities have already established such testing capacity, often in collaboration with the HSE. Such testing would facilitate the safe return to campus-based activities. When lower community infection rates and higher vaccination levels are achieved, it should be possible to safely pilot whether serial rapid testing would allow the relaxation of social distancing in lecture theatres and laboratory-based teaching venues – which in turn would be a good pilot for their potential use at point of entry for other societal activities related to indoor gatherings (e.g., theatres, cinemas, restaurants, sporting events, weddings etc.)

(d) The Department of Agriculture, Food and the Marine and relevant employers should deploy:

- (i) Serial rapid testing, in high-risk employment situations, e.g., meat processing plants, building on the pilots already established by DAFM and the HSE.
 - (e) The Department of Tourism, Culture, Arts, Gaeltacht, Sport and Media, sporting organisations, e.g., GAA, IRFU, FAI, gyms should establish programmes (including pilots) of rapid testing of participants to begin with, and then spectators, to enable a more widespread safe return to both outdoor and indoor sport.
 - (f) Consider establishing rapid testing pilots (and if appropriate, programmes) in any office-based and / or publicly facing Government department or institution where execution of its duties requires presence in an office environment, e.g., Passport Office, Social Services offices, Revenue, Central Bank or close human interaction, e.g, driving test.
- B 1.10 Governance of any testing programme executed by the HSE would clearly fall within its governance structures. However, careful consideration needs to be given to the appropriate governance structures for widespread rapid testing programmes that will involve a high degree of self-sampling, testing and reporting, and programmes executed and paid for by others, e.g., companies, institutions, departments, agencies etc. Clearly there need to be appropriate standards for the procurement and deployment of validated tests, training, consent, reporting and managing results. There needs to be the appropriate level of interaction with Public Health systems. Feasibility pilot studies should not only assess efficacy, acceptability, sustainability, impact, cost effectiveness etc., they should also contribute to the determination of the appropriate governance and management structures including appropriate linkage with the HSE testing framework.
- B 1.11 There are significant gaps in our current knowledge of the effectiveness of deployment of rapid testing and there will be new challenges emerging. Additionally, new improved rapid test systems are emerging at an unprecedented rate. These all require active ongoing research. We therefore recommend that a new 'Safe Sustainable Reopening' research fund is established which would be administered by a lead research funding agency, coordinating all relevant agencies and government departments, as happened in the initial COVID-19 Rapid Response Call. Some of the research studies could be conducted in the settings recommended above. Collaboration with employers, different business sectors, community groups, sporting organisations, education providers, social services etc. would be essential. International collaboration, especially with Northern Ireland and UK would be encouraged.

C. To consider rapid testing in Schools

- C 1.12 The HSE and the Department of Education and Skills should immediately establish at scale a series of pilots and feasibility studies of rapid serial testing in a number of Primary and Secondary Schools, learning from the experience, practices, plans and training material in the UK and involving the cooperation and collaboration of teachers, parents and children. Such testing could start by training and testing in school and then progress to self-testing at home for the child and the entire household. These pilots and feasibility

studies should have clear goals. Execution and evaluation of the pilots should be undertaken, at pace, so that if positive, widespread rapid testing could be deployed in all schools by September 2021. In addition, such a strategy of rapid testing could be deployed before major state examinations, e.g., Junior Certificate or Leaving Certificate including necessary course work or practical classes / exams.

D. To suggest how Ireland could implement any recommendations

- D 1.13 Start Immediately. Testing pilots and feasibility studies should be executed at pace so that if positive, widespread deployment can quickly follow.
- D 1.14 Make rapid testing a shared community action and responsibility – across government departments, agencies, employers, voluntary and community groups and consider giving this programme a new name. Ethical issues as apply to each specific testing setting need to be considered and addressed.
- D 1.15 Establish an agile rapid test knowledge group (e.g. within NSAI or HSE or HPRA, or DFHERIS, including requisite scientific and clinical expertise) to continually monitor the many rapid tests in development and emerging onto the market, to maintain a list of currently validated tests to which anyone (employers, community groups, individuals etc.) could refer, to address issues of batch acceptance, quality assurance, action of recalls, withdrawals and field safety notices, to maintain and update training materials including videos, standard operating procedures etc. to allow anyone to quickly and efficiently establish effective rapid testing. This group would monitor closely and quickly adapt / adopt information, results etc. emerging internationally. It could also act as a rapid entry point for any company / developer wanting to deploy their new rapid test in a research pilot in Ireland. In essence it would become a central hub for freely accessible, up-to-date, reliable information on rapid testing in Ireland.
- D 1.16 All those that test positive on a rapid test (especially in low prevalence scenarios) should obtain a confirmatory PCR diagnostic test within the current HSE testing regime and Public Health reporting systems. In parallel, explore adapting the COVID-19 app to allow it to scan the bar codes of individual LFAT devices and to allow the user to upload the test result to the Covid Care Tracker. Additionally, explore adapting the COVID-19 tracker app to allow the user to upload information about their vaccination status, e.g., dates when vaccinated and manufacturer of the vaccine. Ireland should learn from the UK experience of technology solutions to facilitate the collection of widespread self-administered test results and to potentially enhance the accuracy of the test result readings using smart phone AI interfaces. Only procure LFATs with individual bar codes (as per the UK tender) printed adjacent to the result reading to allow for the better monitoring of LFAT usage. A priority is to ensure that all results are linked to the Covid Care Tracker (CCT) and to the Computerised Infectious Disease Reporting (CIDR) system to enable Public Health action and analysis. When widely deployed, rapid tests have the potential to significantly affect the interpretation of surveillance data unless the information concerning the number of tests performed and the number of positive results is captured centrally, making the upgrading of the current COVID-19 app and IT system a parallel priority with the initial pilot studies.

- D 1.17 Educate and engage the public with respect to all aspects of rapid tests, building on communication tools already developed by others.
- D 1.18 Encourage international collaboration, particularly with Northern Ireland and the UK on both the pilots and widespread deployment of rapid tests.
- D 1.19 Appropriate resources should be allocated to the various government departments and agencies to enable the execution of whichever of these recommendations are chosen for implementation.
- D 1.20 Establish a red team for agile monitoring, pivoting and decision making.

2. Group Membership

Appointed by the Minister for Health, Stephen Donnelly.

Chair:	Professor Mark Ferguson	Director General, Science Foundation Ireland and Chief Scientific Adviser to the Government of Ireland
Members:	Professor Paddy Mallon	Professor of Microbial Diseases UCD, Consultant in Infectious Diseases, St Vincent's University Hospital and Director of the UCD Centre for Experimental Pathogen Host Research
	Professor Mary Horgan	President of Royal College of Physicians in Ireland, Professor, School of Medicine, UCC Consultant in Infectious Diseases, Cork University Hospital
	Professor Kingston Mills	Professor of Experimental Immunology, Trinity College Dublin and Director Trinity Biomedical Sciences Institute.
	Dr Lorraine Doherty	National Clinical Director Health Protection, Health Service Executive
	Dr Darina O'Flanagan	Former Director of the Health Protection Surveillance Centre; Special adviser to NPHE at Department of Health
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This is a majority report supported by Professors Horgan, Mallon, Mills and Ferguson but not by Drs Doherty and O'Flanagan.

3. Terms of Reference

- *To recommend rapid test(s) that could be used in different settings, especially asymptomatic community populations.*
- *To suggest settings where Ireland should prioritise rapid testing.*
- *To consider rapid testing in schools.*
- *To suggest how Ireland could implement any recommendations.*

4. Introduction

4.1 Current situation

Ireland's strategy for managing the COVID-19 pandemic aims to maintain economic and societal function (including education, healthcare, employment, hospitality and interpersonal interactions) to the maximum extent possible, whilst continuing to minimise the spread of SARS-CoV-2 and implementing effective population-level vaccination.

The pillars of controlling a pandemic include: encouraging behaviours that minimise viral transmission; effective surveillance systems to identify and isolate new infections and prevent entry of resistant variants / recombinants (test/trace/isolate); population vaccination; and effective treatments. Through significant investment, Ireland has developed effective public health directed diagnostic testing for individuals with symptoms of COVID-19 and their close contacts, with current capacity for PCR¹ testing at approximately 125,000 tests per week. These tests are professionally administered (from swabbers to accredited laboratories), have high analytic sensitivity to determine a clinical diagnosis and are based on quantitative PCR with a reliable result provided in under 48 hours from referral, in the majority of cases. In addition to this testing, other public health measures to minimise transmission have included mask wearing, social and physical distancing, adequate ventilation, respiratory etiquette, and hand hygiene.

Despite these extensive measures, testing focused on symptomatic individuals and their close contacts will still result in missed opportunities to detect individuals infected with SARS-CoV-2 who significantly contribute to onward transmission^{2,3}. In addition to a significant proportion (Public Health England estimate up to 60%) of individuals with symptoms of COVID-19 who do not attend for testing, it is estimated that at least one third of individuals testing positive for SARS-CoV-2 infection are pre-symptomatic or asymptomatic at the time of testing and that, of these, 75% remain asymptomatic⁴, representing a significant additional pool of infectious individuals who can transmit the virus to others. It is therefore imperative to implement practical measures to enable better identification of these infectious individuals in order to decrease the overall burden of SARS-CoV-2 transmission in Ireland.

4.2 Why expand testing when vaccination is underway

Case numbers of SARS-CoV-2 are currently declining, following implementation of stringent restrictions (with serious societal and economic consequences) to counteract a substantial surge in January 2021, associated with relaxation of restrictions in December and coinciding with introduction of a new, highly transmissible variant (B.1.1.7 variant, first identified in the UK). Vaccine roll-out is underway but will take a number of months to complete. However, even the most efficacious vaccines will not be 100% effective, nor will they have 100% coverage against SARS-CoV-2 infection. UK SAGE

¹ Detection of viral RNA is conducted using real-time reverse transcription polymerase chain reaction (rRT-PCR). This method is also known as quantitative reverse transcription polymerase chain reaction (RT-qPCR). Throughout this report, these terms are abbreviated as "RT-PCR" or "PCR", and are interchangeable *in the context of this report*

² Huff H V., Singh A. Asymptomatic transmission during the Coronavirus disease 2019 pandemic and implications for public health strategies. *Clin Infect Dis*. 2020 Nov 15;71(10):2752–6. <https://doi.org/10.1093/cid/ciaa654>

³Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, Brooks JT, *et al*. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. *JAMA Netw open*. 2021 Jan 4;4(1):e2035057. <https://doi.org/10.1001/jamanetworkopen.2020.35057>

⁴ Oran DP, Topol EJ, The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review. 2021 Jan 22. <https://doi.org/10.7326/M20-6976>

modelling⁵ shows that less than 60% of the population are protected against infection with a vaccine where efficacy is 85% against severe disease, with a vaccine uptake of 79% in the population. When considered alongside the reality that a certain percentage of individuals (globally) will not be vaccinated, threats from new emerging variants and recombinants will remain, especially from those with asymptomatic infection. The need for SARS-CoV-2 monitoring (case detection) and control will remain for long into the future⁶. In addition, although early evidence is promising (see Cambridge preliminary study⁷), there is also the need for more data to establish the impact of vaccination on viral transmission. The potential impact of variants on vaccine efficacy is being continuously monitored, and there is already evidence emerging of a reduction or loss of effectiveness of certain COVID-19 vaccines against the Brazilian (P1) and South African (B.1.351) variants⁸. As vaccine deployment hopefully decreases the severity of the disease, more transmission may occur through individuals with mild / no symptoms. Indeed, a recent review⁹ on COVID-19 superspreading events concludes that 80% of the transmission comes from 20% of the population and “it’s transmission in young (18-40 yrs.) healthy mobile populations that actually does the most damage. Just because you feel well doesn’t mean that you are not infected and potentially spreading”. Superspreading occurs predominantly in confined indoor spaces with poor ventilation and certain social interactions e.g. singing, shouting: these represent high-risk situations where the deployment of LFATs may be useful.

It is therefore imperative to explore every available mechanism to control transmission and to incorporate these mechanisms as integral components of Ireland’s overall armamentarium against SARS-CoV-2 to enable a safe and sustainable re-opening of the economy and society.

4.3 The present period is very challenging

With vaccination underway the expectations of the population for a rapid return to normality are high and the likely continued adherence to restrictions may wane. At the same time, selective pressure on the virus will drive advantageous mutations that allow it to spread more rapidly and escape immune protection from either vaccination or previous infection. We see this already in the variants first detected in the UK (B.1.1.7), South Africa (B.1.351) and Brazil (P.1), where there is evidence of re-infection with new variants. Additionally, individuals can be infected by more than one coronavirus, which has led to the first recombinant SARS-CoV-2 strains being reported in California¹⁰. The SARS-CoV-2 virus continues to evolve; a new variant derived from the B.1.1.7 variant that also contains the immune escape mutation E484K has been recently described in the UK, having arisen independently on at least five occasions in the UK¹¹. In the long term, variants may all be effectively managed by appropriate modifications to vaccines which may be regularly administered – like current influenza

⁵ UK SAGE Meeting 80 Minutes, February 11th, 2021.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963390/S1115_SAGE_80_Minutes.pdf

⁶ Fontanet A. SARS-CoV-2 variants and ending the COVID-19 pandemic; The Lancet VOLUME 397, MARCH 13, 2021 ; [https://doi.org/10.1016/S0140-6736\(21\)00370-6](https://doi.org/10.1016/S0140-6736(21)00370-6)

⁷ Michael Weekes, Nick K Jones, Lucy Rivett, et al. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. *Authorea*. February 24, 2021. DOI: [10.22541/au.161420511.12987747/v1](https://doi.org/10.22541/au.161420511.12987747/v1)

⁸ Mahase E, Covid-19: Where are we on vaccines and variants?, *BMJ* 2021;372:n597. <http://dx.doi.org/10.1136/bmj.n597>

⁹ Lewis D. Superspreading drives the COVID pandemic — and could help to tame it. *Nature*. 2021 Feb 25;590(7847):544–6.

<http://www.nature.com/articles/d41586-021-00460-x>

¹⁰ Harrington D, Kele B, Pereira S, Couto-Parada X, Riddell A, Forbes S, et al. Confirmed Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variant VOC-202012/01. *Clin Infect Dis*. 2021 Jan 9; <https://doi.org/10.1093/cid/ciab014>

¹¹ UK SAGE Meeting 79 Minutes 4th February

2021 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963366/S1082_SAGE_79_Minutes.pdf

vaccines, but until then, the coming year presents a period of peak risk, presenting immediate challenges.

SARS-CoV-2 infections have been reported in different mammalian species, including dogs, cats, tigers, lions, ferrets and minks. As the virus is put under selective pressure, the risk of transmission to different species is increased, potentially resulting in infectious reservoirs in wild animals, where the virus can further mutate and re-infect humans.¹² Transmission of the virus from infected mink to humans has been reported.¹³ It has also been shown that, unlike the initial virus, circulating variants (including UK (B.1.1.7), South Africa (B.1.351) and Brazil (P.1) were able to bind to rat ACE2 receptor more efficiently, suggesting that rats and mice may be able to harbour and spread these variants.¹⁴ Due to the antigenic diversity of these viruses, MacLean et al, underline the need for widespread surveillance at the human–animal interface to monitor carefully for emergence of future virus variants that could be sufficiently divergent to evade either natural or vaccine-induced acquired immunity, as demonstrated for SARS-CoV-1 versus SARS-CoV-2.¹⁵

The worst-case scenario would be introduction or emergence of a new, highly transmissible strain, that escapes current immunity (induced post-infection or vaccine induced) and causes more serious widespread disease in a population where a high percentage had already been vaccinated, requiring severe lockdown measures to control, similar to those imposed at the onset of the COVID-19 pandemic. Such a scenario would cause serious societal and economic damage. It is therefore vital to take all measures to minimize this predictable scenario and to be best placed to manage risks and threats we cannot predict through widespread testing, tracing and isolation of infectious cases. Additionally, widespread surveillance and genomic sequencing of the identified cases to monitor the emergence of variants is essential¹⁶ and this can be accomplished using samples for PCR or LAMP analysis and from the membranes of LFAT devices.

Although conventional public health advice would be to decrease testing when the prevalence of the virus is low, the above considerations indicate that continuing widespread testing should be considered as an insurance policy until officials are confident that all variants are adequately covered by global vaccination programmes and that the risk of reinfection from animals is low, in addition to considerations of viral prevalence, transmission and disease severity.

4.4 Fast development of many new rapid tests

The COVID-19 pandemic has been accompanied by unprecedented advances in research and technology, resulting in rapid adaptation and deployment of novel technologies, including testing platforms, for use in control of SARS-CoV-2. As each testing platform has its own advantages and limitations, their use should be considered as a component to complement overall public health measures rather than alternatives to established, functioning testing systems. No one test has characteristics that meet all of society's needs but a variety of specific risk reduction approaches, used effectively in particular settings that exploit their favourable characteristics, can contribute to overall

¹² Mallapaty S. The Hunt for Coronavirus Carriers. *Nature* 591, 26-28 (2021) doi: <https://doi.org/10.1038/d41586-021-00531-z>

¹³ Rabalski L. Zoonotic spillover of SARS-CoV-2: mink-1 adapted virus in humans; bioRxiv March 2021; <https://doi.org/10.1101/2021.03.05.433713>

¹⁴ Weitong Y et al. 2021. Circulating SARS-CoV-2 variants B.1.1.7, 501Y.V2, and P.1 have gained ability to utilize rat and mouse Ace2 and altered in vitro sensitivity to neutralizing antibodies and ACE2-Ig. bioRxiv doi: <https://doi.org/10.1101/2021.01.27.428353>

¹⁵ MacLean OA et al. (2021) Natural selection in the evolution of SARS-CoV-2 in bats created a generalist virus and highly capable human pathogen. *PLOS Biology* 19(3): e3001115. <https://doi.org/10.1371/journal.pbio.3001115>

¹⁶ Fontanet A. SARS-CoV-2 variants and ending the COVID-19 pandemic; *The Lancet* VOLUME 397, MARCH 13, 2021 ; [https://doi.org/10.1016/S0140-6736\(21\)00370-6](https://doi.org/10.1016/S0140-6736(21)00370-6)

risk reduction of SARS-CoV-2 transmission, better pandemic control and help prevent future lockdowns.

Numerous countries are currently evaluating and using rapid antigen tests which are inexpensive, do not require a laboratory setting, yield results in less than 30 minutes and identify infectious individuals. Many such SARS-CoV-2-specific rapid antigen tests are now commercially available and take the format of a lateral flow test (as is used for a standard pregnancy test). In most jurisdictions where these are used or being considered, they are employed as an additional component in the control of SARS-CoV-2 transmission, not as a replacement for individual diagnostic testing of symptomatic individuals conducted in clinical labs. There are exceptions, in particular in parts of the world where laboratory-based PCR diagnostics are not widely available for either geographical or economic reasons.

It is also important to highlight that the specification and performance of tests available has, and will continue, to improve over time, given rapid innovation and technological advances, incentivised by significant investment, and a greater understanding of the biology of SARS-CoV-2 transmission. The NIH has, for example, invested more than \$100M in its Rapid Acceleration of Diagnostics (RADx) initiative¹⁷, aimed specifically at COVID-19 testing innovation. A number of organisations (FindDx¹⁸, Arizona State University¹⁹, 360Dx²⁰) maintain catalogue listings of various types of tests in development – which currently number more than 1000. Continuous monitoring and evaluation of the state of the art is needed with new tests gaining regulatory approval at an unprecedented rate.

The goal of reducing viral spread, as parts of society and the economy are sustainably re-opened is paramount. The option of proactive testing to detect mild or asymptomatic infection in specific settings, in addition to public health measures that reduce the risk of transmission, is essential to maximally control spread of SARS-CoV-2.

4.5 Limitations of the current testing system

Currently, Public Health England estimates that only approximately 40% of new cases are identified through PCR testing each day in the UK²¹. Some symptomatic individuals may not present for testing, either because symptoms are mild, they are unclear whether their symptoms relate to SARS-Cov-2 infection or because they have no incentive (and perhaps have disincentives) to present for testing. In addition to these, a significant number of individuals will have asymptomatic infection and may represent a high proportion of the infected population contributing to transmission in the community. Currently in Ireland, testing of asymptomatic individuals in the community is only conducted under specific situations, including in contact tracing or limited targeted testing in nursing homes. In addition, pilots are being conducted in certain community settings including meat processing plants. As asymptomatic infection is more likely in the young (18-40 yrs.), we may be missing a high proportion of such asymptomatic individuals who have been identified as key contributors to early re-emergence of waves of infections^{22,23}. It is clear that more widespread rapid testing, to focus on infectious

¹⁷ NIH. RADx | National Institutes of Health (NIH). <https://www.nih.gov/research-training/medical-research-initiatives/radx>

¹⁸ FIND. SARS-CoV-2 diagnostic pipeline. Foundation for Innovative New Diagnostics. 2020 <https://www.finddx.org/covid-19/pipeline/>

¹⁹ Arizona State University; COVID-19 Diagnostics Commons: <https://chs.asu.edu/diagnostics-commons/testing-commons>

²⁰ Coronavirus Test Tracker: Commercially Available COVID-19 Diagnostic Tests | 360Dx. 2020 <https://www.360dx.com/coronavirus-test-tracker-launched-covid-19-tests?page=8>

²¹ Personal correspondence, S. Hopkins, NHS Test and Trace, Innova Evaluation Update, PHE February 2021

²² Silcox C, Anderson D, Zavodszky A, Borre E, Dentzer S, G AM, et al. A National Decision Point: Effective Testing and Screening for Covid-19 - The Rockefeller Foundation [Internet]. 2020. Available from: <https://www.rockefellerfoundation.org/wp-content/uploads/2020/09/A-National-Decision-Point-Effective-Testing-Screening-for-Covid-19-Full-Report.pdf>

²³ Lewis D. Superspreading drives the COVID pandemic — and could help to tame it. Nature. 2021 Feb 25;590(7847):544–6. <http://www.nature.com/articles/d41586-021-00460-x>

individuals, is required to effectively control transmission of SARS-CoV-2 infection, and thereby allow safer functioning of society and return of normal economic activity. Professionally administered, PCR testing should remain the diagnostic test for all symptomatic individuals and for highly vulnerable groups, but it is unsuitable for widespread testing due to its expense, requirement for dedicated personnel and labs and slow turnaround time from referral to reporting a result. So why have rapid tests such as LFATs not been widely deployed in Ireland to satisfy the requirement for widespread screening or testing? First, it is important to recognise that the field is developing rapidly. New tests are being approved for use every week – indeed the first tests for use in asymptomatic individuals received an EU CE mark of approval approximately two months ago. Everything is improving – accuracy and reliability, costs are decreasing, and availability is increasing. Some early challenges have or will be resolved. We highlight some of these challenges and their resolution here in the introduction and provide more detail in the body of the report.

4.6 Test accuracy

The accuracy of any test result depends upon the quality of the sample, the test itself, the reading and reporting of the result. In general, professionally administered tests, involving professional sampler / swabber, accredited laboratory procedure etc., will be more accurate than a self-administered test. However, any trade-off in accuracy needs to be balanced against the ability to: maximally and cheaply scale the testing to a large number of individuals, and to receive rapid results, identify infectious individuals usually within 15-30 minutes of testing, that enable effective, meaningful and immediate actions to prevent onward transmission. The accuracy of self-sampling improves significantly, not only with new technology but also with training and repeat performance. The accuracy of the tests is improving significantly with better knowledge of intelligent deployment (e.g. serial testing, bubble testing), familiarity with use of the tests (most errors occur with not waiting the full time for the result or not reading the band correctly) and smart use of companion technologies (e.g. individual lateral flow device barcoding to link the test with an individual and point in time, or smart phone enabled AI to improve interpretation and reporting). The predictive value of any test depends on the prevalence of the disease. In times of high disease prevalence, a positive test is more likely to be a true positive and in times of low disease prevalence a negative test is more likely to be a true negative. The epidemiological situation in specific settings will influence the choice of the most appropriate testing strategy at the time. The current prevalence in Ireland is estimated at 0.3%. With a hypothetical 80% sensitivity and 99.9% specificity testing 100,000 people detects 240 true positives, 100 false positives and 60 false negatives. As the prevalence of SARS-CoV-2 in a population drops, the proportion of false positives increases, albeit in the context of an overall lower number of positive cases. It is therefore crucial that those being tested understand the limitations as well as the benefit of any testing programme.

4.7 Is there a gold standard?

In most studies, rapid tests have been compared to SARS-CoV-2 PCR, which is a highly sensitive technique that detects even small amounts of viral nucleic acid. The key requirement for test, trace and isolate is to rapidly determine when an individual is infectious. Individuals are normally more infectious earlier in the course of infection when the viral load is higher. That is where LFATs perform best. Later, when viral loads have reduced, the individual is less likely to be infectious, may not have live or culturable virus, but may still test positive on PCR. Therefore, if lateral flow tests are compared to PCR, they perform worse and this has been the conclusion of early studies. Rapid LFATs are a

measure of infectiousness at the point in time when they are administered. They do not predict future infectiousness, nor do they measure if a person has been infected. At the very earliest stage of infection (when the person is not infectious), LFAT results may be negative, but the individual will go on to become infectious and LFAT positive in a few days – for this reason serial testing with LFATs is recommended.

A published comment in the *Lancet*²⁴ clarifies the evidence on rapid antigen tests in public health responses to COVID-19 by highlighting the differences between PCR and LFAT test results at different stages of the epidemic curve in Liverpool and Birmingham. Public Health England have stated that RT-PCR is an inadequate test for predicting infectiousness with a categorical result of approx. 50%.²⁵ Indeed, PCR tests are now being qualified by cycle threshold (Ct) values (themselves highly variable, depending on the machine, reagents etc. with no international standardization between laboratories and assays) which are a measure of the degree of viral RNA amplification. Emerging evidence supports that cases, both symptomatic and asymptomatic, with Ct values above 27 are less likely to be infectious^{26,27} and in some countries (e.g. screening of German Meat Plant workers) higher Ct values are not reportable.²⁸ To that end, good lateral flow tests may be a better measure of infectiousness than PCR. In a population study, the likelihood of onward transmission dropped off dramatically when the viral load of the index case fell below 0.8×10^6 copies/ml, within the detection range of LFAT.²⁹ Public Health England state that LFATs perform better than PCR in minimising unnecessary instruction to quarantine except in low prevalence situations where confirmatory PCR is desirable. A large (300,000 individuals) study of contact, test and trace in the UK concluded that under the best conditions using LFATs to identify and quarantine people could have prevented 90% of transmission events and under the worst conditions, prevented 67% of transmission events.^{30,31}

A test that identifies infectious subjects must be able to detect people with replicating / transmissible infectious virus – for which there is currently no gold standard. Arguably the gold standard should be the ability to culture live virus from the individual's sample at a level above the likely minimum infectious dose. Indeed, a recent study determined a sensitivity of 92.6% for rapid antigen tests in detecting samples that subsequently retrieve culturable virus.³² Public Health England (and others) state that for antigen tests (which aim to detect infectiousness) it is not relevant to consider overall RT-PCR positivity as a single gold standard. A recent international commentary³³ goes further “Comparing widespread, frequent rapid testing today to targeted, infrequent molecular testing is a false equivalency that leads to harm”.

²⁴ Mina MJ, Peto TE, García-Fiñana M, Semple MG, Buchan IE. Clarifying the evidence on SARS-CoV-2 antigen rapid tests in public health responses to COVID-19. *Lancet*. 2021 Feb 17. [https://doi.org/10.1016/S0140-6736\(21\)00425-6](https://doi.org/10.1016/S0140-6736(21)00425-6)

²⁵ Personal correspondence, NHS Test and Trace, Innova Evaluation Update, PHE February 2021

²⁶ Yamayoshi S. et al, Comparison of Rapid Antigen Tests for COVID-19. *Viruses* 2020, 12(12), 1420; <https://doi.org/10.3390/v12121420>

²⁷ Aarons MM et al, Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *N Engl J Med* 2020 May 28;382(22):2081-2090. <https://www.nejm.org/doi/10.1056/NEJMoa2008457>

²⁸ Personal Communication, D. Sammin, Department of Agriculture Food and the Marine (DAFM)

²⁹ Personal Communication, T Peto, Oxford University.

³⁰ Personal Communication, S. Hopkins, PHE February 2021 NHS Test and Trace, Innova Evaluation Update.

³¹ Lee LYW et al, An observational study of SARS-CoV-2 infectivity by viral load and demographic factors and the utility lateral flow devices to prevent transmission http://modmedmicro.nsms.ox.ac.uk/wp-content/uploads/2021/01/infectivity_manuscript_20210119_merged.pdf

³² Prince-Guerra JL, Almendares O, Nolen LD, Gunn JKL, Dale AP, Buono SA, et al. Evaluation of Abbott BinaxNOW Rapid Antigen Test for SARS-CoV-2 Infection at Two Community-Based Testing Sites — Pima County, Arizona, November 3–17, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70(3):100–5. <https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7003e3-H.pdf>

³³ Johnson-León M, Caplan AL, Kenny L, Buchan I, Fesi L, Olhava P, et al. Executive summary: It's wrong not to test: The case for universal, frequent rapid COVID-19 testing. *EClinicalMedicine* 2021 Feb;0(0):100759. <https://doi.org/10.1016/j.eclinm.2021.100759>

4.8 The accuracy of different lateral flow tests is highly variable

The performance of different commercial tests is highly variable, e.g. the UK performed validation tests on over 140 different commercial tests and found 12 that met their specifications. Validation is therefore key and requires appropriately powered studies with adequate sample sizes, which may be high in times of low prevalence. Even then experience in the UK and Ireland shows considerable batch-to-batch variation in validated commercial tests, so confirming sensitivity and specificity in commercial test batches is currently required. As the technology improves, the testing standards increase, quality control of manufacture increases and the competition between commercial manufacturers increases, this problem will likely decrease with time.

4.9 Behaviours elicited following a real or false positive or negative test

A potential concern stemming from test accuracy is the possibility of behavioural changes following a false negative test. All tests have the potential for false negative or false positive results. In one recent Irish study, 9 of 336 individuals (2.7%) presenting with suspected SARS-CoV-2 infection had negative PCR results but compatible symptomatology and positive SARS-CoV-2 antibody detected.³⁴ Similarly, rapid LFAT also produce false positives, albeit at a very low frequency in asymptomatic individuals; only 3 of 5,111 (0.039%) tests in a recent HSE validation study. Opponents of rapid testing assert that widespread use of LFAT, through missing potentially infectious cases, may result in people who are infectious engaging in activities that could spread the virus, e.g., social mixing. This is a risk compensation argument which has been advanced previously for many interventions e.g., seatbelts, condoms etc.³⁵ Advocates of rapid testing assert that such individuals will engage in such activities anyway and are unlikely to test in the first place. Advocates liken rapid testing to a Health and Safety measure, designed to decrease the risk of virus transmission, e.g., by reducing the number of infectious people at work. To that end, they counter “Do cycle helmets make you cycle more dangerously?”. There is a regulatory paradox, both the EU and US regulators have indicated they would approve a vaccine where efficacy was 50% or higher but we expect a higher percentage performance from a diagnostic test. What is the hypothetical behaviour difference between someone who has an ineffective response to a vaccine and someone with a false negative rapid antigen test? Behavioural data from the widespread deployment of rapid testing are just emerging. Much of it is positive, but more is needed. Reports suggest that people who self-test feel empowered, and people who test positive are more likely to comply with isolation (you did the test yourself and you have the result in your hand) and that knowledge of the widespread distribution of the virus in asymptomatic young people encourages them to act responsibly.

4.10 Widespread rapid testing is a community benefit

Widespread rapid testing benefits the community, often more than the individual, and to this end is different from an individual diagnostic test. Perhaps it needs a distinguishing name. It is more like a Health and Safety measure to reduce harm by identifying infectious individuals and encouraging them to isolate and not spread the disease. Although it may not be 100% accurate the question is: what

³⁴ Mallon PWG et al, Dynamic change and clinical relevance of post-infectious SARS-CoV-2 antibody responses. medRxiv, 2021 <https://doi.org/10.1101/2021.01.24.20248381>

³⁵ Tufekci Z. The Atlantic 5 Pandemic Mistakes We Keep Repeating. February 26 2021. <https://www.theatlantic.com/ideas/archive/2021/02/how-public-health-messaging-backfired/618147/>

risk does someone who has immunity through immunisation or prior infection and who tests negative on a rapid test pose in engaging in social and economic activities in a responsible way (i.e., complying with public health measures such as mask wearing, social distancing etc.)? To this end, Germany has recently approved seven commercial lateral flow tests for home use and is planning to encourage their widespread availability in many shops and on the internet and is considering utilising state aid to subsidise their cost (to be €1 - €2) so that everyone can afford to purchase and use them.³⁶ Austria provides five rapid antigen self-test kits per person, per month, for personal use of its citizens.

4.11 Mass testing, targeted testing and economics

Since the beginning of the pandemic (long before vaccines or therapeutics were developed), Professor Paul Romer of New York University and Nobel Prizewinner in Economics has argued that regular, serial mass testing, combined with rapid isolation of infectious cases was a way of managing the pandemic without the need for damaging lockdowns.³⁷ Subsequent studies⁶⁰ report that weekly testing reduces transmission by 40-50% whilst testing the entire population approximately twice per week with appropriate isolation of positive cases could contain the pandemic without the need for lockdowns. This became known as mass testing. Even with professionally administered sample collection and PCR testing, Romer showed that the economic cost of mass testing was much less than the economic cost of lockdowns. With the advent of rapid, cheap, self-administered lateral flow antigen tests, the economics of mass testing versus lockdown are compelling.³⁸ In Ireland, mass testing the population of approximately 4.8M people twice per week would mean conducting approx. 1.4M tests per day. The UK aim to test their entire population of approximately 60M people twice per week, i.e. approximately 20M rapid flow antigen tests per day. Taking a science-led approach, combined with existing public health measures, e.g., mask wearing, respiratory etiquette, ventilation etc., the UK believe that they will maximise the chances of having a safe sustainable reopening with no further lockdowns through a combination of rapid widespread vaccination and widespread, serial, self-administered testing, using lateral flow antigen tests, followed by rapid isolation of positive cases and extensive surveillance for outbreaks, variants and recombinants.³⁹ A recently published international commentary⁴⁰ goes further “In the midst of a raging plague, it is inequitable and unethical not to deploy high quality rapid tests alongside existing public health interventions”. Another commentary argues that widespread testing may avoid sharp trade-offs between unduly broad restrictions and the perils associated with wholesale loosening of restrictions.⁴¹

Of course, the advent of vaccines and increased knowledge of SARS-CoV-2 natural history and immunity has led to more focused strategies to limit its spread. This targeted testing⁴² becomes a more attractive option to mass testing. Indeed, a sensible way of commencing any rapid testing programme is to introduce it into selected situations first (targeted testing) and then expand its use. This can facilitate rapid learning and hence iterative improvements, as well as providing an

³⁶ News Article, Germany. February 26, 2021: <https://www.iamexpat.de/expat-info/german-expat-news/germany-approves-rapid-corona-tests-home-use-what-you-need-know>

³⁷ Chotiner BI. Paul Romer’s Case for Nationwide Coronavirus Testing. *The New Yorker*. 2020;1–9. <https://www.newyorker.com/news/g-and-a/paul-romer-on-how-to-survive-the-chaos-of-the-coronavirus>

³⁸ Romer P, Mina M, Badger D, Fishpaw M. Rapid COVID Tests: A Cure for Lockdowns, a Complement to Vaccines. 2021. <http://report.heritage.org/hl1319>

³⁹ HM Government COVID-19 Response, Spring 2021 <https://www.gov.uk/government/publications/covid-19-response-spring-2021>

⁴⁰ Johnson-León M, Caplan AL, Kenny L, Buchan I, Fesi L, Olhava P, *et al*. Executive summary: It’s wrong not to test: The case for universal, frequent rapid COVID-19 testing. *EClinicalMedicine*. 2021 Feb;0(0):100759. <https://doi.org/10.1016/j.eclinm.2021.100759>

⁴¹ Studdert DM, Hall MA, Disease Control, Civil Liberties, and Mass Testing — Calibrating Restrictions during the Covid-19 Pandemic, *N Engl J Med* 2020; 383:102-104, DOI: [10.1056/NEJMp2007637](https://doi.org/10.1056/NEJMp2007637)

⁴² Crozier A, Rajan S, Buchan I, McKee M. Put to the test: use of rapid testing technologies for covid-19. *BMJ*. 2021 ;n208. Available from: <https://dx.doi.org/10.1136/bmj.n208>

ongoing cost benefit analysis as to when it is sensible to stop promoting the expanded use of rapid testing. In this report, we use the term widespread testing to describe this scenario.

4.12 The value of testing and isolation

In a recent piece⁴³, Paul Romer addresses misunderstandings about tests with the provocative question, “How can it be that a test for a virus has little value for a doctor treating a patient and enormous value to a nation in coping with a pandemic?” Romer addresses, in quantitative form, the challenge of false positive results which arise from less accurate tests widely deployed in situations of low virus prevalence. He calculates the predictive power of a test under different levels of prevalence. He assumes a worst case for the predictive power of a rapid test, i.e., that it is given only once to a randomly selected group of people (in practice the predictive power of any test is improved by intelligent deployment, e.g., testing people in some sub-populations where the prevalence [or risk] is higher, repeat and serial testing, bubble / community testing and retesting with PCR those who test positive). He shows that lockdown is always worse than test and isolate, no matter the level of prevalence. To stop the rate of growth of infections, lockdown must restrict activity to a far greater extent than test and isolate. For example, when the prevalence of infection is 1%, lockdown requires restrictions that are 33 times more limiting than the restrictions generated by test and isolate. Interestingly, when the prevalence is lower (as may occur when a significant proportion of the population are vaccinated) the relative advantage of test and isolate over lockdown is even greater. When 0.1% of the population is infected, lockdown requires restrictions that are 46 times as limiting as test and isolate. Romer points out that the familiar calculation from probability theory that “the positive predictive value of a test is lower when the ex-ante probability of infection is lower” is correct but that the inference often drawn from this is that “tests are less valuable when the prevalence is lower” is wrong. Romer shows that a parallel (and underappreciated) calculation from probability theory shows that widespread testing is actually more valuable when the prevalence of infection is lower.

4.13 Ethical Considerations

The Ethical Framework for Decision-Making in a Pandemic was published by the Department of Health in March 2020.⁴⁴ It outlines how the goals of a public health response to a pandemic should be to minimise the negative health impact and to maintain a functioning society. The Framework identifies seven ethical principles regarding decision making during a pandemic. It acknowledges that decisions may have to be made despite uncertainty and that the ability to adapt in light of new information is of particular importance. In making decisions, it is important to uphold the procedural values, which include reasonableness, openness and transparency and responsiveness. Clear and regular communication on the use of new technology and measures, including associated benefits and limitations, is important in gaining public trust and understanding. There is also an ethical obligation for scientists and governments to rapidly share information on new technologies that protect the public (according to Findable, Accessible, Interoperable and Reusable (FAIR) principles).⁴⁵ In order to inform the public health response and to provide for appropriate scientific evaluation of a new intervention or medicine, research which includes risk management and assessment is required.

⁴³ https://mybinder.org/v2/gh/paulromer149/tests/HEAD?urlpath=lab/tree/Tests_b.ipynb

⁴⁴ <https://www.gov.uk/government/publications/dbf3fb-ethical-framework-for-decision-making-in-a-pandemic/>

⁴⁵ Wilkinson, M., Dumontier, M., Aalbersberg, I. *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 3, 160018 (2016). <https://doi.org/10.1038/sdata.2016.18>

Testing is a component of a wider strategy of controlling spread of infection during a pandemic. Non-maleficence, beneficence, justice and autonomy are important ethical considerations in any discussions or decisions on the use of new testing platforms. An ethical framework for COVID-19 testing of UK NHS workers was published in July 2020,⁴⁶ and it outlines practical recommendations to be considered in a testing programme, which are an important component of an implementation plan. This report focuses specifically on antigen-based testing regimes and serves as a good reference point for consideration of specific ethical considerations. In summary, key recommendations include the need for clear communication in relation to the goals of the programme; the need to ensure that access to testing does not discriminate any groups and that any prioritisation or eligibility for testing is clearly communicated; the need to acknowledge the advantages and limitations of any testing platform and clarity on choice in relation to testing including the need to be explicit about consequences arising from testing; clarity must also be provided about how personal information will be handled, used or shared. Trustworthiness and legitimacy and good communication are essential for safe and effective operation of a testing programme. The need for clear guidance and standards in relation to the use and choice of rapid tests is emphasised also in the context of ethical and regulatory challenges that may arise with an increasing “direct to consumer” market where potential misinterpretation of results or misleading claims made by manufacturers could have a negative impact.⁴⁷

4.14 HIQA Report

In compiling this report, the review group acknowledges the extensive body of knowledge documented and reviewed in the 2020 HIQA report *“Rapid health technology assessment (HTA) of alternatives to laboratory-based real-time RT-PCR to diagnose current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”*⁴⁸ which will not be repeated here.

To complement this, the group has focused on recent developments and publications in this fast-moving field and consulted a number of individuals internationally who are at the forefront of thinking about and implementing widespread rapid testing. Our report is forward-looking, focusing on what is required now and this year. Testing of symptomatic individuals in healthcare settings was not considered for this review, nor was the use of antibody testing to measure immunity resulting from past infection or vaccination.

⁴⁶ <https://www.thisinstitute.cam.ac.uk/research-articles/testing-times-ethical-framework/>

⁴⁷ The promise of direct-to-consumer COVID-19 testing: ethical and regulatory issues; <https://academic.oup.com/ijb/article/7/1/Isaa069/5910046>

⁴⁸ Health Information and Quality Authority (HIQA). Rapid health technology assessment (HTA) of alternatives to laboratory-based real-time RT-PCR to diagnose current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). 2020. <https://www.hiqa.ie/sites/default/files/2020-10/Rapid-HTA-of-alternative-diagnostic-tests.pdf>

5. Rapid Tests that could be used in different settings

5.1 Overview of types of testing

The majority of available tests are designed to detect SARS-CoV-2 genetic material (SARS-CoV-2 RNA) or viral proteins (antigens). There are also a number of more experimental types of testing for SARS-CoV-2 infection under development. These include measurement of anosmia (loss of smell), measurement of changes in breath biochemistry or the use of trained sniffer dogs to detect distinct patterns of volatile organic compounds resulting from SARS-CoV-2 infection. These more experimental approaches are not considered further as part of this review.

Widespread temperature checks including thermal scanning have been employed in numerous community settings as a rapid screening tool for potential infection, even though this non-specific approach has been determined to be ineffective⁴⁹ and Public Health guidance in Ireland advises against mass temperature screening.⁵⁰

Detection of anti-SARS-CoV-2 antibodies generated by the immune system in response to infection with the virus or vaccination is important to understand infection and immunity. Antibodies against SARS-CoV-2 viral antigens (e.g., S and N proteins) are generated during infection and can persist for some months and are therefore a useful measure of previous but not current infection. In addition, specialist virus “*in vitro*” neutralisation assays can assess the capacity of antibodies within an individual’s blood to neutralize SARS-CoV-2 virus. Although it is widely debated that not all individuals who are infected with SARS-CoV-2 develop antibodies, the consensus view is that the majority of those with symptomatic infection and most with asymptomatic infection do develop anti-SARS-CoV-2 antibodies especially against the S protein. Depending on the type of antibody class, some antibody classes can persist for up to 6-8 months. Most studies have measured IgG and IgM levels in blood. IgA antibodies in saliva are also informative. Antibody tests will not be considered further as part of this review.

SARS-CoV-2 infection is currently detected using two main approaches:

Detection of SARS-CoV-2 viral RNA, the genetic material of the virus, which is usually amplified in nucleic acid tests to enable the detection of very low levels of SARS-CoV-2 RNA. This can also be referred to as nucleic acid amplification testing. There are a range of nucleic acid tests, which vary according to throughput (samples analysed per unit time) and resources required. These include RT-qPCR, LAMP, CRISPR (e.g., SHERLOCK, FALUDA) and sequencing-based technologies (e.g., RNAseq, COVIDSeq, Swabseq, LAMPore). The latter require centralised labs with high-tech equipment, while LAMP and CRISPR-based lateral flow tests have been developed for decentralised high-throughput rapid-testing. Specific, nucleic acid-based tests can be designed to differentiate between the different variants of concern.

⁴⁹ ECRI. Infrared Temperature Screening to Identify Potentially Infected Staff or Visitors Presenting to Healthcare Facilities during Infectious Disease Outbreaks [Internet]. 2020. Available from: <https://assets.ecri.org/PDF/COVID-19-Resource-Center/COVID-19-Clinical-Care/COVID-ECRI-Temperature-Screening.pdf>

⁵⁰ HSE. Is there evidence that temperature checks for healthcare workers (HCWs) reduce the transmission of COVID-19 in healthcare settings? <https://hselibrary.ie/is-there-evidence-that-temperature-checks-for-healthcare-workers-hcws-reduce-the-transmission-of-covid-19-in-healthcare-settings/>

Detection of SARS-CoV-2 viral antigens, key structural components (proteins or antigens) of the virus that are recognized by the immune system e.g. by antibodies. Testing for viral antigen is more amenable to decentralised high-throughput rapid testing approaches.

Although both types of tests seek to identify individuals who are infected with SARS-CoV-2, they fundamentally differ in what component of SARS-CoV-2 they detect. PCR-based tests detect viral genetic material and make copies of this through many amplification cycles, so they can detect very low quantities of viral material, including non-viable virus. Antigen tests detect SARS-CoV-2 proteins, and the signal is not amplified, therefore a positive antigen test is more likely to align with a high viral load (of intact virus), whereas a positive molecular test may result from a low viral load and will be detectable over a longer period of time. Therefore, whilst PCR can detect all cases of SARS-CoV-2 infection, the antigen assays detect those individuals who are potentially infectious.

More detail on types of tests is provided in Appendix 1.

5.2 Overview of sampling approaches

There are three commonly used sample-collecting approaches for diagnostic testing for SARS-CoV-2:

Nasopharyngeal or oropharyngeal swabs: nasopharyngeal (NP) swabbing involves collecting a specimen from deep at the back of the nostril by inserting and rotating a swab at the posterior wall of the nasopharynx, whereas oropharyngeal swab involves collecting a specimen from the throat by inserting and rotating a swab toward the rear wall of the oropharynx. Nasopharyngeal specimens appear to be more reliable than oropharyngeal specimens for detection of SARS-CoV-2 RNA,⁵¹ however, both are often performed together. Nasopharyngeal and oropharyngeal swabbing are the most commonly used approaches for collecting biological specimens for SARS-CoV-2 PCR testing, but they are invasive and uncomfortable (particularly nasopharyngeal swabbing) for the person and require qualified healthcare professionals, in PPE, to take samples. Nasopharyngeal or oropharyngeal swabbing is not scalable to widespread frequent serial testing, although Nasopharyngeal swabbing is used in HSE serial testing programmes in some nursing homes and meat processing plants.

Anterior nasal (AN) swabs or mid-turbinate swabs: This swabbing involves inserting a swab approximately 2 cm into each nostril, and rotating the swab 3-4 times against the nasal walls on each side. This may be supplemented by swabbing the tonsil (See UK guidance, instructions and video).⁵² There is evidence to suggest that it is as sensitive as nasopharyngeal swabbing.⁵³ This approach is less invasive, causes less discomfort, allows individuals to self-sample and enables scaling of testing strategies. This method is also considered more acceptable for repeated testing.

Saliva: Saliva is a recognized source of virus in SARS-CoV-2 infected individuals and can be collected by drooling and dribbling/spitting into a collecting tube. Alternatively, saliva sponges can be used where a sponge on a stick is inserted into the mouth and gently moved around the upper and lower cheek pouches on both sides of the mouth to soak up saliva. Viral RNA testing based on saliva samples

⁵¹ Kujawski SA, Wong KK, Collins JP, Epstein L, Killerby ME, Midgley CM, *et al.* Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nat Med.* 2020 Jun 1;26(6):861–8. <https://doi.org/10.1038/s41591-020-0877-5>

⁵² UK Instructions for Self-Test <https://www.gov.uk/government/publications/instructions-for-covid-19-self-test>

⁵³ Lindner AK, Nikolai O, Kausch F, Wintel M, Hommes F, Gertler M, *et al.* Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected anterior nasal swab versus professional-collected nasopharyngeal swab. *medRxiv.* 2020;2–9. <https://doi.org/10.1101/2020.12.03.20243725>

is slightly less sensitive than that based on nasopharyngeal swab tests (91% versus 98% for previously confirmed COVID-19 in a metanalysis).⁵⁴

A recent study indicates that saliva and/or nasal swabs may be superior for diagnostics of infectiousness than nasopharyngeal swabs, where positives may be detected up to 100 days post infection.⁵⁵ Despite being considered as a gold-standard, the study suggests that nasopharyngeal swabs are an inappropriate comparator for the evaluation of novel testing assays and sample types. Taking saliva samples is currently the least invasive sampling approach that is most suitable for self-sampling and scaling. Although saliva samples have been used successfully for both PCR and LAMP-based assays, saliva has not to date demonstrated good sensitivity with rapid antigen tests. Saliva sampling has been shown to enable accurate virus detection in both symptomatic and asymptomatic individuals.⁵⁶

Samples for diagnostic tests for SARS-CoV-2 can also be taken by nasal aspirate or nasal wash or from lower respiratory tract, using sputum, tracheal aspirate or bronchoalveolar lavage, or faeces can be used. However, these are less relevant to routine testing or screening.

⁵⁴ Czumbel LM, Kiss S, Farkas N, Mandel I, Hegyi A, Nagy Á, *et al.* Saliva as a Candidate for COVID-19 Diagnostic Testing: A Meta-Analysis. *Front Med* . 2020 Aug 4;7:465. <https://www.frontiersin.org/article/10.3389/fmed.2020.00465/full>

⁵⁵ Turner F, VandenBerg A, Slepnev VI, Car S, Starritt RE, Seger M V, *et al.* Post-disease divergence in SARS-CoV-2 RNA detection between nasopharyngeal, anterior nares and saliva/oral fluid specimens - significant implications for policy & public health. *medRxiv* . 2021 Jan;preprint:2021.01.26.21250523. <https://doi.org/10.1101/2021.01.26.21250523>

⁵⁶ Vogels CBF *et al.* SalivaDirect: A simplified and flexible platform to enhance SARS-CoV-2 testing capacity. *Med*; March 2021. <https://doi.org/10.1016/j.medj.2020.12.010>

6. Availability and Validation of Rapid Tests

6.1 Current Rapid Antigen Test Guidelines

An increasing number of rapid antigen detection tests for SARS-CoV-2 are being placed on the market or are potentially exportable to EU countries with CE marking. Reagents, control materials, testing kits, and instruments intended for medical use are referred to as *in vitro* diagnostic medical devices (IVDs). The currently applicable legislative framework for these devices at EU level is Directive 98/79/EC.⁵⁷

The CE-marking for SARS-CoV-2 rapid tests is mostly based on a self-assessment and a self-declaration by the test manufacturer, including the claims on test performance, for which the manufacturer needs to have appropriate technical documentation and studies to back up the claims. Performance estimates are based on analytical rather than operational sensitivities and specificities – that is, they represent ideal circumstances. It is noteworthy that from May 2022, Directive 98/79/EC will be replaced by Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices, meaning that rapid antigen tests will be subject to reinforced requirements on device performance and a thorough assessment by a notified body. This should, in the future, reduce the additional effort required for the validation of these tests prior to their use.

In a technical report on rapid antigen tests published in November 2020, the European Centre for Disease Prevention and Control (ECDC)⁵⁸ advised that *“the use of rapid antigen tests can be recommended for testing individuals regardless of symptoms in settings in which the proportion of test positivity is expected to be $\geq 10\%$ ”*. In the report guidelines, they recognise that rapid antigen tests *“perform best in cases with high viral load, in pre-symptomatic and early symptomatic cases”*, the report also states that *“the use of rapid antigen tests is appropriate in high prevalence settings when a positive result is likely to indicate true infection, as well as in low prevalence settings to rapidly identify highly infectious cases”*. They also advise that rapid antigen tests can be used for testing asymptomatic close contacts and for screening and serial testing (every two to three days) of residents and staff in semi-closed and closed settings. Furthermore, they advise that when considering the use of rapid antigen tests the need for confirmatory testing and supplies for those, needs to be considered.

The EU Commission has advised that *“In epidemiological situations or areas where the proportion of test positivity is high or very high (e.g. $> 10\%$), rapid antigen tests can be used for population-wide screening, taking into consideration and putting in place an adequate evaluation scheme to measure impact.”* They advise that rapid antigen testing can be used to further strengthen countries overall testing capacity, in particular where there is low PCR-capacity or long turnaround times; that testing should be conducted by trained operators in accordance with manufacturer’s instruction and QC; that testing is registered in respective national data collection and reporting systems. They also recommend that rapid antigen testing may be used in outbreak cluster scenarios for early detection and isolation of cases and in high-risk and closed settings. Serial testing is recommended in these cases.

⁵⁷EU Parliament. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. 1998. Available from: <http://data.europa.eu/eli/dir/1998/79/oj>

⁵⁸ European Centre for Disease Prevention and Control. Options for the use of rapid antigen tests for COVID-19 in the EU/EEA and the UK Key messages. 2020. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/Options-use-of-rapid-antigen-tests-for-COVID19-19-11-2020.pdf>

The Commission has also recommended that Member States carry out independent and setting-specific validations of rapid antigen tests before their implementation. Further details are provided by the EU Council in its recommendation of a common framework⁵⁹ for the use and validation of rapid antigen tests, including the recommendation that Member States mutually recognise the test results for public health measures.⁶⁰ EU Commissioner for Health and Food Safety, Stella Kyriakides has stated that *“Rapid antigen tests are crucial to slow down the spread of COVID-19 and should be part of our overall response to the pandemic. If negative COVID-19 tests are to be required or recommended for any activity, it is essential that they are mutually recognised, and result in certificates recognised across the EU. This is essential, particularly in the context of travel. Our citizens need clarity and predictability.”*

The ECDC issued a technical report on considerations for the use of self-tests for COVID-19 in the EU/EEA on 17th March 2021. The ECDC report lays out a number of public health considerations and indicates *“Self-tests can complement but not replace other sampling and testing methods to improve accessibility to testing, expedite diagnosis, and facilitate the timely isolation of cases and quarantine of contacts”* and *“Self-tests can contribute to overall COVID-19 testing capacity by supporting the early detection of infectious cases and reducing further community transmission by allowing the rapid isolation of infectious cases”*.⁶¹

Although focusing on public health considerations of self-administered LFATS, such as the effects on surveillance data and the chances of false positive or negative results under conditions of differing viral prevalence, the ECDC report is in general accord with this report although it may have been drafted earlier as some sections are now incorrect, e.g. it states that no rapid antigen test has been CE marked for use in asymptomatic individuals or for self-testing at home, whereas for example the Abbott Panbio test was CE marked for such use in January 2021.

The WHO recognises that despite lower sensitivity than molecular tests, antigen tests offer the possibility of rapid, inexpensive detection of SARS-CoV-2 in individuals who have high viral loads and hence are at high risk of transmitting the infection to others.

6.2 Current Rapid Antigen Test Availability and Selection Guidelines

The vast majority of commercial and affordable rapid tests detect antigens (viral proteins), although development of rapid molecular tests (which detect viral RNA) is also increasing. When initially developed in 2020, rapid antigen detection tests for SARS-CoV-2 had poor reliability that precluded their general use, however, the new generation of tests have substantially improved reliability.

As of February 2021, there were ~163 rapid antigen tests with a CE-marking listed on the FindDx database and this number is continuously growing.⁶² Also in February 2021, the EU Health Security Committee identified 16 rapid antigen tests that met their required criteria: i.e. Carry CE marking; demonstrate minimum performance requirements of $\geq 90\%$ sensitivity and $\geq 97\%$ specificity; are

⁵⁹Council of the EU. Council agrees on strengthening the use of rapid antigen tests and on the mutual recognition of COVID-19 test results - Consilium. 2021. <https://data.consilium.europa.eu/doc/document/ST-5451-2021-INIT/en/pdf>

⁶⁰ European Commission. A common list of COVID-19 rapid antigen tests, including those of which their test results are mutually recognised, and a common standardised set of data to be included in COVID-19 test result certificates. 2021 Available from: https://ec.europa.eu/health/sites/health/files/preparedness_response/docs/covid-19_rat_common-list_en.pdf

⁶¹ ECDC, March 2021. Considerations on the use of self-tests for COVID-19 in the EU/EEA.

<https://www.ecdc.europa.eu/sites/default/files/documents/Considerations-for-the-use-of-self-tests-for-COVID-19-in-the-EU-EEA.pdf>

⁶² FIND. SARS-CoV-2 diagnostic pipeline. Foundation for Innovative New Diagnostics. 2020. Available from: <https://www.finddx.org/covid-19/pipeline/>

validated by at least one Member State for use in the context of COVID-19; are in use by at least three Member States in practice. WHO have recommended minimum performance criteria for antigen tests of $\geq 80\%$ sensitivity and $\geq 97\%$ specificity.⁶³

In the UK, the selection process⁶⁴ for suppliers of rapid antigen tests are weighted according to a number of criteria including, but not limited to (1) nature of the sample the test can use (Anterior Nasal Swab preferable); (2) Suitability for asymptomatic and /or symptomatic individuals (both preferable) (3) self-swabbing and self-testing both preferable over the need for specialist support at any point; (4) Cost per unit which must not exceed £5; LFATs must not be designed to detect the Spike (S) antigen, given high prevalence of Spike variants. In addition, suppliers must have their tests validated to minimum performance criteria at PHE Porton Down.⁶⁵ Validation in the UK also requires LFATs to reach specificity of $>97\%$ and sensitivity of $>80\%$ to detect high viral load. Batch-to-batch variation has also been highlighted as a critical factor that needs to be carefully monitored.

A short list of more commonly used tests is included in the table below for reference, including an indication of use in EU Member States (MS). Two of these tests (SD BioSensor and Abbott Panbio) and others are being explored in pilots in Ireland. It is also noteworthy that the Panbio test has recently been approved for use in asymptomatic individuals.⁶⁶

Manufacturer	Commercial Rapid Test	Clinical Performance				MS (and other) using in practice **	MS currently validating this rapid test**	Comment
		Antigen	Sensitivity	Specificity	Sample*			
SD BIOSENSOR Inc/Roche	STANDARD Q COVID-19 Ag	N	96.5%	99.7%	AN/NP Swab	AT, BE, BG, CY, DE, ES, FI, FR, HR, IT, LU, LV, MT, NL[5], RO, SE, SK, SI, ME, NO, CH	HR, IE, LU, SI, SE	Validating in Ireland
Abbott Rapid Diagnostics	Panbio COVID-19 Rapid Test	N	98.1%	99.8%	AN/NP Swab	AT, BE, BG, CY, CZ, DE, EL, ES, FR, HR, IT, MT, NL, PL, PT, RO, SE, SK; CH, ME, MK, NO, UK, UA, CA	CY, ES, HR, HU, IE, LU, PT, SE, CA	Validating in Ireland
Abbott Diagnostics Scarborough, Inc.	BinaxNOW COVID-19 Ag Card Home Test	N	97.1%	98.5%	AN/NP Swab	USA	USA	This test is biologically identical to Panbio
Xiamen Biotime Technology Co Ltd Distributed by UK Tried and Tested	Innova SARS-Cov-2 Antigen Test	N	99.0%	100.0%	AN/NP Swab	UK	UK	Not on EU mutually recognised list; Widespread use in UK

*AN – (Anterior Nasal); NP (Nasopharyngeal) / ** examples of countries only, as lists are continually expanding

⁶³ World Health Organization. COVID-19 Target product profiles for priority diagnostics to support response to the COVID-19 pandemic v.0.1. 2020;(September):1–38. <https://www.who.int/publications/m/item/covid-19-target-product-profiles-for-priority-diagnostics-to-support-response-to-the-covid-19-pandemic-v.0.1>

⁶⁴UK Government. Lateral Flow Testing <https://www.contractsfinder.service.gov.uk/notice/da6f739f-90e5-491d-988d-8c90ea591e4a?origin=SearchResults&p=1>

⁶⁵ UK Government. Protocol for evaluation of rapid diagnostic assays for specific SARS-CoV-2 antigens (lateral flow devices). <https://www.gov.uk/government/publications/assessment-and-procurement-of-coronavirus-covid-19-tests/protocol-for-evaluation-of-rapid-diagnostic-assays-for-specific-sars-cov-2-antigens-lateral-flow-devices>

⁶⁶ Abbott's Panbio Rapid Antigen Test Receives CE Mark for Asymptomatic Screening and Self-Administered Sample Collection with Nasal Swab - Jan 26, 2021. <https://abbott.mediaroom.com/2021-01-26-Abbotts-Panbio-Rapid-Antigen-Test-Receives-CE-Mark-for-Asymptomatic-Screening-and-Self-Administered-Sample-Collection-with-Nasal-Swab>

6.3 Negative and Positive Predictive Values of Rapid Antigen Tests

Data on “real-world” performance of many tests remains limited and further independent validation of their accuracy in specific settings, as determined by both their positive predictive value (PPV - proportion of positive results that are true positive results) and the negative predictive value (NPV - the proportion of negative results that are true negative results) is needed. In validating, the definition of what constitutes a 'positive' is key; a 'positive' defined as a case that is infectious is very different to a 'positive' that is defined as a case that is PCR positive. This differentiation will be a key consideration in validating any test for “real-world” use. Recently the UK published a report on the performance of LFATs in over 1.7 million community test settings and nearly 1 million schools / college tests. They concluded that LFATs have a specificity of at least 99.9%, are accurate, reliable and have extremely low false positive rates.⁶⁷

The relationship between test sensitivity and specificity, coupled with viral prevalence in a given setting, will impact on the PPV and the NPV as described in a recent paper.⁶⁸ Consideration must therefore be given to appropriate mitigation strategies that are needed to manage potential consequences arising from either high PPV or NPV, such as the need for a confirmatory PCR test, intelligent deployment e.g., serial testing and continued adherence to public health guidelines. The quick availability of results and the frequency of testing have been shown in modelling studies to be more important than sensitivity.⁶⁹ Future improvements in test performance and selection criteria should aim in particular to reduce LFAT false negatives. Peeling et al⁵⁹ conclude “Ag-RDT’s [antigen rapid detection tests] when used appropriately are promising tools for scaling up testing and ensuring patient management and public health measures can be implemented without delay. Wide availability of Ag-RDT’s and the rapid result time offer the promise of efficiently testing a large number of people in community settings to ensure safe environments for resumption of activities, which are important for social, educational and economic reasons.”

6.4 Rapid Molecular Tests

Isothermal amplification based on RT-LAMP and CRISPR platforms have been emerging as good alternatives to RT-qPCR in the diagnosis of SARS-Cov-2. Both techniques are highly sensitive, faster and cheaper than RT-qPCR and require just basic heating equipment. Although these techniques offer promise as point-of-need diagnostic tests, the development of commercial kits is at an early-stage and there are less options currently available on the market at the low costs offered by rapid antigen tests. But the landscape is evolving and needs to be monitored.

In mid-February 2021, the FDA had assigned Emergency Use Approval (EUA) for five commercial kits, for use in certified laboratories, and one of these has also been approved as a home-test. The Lucira⁷⁰ COVID-19 All-In-One Test Kit is the first FDA EUA authorized prescription at-home molecular test (LAMP-based) for individuals 14 years and older. The FDA has also approved Sherlock Biosciences for its CRISPR-based test, for use in clinical laboratories. Three additional companies have received FDA

⁶⁷ UK Government. Lateral flow device specificity in phase 4 (post marketing) surveillance; March 2021; https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/968095/lateral-flow-device-specificity-in-phase-4.pdf

⁶⁸ Peeling RW et al. Scaling up COVID-19 rapid antigen tests: promises and challenges. *Lancet Infect Dis* 2021 [https://doi.org/10.1016/S1473-3099\(21\)00048-7](https://doi.org/10.1016/S1473-3099(21)00048-7)

⁶⁹ Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening. *Sci Adv* . 2021 Jan 1;7(1):1–11. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7775777/>

⁷⁰ COVID-19 At-home Test - Lucira Health. Available from: <https://www.lucirahealth.com/>

approval for in-house RT-LAMP or DETECTR CRISPR tests, where samples are sent for testing. More tests are under assessment. DARPA in the US has recently invested more than \$30M in the development of this technology as a potential low-cost point of care diagnostic.⁷¹ The FDA has also approved a number of Next Generation Sequencing (NGS) tests (e.g. Swabseq) in certified labs and a small number of commercial LAMP-based assays have also received CE mark for use in a laboratory setting.

A number of lab-based validation studies have been carried out. In the UK, the Department of Health and Social Care conducted an evaluation of the OptiGene RT-LAMP assay (which is designed for use in a laboratory setting) across nine NHS trusts and university partners including an NHS asymptomatic staff pilot study.⁷² The evaluation compared direct and RNA extraction steps and both swabs and saliva samples were included. The study reported sensitivity of 95% and specificity of 99% with nasal swab samples. The use of saliva, without RNA extraction, resulted in a sensitivity of 79% and specificity of 100% across all samples tested. The sensitivity increased to 94% for those samples with a higher viral load (Ct <25 by RT-qPCR). The authors of the study concluded that the saliva-based LAMP assay demonstrated viral detection with sufficient sensitivity and specificity for an effective regular interval-based testing system, as indicated by the hospital and community programmes. It is noted that there are supply chain issues currently for OptiGene in Ireland.

⁷¹Genetic Engineering & Biotechnology News (GEN). DARPA to Fund CRISPR Diagnostics Using Mammoth, IDbyDNA Technologies 2021. Available from: <https://www.genengnews.com/news/darpa-to-fund-crispr-diagnostics-using-mammoth-idbydna-technologies/>

⁷² UK Government. Rapid evaluation of OptiGene RT-LAMP assay (direct and RNA formats). 2020. <https://www.gov.uk/government/publications/rapid-evaluation-of-optigene-rt-lamp-assay-direct-and-rna-formats/rapid-evaluation-of-optigene-rt-lamp-assay-direct-and-rna-formats>

7. Testing for Asymptomatic Infection

Although Ireland has a well-established testing programme and infrastructure for individuals with symptomatic COVID-19 and their contacts (symptomatic and asymptomatic), the SARS-CoV-2 virus can cause mild and asymptomatic infection that can still transmit between individuals, perpetuating the pandemic. Approaches that can rapidly identify individuals who are infectious, but potentially either asymptomatic or presymptomatic, are crucial to enabling a safer reopening of society while keeping our population protected. Use of alternative technologies to RT-PCR that can provide cheaper, more rapid results focused on identifying infectious, but asymptomatic cases, will contribute to breaking chains of transmission. However, such approaches have raised concerns around logistics, false reassurance, impact on continuing safe COVID-19 behaviours and public buy-in (education) around their appropriate use, as well as their use at times of low viral prevalence (see section 6.3).

Such legitimate concerns need to be placed in context; a test is only as good as the programme within which it is embedded, and all components of a testing programme are important.⁷³ The aims and objectives of any testing programme or risk-reduction approach need to be clear; the overall aim is to reduce serious illness and deaths in the population, whilst enabling safe functioning of society. Within this context, a key objective is for a risk-reduction approach to provide a route to rapidly detect active, transmissible cases, reduce the risk of onward transmission, and achieve this at an affordable cost. Detection of infectious, asymptomatic individuals that will lead to reduction in transmission is key. Testing alone does not stop transmission, testing followed by appropriate action does. In addition, it allows individuals to take control of their health and wellbeing.

The use of a risk-reduction approach differs from traditional testing where a robust predictive test must determine a clinical diagnosis. Risk-reduction approaches rather provide an overall meaningful benefit but within a range of uncertainty. According to Paul Romer, the 2018 recipient of the Nobel Prize in Economic Sciences, the net outcome of an effective risk reduction approach is to provide a societal benefit; Regular testing, in spite of the inconvenience for individuals, would enable more targeted restrictions to be imposed on the few who are identified as infectious as opposed to imposing lockdowns on the many who are identified as not infectious.

Acknowledging uncertainty is an important concept in the approach to control pandemics.⁷⁴ Although healthcare policy is normally based on a rich evidence base that can take years to accumulate, policy making in a pandemic requires rapid implementation and decisions based on the balance of probabilities of harm reduction while enabling science to continue gathering the evidence necessary to enhance implementation through a reflective learning culture. In a recent international commentary⁷⁵ the authors describe how understanding the advantages and limitations of using rapid antigen testing in different populations across a prevalence range will allow molecular and antigen tests to be deployed concomitantly to improve the COVID-19 response.

Within this vein, this section of the report explores characteristics of risk-reduction approaches that can deploy rapid antigen tests to limit spread of COVID-19 as societal restrictions are eased, with a focus on a strategy to identify asymptomatic, infectious individuals to reduce risk in specific settings.

⁷³ Raffle AE, Gray JAM. [Screening: Evidence and practice. Screening: Evidence and Practice](#). Oxford University Press; 2009. 1–336 p.

⁷⁴ Davey Smith G, Blastland M, Munafò M. Covid-19's known unknowns. Vol. 371, *The BMJ*. BMJ Publishing Group; 2020. <http://dx.doi.org/10.1136/bmj.m3979>

⁷⁵ Peeling RW et al. Scaling up COVID-19 rapid antigen tests: promises and challenges. *Lancet Infect Dis* 2021 [https://doi.org/10.1016/S1473-3099\(21\)00048-7](https://doi.org/10.1016/S1473-3099(21)00048-7)

7.1 Viral Infection Profile

During acute infection, the amount of virus in an individual rises rapidly to very high viral loads and then falls over time following initial infection. The time period from infection to peak viral load is circa 5 days and the vast majority of cases harbour infectious virus no more than 8 to 9 days after symptoms first appear. Isolation of replication-competent virus beyond 20 days has not been demonstrated and virus isolation is rarely successful in an asymptomatic individual beyond 10 days. PCR-based tests are highly sensitive and detect small amounts of genetic material, so can have RNA detected long after a person is no longer infectious. Antigen tests detect the presence of viral proteins expressed during replication and can therefore be positive when a person has a high viral load and is most infectious. Due to the viral load increases, any rapid testing (whether antigen or nucleic acid) to identify infectious asymptomatic individuals should be done on a serial testing basis, ideally at least twice per week.⁷⁶ Figure 1 below illustrates indicative viral load trajectory following infection.

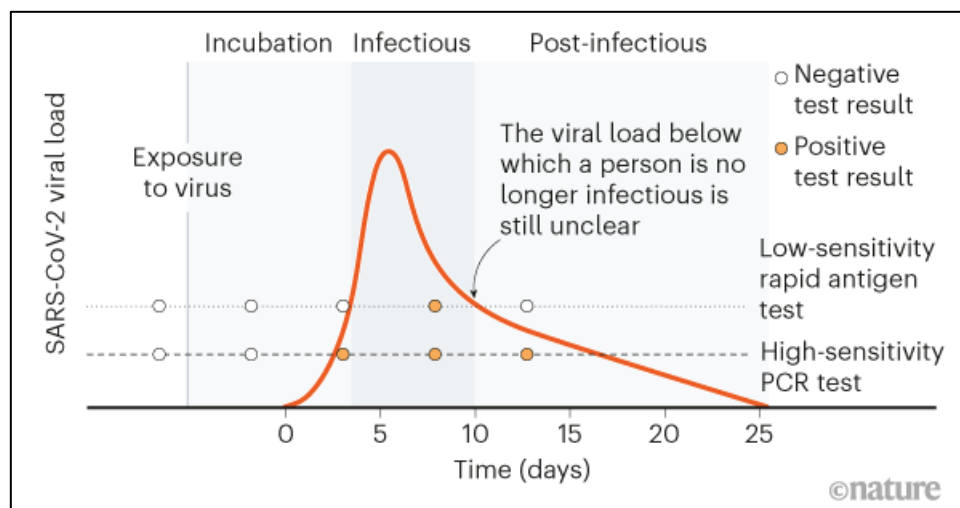


Figure 1: Adapted from Nature. Based on A Crozier et al, BMJ 2021;372:n208⁷⁷ ©Nature Publishing

During a SARS-CoV-2 infection, the amount of virus in the body rises and falls (orange curve). PCR-based tests can detect small amounts of viral genetic material and can therefore be positive post-infectious stage (lower dashed line). Rapid antigen Tests detect the presence of viral proteins and can be positive when a person is most infectious and may not detect low levels of virus pre- or post-infection (upper dashed line). The figure is not an accurate representation of exactly when a positive test is likely to signify that a case is infectious and duration of infectivity may vary.

There is a rapidly accumulating body of evidence that describes the characteristics of rapid antigen tests. The evolving understanding from several studies of what constitutes an 'infective' case of SARS-CoV-2 aligns to Ct (cycle threshold) values that support use of rapid antigen tests. RT-PCR cycle threshold (Ct) refers to the number of cycles needed to amplify viral RNA to reach a detectable level. Ct levels are inversely proportional to the amount of target nucleic acid; the lower the Ct level the greater the amount of target nucleic acid in the sample.

⁷⁶ Quilty BJ, Clifford S, Hellewell J, Russell TW, Kucharski AJ, Flasche S, et al. Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. Lancet Public Heal. 2021 Jan 20 [https://doi.org/10.1016/S2468-2667\(20\)30308-X](https://doi.org/10.1016/S2468-2667(20)30308-X)

⁷⁷ Guglielmi G. Rapid coronavirus tests: a guide for the perplexed. Nature. 2021 Feb 11;590(7845):202–5. <https://doi.org/10.1038/d41586-021-00332-4>

Compared to other common respiratory viruses (such as flu), SARS-CoV-2 has much higher levels of virus. A SARS-CoV-2 viral load at an acute stage of infection generating a Ct of ≤ 15 is not uncommon. Therefore, if a sample collected later in the course of infection had a Ct of 26, although this result would have been regarded as a high viral load for other viruses, this may actually indicate a resolved SARS-CoV-2 infection, with no detectable SARS-CoV-2 antigen. Therefore, it is possible to get a positive PCR and a negative antigen test in a non-infectious individual even though the Ct may remain in the high 20's.

This concept is supported by clinical studies. In one study of upper respiratory samples positive by PCR for SARS-CoV-2, viable virus was isolated from 21/48 (43.8%) samples with a Ct value < 27.5 but only from 3/28 (10.7%) samples with a Ct > 27.5 .⁷⁸ Furthermore, in a study using the Abbott Panbio™ LFAT in 412 respiratory samples of whom 54 (13.1%) were PCR positive, sensitivity of the RADT was 93.5% in samples with a Ct ≤ 28 . Of the 11 'false negative' samples (PCR+ but LFAT-), all had Ct ≥ 26 and none had cultured viable virus.⁷⁹

Together these results suggest that rapid tests using LFATs with a high sensitivity cut off ($> 90\%$) for detecting cases of SARS-CoV-2 with RT-PCR Ct ≤ 27 will pick up the vast majority ($> 90\%$) of infectious SARS-CoV-2 cases.

In tests performed by the UK COVID-19 Lateral Flow Oversight Team⁸⁰ viral load and average Ct values were compared against four lateral flow kits. Results were depicted in a recent Nature commentary,⁸¹ see figure below. Antigen tests had similar sensitivity at high viral loads, but different sensitivities when viral loads were low.

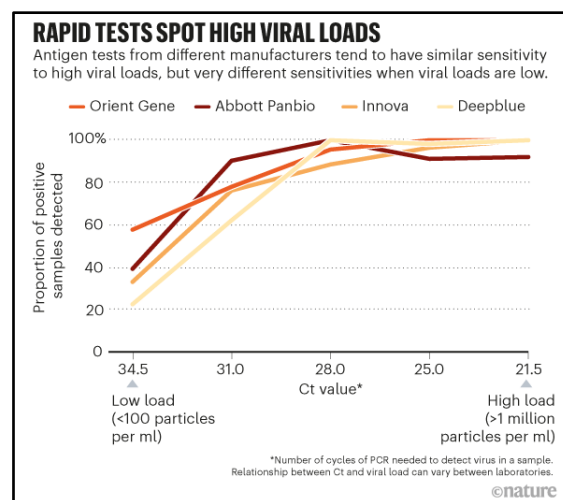


Figure 2: Adapted from Nature Review © Nature publishing

⁷⁸ Yamayoshi S, Sakai-Tagawa Y, Koga M, Akasaka O, Nakachi I, Koh H, et al. Comparison of Rapid Antigen Tests for COVID-19. *Viruses*. 2020 Dec 10;12(12). Available from: <https://pubmed.ncbi.nlm.nih.gov/33322035/>

⁷⁹ Albert E, Torres I, Bueno F, Huntley D, Molla E, Fernández-Fuentes MÁ, et al. Field evaluation of a rapid antigen test (Panbio™ COVID-19 Ag Rapid Test Device) for COVID-19 diagnosis in primary healthcare centres. *Clin Microbiol Infect* 2020 Nov 13 ;(2021):4–7. Available from: <https://doi.org/10.1016/j.cmi.2020.11.004>

⁸⁰ Peto T. COVID-19: Rapid Antigen detection for SARS-CoV-2 by lateral flow assay: a national systematic evaluation for mass-testing. *medRxiv*. 2021 Jan 15;2021.01.13.21249563. <https://doi.org/10.1101/2021.01.13.21249563>

⁸¹ Guglielmi G. Rapid coronavirus tests: a guide for the perplexed. *Nature*. 2021 Feb 11;590(7845):202–5. <https://doi.org/10.1038/d41586-021-00332-4>

8. Rapid Testing in Community Settings

In recent months large-scale pilot studies to validate rapid antigen tests in a range of real-world settings including asymptomatic individuals, are being conducted in many countries including but not limited to the UK, the US, Canada, Slovakia, Austria, Poland, Czech Republic, Germany, Spain and France.^{82,83}

The numbers of new COVID-19 cases in east Asia and the Pacific (<10 new cases per million per day in most countries) have been consistently below those of Northern America and Europe. The lower numbers of COVID-19 cases in these countries result from the implementation of comprehensive containment measures and widespread testing: border restrictions and other limits on movement; behavioural changes including widespread use of face masks and physical distancing; active surveillance by public health systems, including mass testing (using both PCR and rapid tests), backward tracing (to identify the sources of outbreaks), and forward tracing (to identify the contacts of new cases); and the quarantine of all suspected cases and the use of facility-based isolation of confirmed cases of COVID-19. As soon as the first case was reported, South Korea turned its focus toward preparing for large-scale testing incentivising development of new rapid tests combined with roll out of widespread PCR testing to detect cases.⁸⁴

In the first few months of 2021, a number of countries have gone further than conducting pilot studies for detection of asymptomatic infection and are employing rapid antigen tests in specific community settings or making them more widely available. Some examples are given below.

In March 2021, in Switzerland, the Swiss Federal Council announced that they plan to roll out widespread testing to improve the prevention and early detection of outbreaks with a focus on schools and companies. They plan to spend over €900 million in 2021 to accelerate a transition to a more normal society. They plan to use a mix of saliva-based PCR and rapid antigen pharmacy and home-tests, in different settings. Any detection of positives by the saliva PCR test or the antigen test would lead to a referral for a swab-based PCR test.⁸⁵

In January 2021, the Austrian Government, signalled that it would roll out SARS-CoV-2 tests for school pupils, as they re-open schools. These are voluntary tests, taken twice weekly by staff and students. Similar to the UK, parents are asked to test their younger children at home, while older students will be able to test themselves at school. In one week in February, Austrians conducted 3 million rapid tests, with half of those in schools and the other half in community settings and in companies.⁸⁶

In March 2021, the German Medical Devices Act, approved seven rapid antigen tests for home use, to be sold through supermarket chains and pharmacies.⁸⁷ The list of tests is to be monitored and updated over time. Rapid antigen test use will also be expanded at existing test sites. In some states, regular testing of students and staff is being implemented. All positive results are to be confirmed by PCR.

⁸² Crozier A, Rajan S, Buchan I, McKee M. Put to the test: use of rapid testing technologies for covid-19. *BMJ*. 2021 ;n208. Available from: <http://dx.doi.org/10.1136/bmj.n208>

⁸³ European Centre for Disease Prevention and Control. Options for the use of rapid antigen tests for COVID-19 in the EU/EEA and the UK Key messages. 2020. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/Options-use-of-rapid-antigen-tests-for-COVID19-19-11-2020.pdf>

⁸⁴ News Article; Reuters. March 2020. <https://www.reuters.com/article/us-health-coronavirus-testing-specialrep/special-report-how-korea-trowned-u-s-in-race-to-test-people-for-coronavirus-idUSKBN2153BW>

⁸⁵ <https://www.admin.ch/gov/en/start/documentation/media-releases/media-releases-federal-council.msg-id-82600.html>

⁸⁶ <https://medicalxpress.com/news/2021-02-austria-millions-covid-.html>

⁸⁷ German Federal Institute for Drugs and Medical Devices. March 2021; https://www.bfarm.de/EN/MedicalDevices/AntigenTests/_node.html

Since 1st March 2021, rapid antigen testing in the Czech Republic is mandatory for all companies with more than 50 employees and as of 16th March 2021, the Czech Government announced that this measure is to be extended to companies with more than 10 employees⁸⁸

A number of more detailed examples of testing programmes are also included below.

8.1 Rapid Antigen Testing in the UK

Towards the end of 2020, the UK Government began implementing rapid antigen testing pilots as part of its SARS-CoV-2 testing strategy. Rather than testing self-reported, symptomatic individuals, the pilots involve asymptomatic testing of defined groups; either through universal provision of accessible testing to a specific group or as a requirement before entering a particular setting.

Following evaluation, Public Health England selected the Innova Lateral Flow test for large scale pilot studies across the UK. Clinical evaluation of the Innova platform reported specificity of ~99% and varying sensitivity from ~58% to ~79% depending on the experience of the individual who took the sample and conducted the test.

In December 2020, interim results from the Liverpool in-field pilot were published.⁸⁹ A range of approaches and settings were evaluated including the use of military personnel to supervise self-swabbing (nose and throat) by asymptomatic individuals who presented at community test centres. In the majority of cases side-by-side comparison with PCR was conducted. The Innova lateral flow device sensitivity was low, at ~40% overall, but examination of PCR cycle threshold (a surrogate for viral load) indicated that two thirds of cases with higher viral loads (~Ct<25) were identified. The study authors concluded that the time and scale gained from a low-cost, no-lab test could serve as an additional Covid-19 control measure with targeted and clearly explained use. The study was criticised by those who considered that more targeted testing in-field settings should have been conducted prior to the mass-testing and large-scale procurement (c. £1billion) of the Innova platform.⁹⁰ This criticism has been rebuffed in a recent Lancet commentary highlighting the differences between PCR and lateral flow testing at different stages of the epidemic.⁹¹ Related pilots are ongoing across the UK in schools, universities, and care home settings. All field studies use self-swabbing to enable widespread use.⁹² Most recently, in February 2021, the UK government has encouraged cross-sectoral uptake of rapid antigen testing in both the public and private sector with test sites established for emergency workers including those in transport, policing, prisons, border control and retail and in its COVID-19 Response Spring 2021 report, it is stated that ~2.4M rapid tests are being conducted per week. This includes twice weekly testing for essential workers who cannot work from home, university students and staff and that the rapid testing regime will be expanded to include school staff, secondary students and households of primary school children.⁹³ In March 2021, the UK reported that 3,500 businesses were signed up to offer workplace testing programmes, and over 14,000 had

⁸⁸ News Article. March 2021. <https://www.dlapiper.com/en/czech/insights/publications/2021/03/zasadni-zmeny-v-povinnostech-zamestnavatele-v-souvislosti-s-pandemii-covid19/>

⁸⁹ University of Liverpool. Liverpool Covid-19 Community Testing Pilot: Interim Evaluation Report. 2020. https://www.liverpool.ac.uk/media/livacuk/coronavirus/Liverpool_Community_Testing_Pilot_Interim_Evaluation.pdf

⁹⁰ Deeks JJ, Raffle AE. Lateral flow tests cannot rule out SARS-CoV-2 infection. Vol. 371, The BMJ. BMJ Publishing Group; 2020. <http://dx.doi.org/10.1136/bmj.m4787>

⁹¹ Mina MJ, Peto TE, García-Fiñana M, Semple MG, Buchan IE. Clarifying the evidence on SARS-CoV-2 antigen rapid tests in public health responses to COVID-19. Lancet. 2021 Feb 17. [https://doi.org/10.1016/S0140-6736\(21\)00425-](https://doi.org/10.1016/S0140-6736(21)00425-)

⁹² Personal Communication, S. Hopkins, PHE February 2021 NHS Test and Trace, Innova Evaluation Update.

⁹³ UK Government. COVID-19 Response - Spring 2020:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963491/COVID-19_Response_-_Spring_2021.pdf1

registered interest. Recent data from the asymptomatic community testing demonstrated that LFATs were shown to have high specificity (99.9%) meaning that just one false positive test would be expected in every 1000 tests.⁹⁴

In March 2021, it was announced in Northern Ireland that asymptomatic testing would be rolled out in certain sectors including agri-food, essential retail, manufacturing and construction. It is envisaged that further settings will be considered at a later stage.⁹⁵

We comment further on rapid testing in the UK in the schools section below.

8.2 Rapid Antigen Testing in the US

Results from multiple US-based rapid antigen test pilot studies have been reported in recent months. Many of these have employed the Abbott BinaxNOW COVID-19 antigen card test, as the US federal government distributed 150 million of these tests across the country. (The BinaxNOW card includes an optional QR code which integrates with a mobile app). Similar overall trends were reported across several pilots where swabs were taken by trained operators, lab assistants or health care workers. In all cases anterior nasal swabs were employed. In one of these studies in Arizona,⁹⁶ the sensitivity of the BinaxNOW antigen test, when compared with PCR, was lower when used to test specimens from asymptomatic (35.8%) than from symptomatic (64.2%) individuals. Overall specificity was high. Sensitivity was however higher for culture-positive specimens (92.6% and 78.6% for those from symptomatic and asymptomatic persons, respectively), indicating that the test was effective at identifying high viral load cases; Overall false positives were low. The study authors concluded that community testing strategies focused on preventing transmission using antigen testing should consider serial testing in order to improve test sensitivity in detecting infection; In a similar study in Massachusetts⁹⁷ BinaxNOW resulted in 96.5% sensitivity and 100% specificity in adults within 7 days of symptoms, while sensitivity and specificity in asymptomatic adults were 70.2% and 99.6%, respectively. It was also noted that in all groups, BinaxNOW sensitivity followed Ct value distribution, with 95.8% sensitivity observed in all individuals with Ct < 30, concluding that false negative BinaxNOW results were largely confined to those least likely to transmit SARS-CoV-2.

BinaxNOW is the US-focused sister test to Panbio test. They use the same biologics but are in different formats: Panbio uses a small cassette whereas BinaxNOW is a card. BinaxNOW was authorised by the FDA but will not be released in Europe; likewise, Abbott will not be seeking FDA authorisation for Panbio, which has a CE mark.

8.3 Rapid Antigen Testing in Ireland

Currently in Ireland, use of rapid antigen testing is recommended in symptomatic individuals in hospitals as outlined in a comprehensive document and letter to HG CEOs on 29th January 2021.

⁹⁴ UK Government. Lateral flow device specificity in phase 4 (post marketing) surveillance; March 2021; https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/968095/lateral-flow-device-specificity-in-phase-4.pdf

⁹⁵ Department of Health, Northern Ireland, March 2021; <https://www.health-ni.gov.uk/news/workplace-covid-testing-key-sector-employers>

⁹⁶ Prince-Guerra JL, Almendares O, Nolen LD, Gunn JKL, Dale AP, Buono SA, *et al.* Evaluation of Abbott BinaxNOW Rapid Antigen Test for SARS-CoV-2 Infection at Two Community-Based Testing Sites — Pima County, Arizona, November 3–17, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70(3):100–5. <https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7003e3-H.pdf>

⁹⁷ Pollock NR, Jacobs JR, Tran K, Cranston A, Smith S, O’Kane C, *et al.* Performance and implementation evaluation of the Abbott BinaxNOW Rapid Antigen Test in a high-throughput drive-through community testing site in Massachusetts. *medRxiv*. 2021;preprint:2021.01.09.21249499. <https://doi.org/10.1101/2021.01.09.21249499>

Responsibility for the roll-out of rapid antigen testing within hospitals is currently left to the discretion of the hospitals, in line with the recommendations in the HSE guidance.⁹⁸ Currently there are no recommendations for use of rapid tests outside hospital settings, although LFATs may be used as directed by Public Health in the early identification of and wider testing in outbreaks. Validation pilot studies have also been conducted in several settings including food processing plants. The reports from these validation studies should inform future use of LFATs.

8.4 Widespread pilot molecular community testing in Irish Universities

Trinity College Dublin has established the Trini-Screen,⁹⁹ a SARS-CoV-2 screening programme developed by Prof Orla Sheils at Trinity Translational Medicine Institute, supported by the COVID-19 Research Hub headed by Prof Kingston Mills and Prof Aideen Long and funded by Science Foundation Ireland. The programme, which started in September 2020, uses the LAMP assay on saliva samples. The screening was initially aimed at students in halls of residence and was then made available to staff, first in Estate and Facilities and research institutes, including Trinity Biomedical Science Institute, Trinity Translational Medicine Institute and Trinity College Institute of Neuroscience. An early problem with low pH of saliva, which resulted in false positives in the colorimetric readout, was resolved by buffering the samples prior to testing. Around 5% of saliva samples are not usable because of the quality of the samples. All positive tests are referred to the testing centre in the TCD health centre for confirmation by PCR using a nasopharyngeal swab (NPS) sample. For validation purposes, saliva collected from patients with confirmed SARS-CoV-2 have been processed and have yielded 95% concordance with LAMP. Poor sample quality (sputum rather than saliva) was the main contributing factor in discordant paired samples. The LAMP assay is performed in less than 30 minutes, does not require RNA extraction, requires basic commercially available reagents and the only equipment required is an oven or heat block.

NUI Galway have established the Science Foundation Ireland funded SalivaScreen¹⁰⁰ programme headed by Prof Charles Spillane, Genetics & Biotechnology Lab, Ryan Institute that involves a collaboration with HSE West (Dr. Breda Smyth), where they are using saliva samples and a qRT-PCR protocol that does not require RNA extraction. They are testing matched saliva and NPS samples collected from the HSE testing centres on NUI Galway and at Galway airport. They currently have a 99.4% correspondence rate between saliva and NPS test results based on the 168 matched samples screened to date. They have concluded that saliva is as good as NPS for SARS-CoV-2 testing, and superior for any serial testing. When combined with qRT-PCR without RNA extraction is quicker and cheaper to perform. They have also carried out serial screening of asymptomatic cohorts using saliva from volunteers in NUI Galway research buildings and the workforce of a manufacturing company in Galway twice each week since December and are currently extending their serial screening to households with infected members in Galway city. They have also developed protocols for scaling saliva-screening based on pooling and deconvolution strategies that work well for scaling numbers for surveillance screening, serial-screening or mass-testing. Working closely with the HSE, they have integrated their SalivaScreen system with HSE swab collection and testing systems (including sample labelling, text notifications, etc). Any saliva samples that test positive in the SalivaScreen assay and which have not been tested by swab testing by HSE, are referred to HSE for further confirmation by PCR using a NPS sample. Any saliva samples testing positive but testing negative by HSE NPS testing, are re-tested by the SalivaScreen PCR assay and if positive, the HSE offers a repeat swab test to the individual. In summary, they have developed a robust saliva screening platform with HSE compatible workflows and systems for surveillance and serial-screening that has an estimated specificity of 100%.

⁹⁸ HPSC [Interim guidance on the use of Antigen Detection Tests \(ADTs\) in the public health system in Ireland](#) January 2021

⁹⁹ Trinity College Dublin. Trini-Screen Covid - Screening of Staff and Students for SARS-CoV-2 in Trinity College Dublin. <https://www.tcd.ie/ttmi/triniscreen/>

¹⁰⁰ Saliva Screen – 2020, Ireland. <https://salivascreen.org/>

They are using PCR to screen for variants and are sequencing SARS-CoV-2 strains from the positive samples and are also working on investigation of CRISPR-based tests for SARS-CoV-2.

UCC (Profs John MacSharry and Liam Fanning) have established RT-PCR assay for SARS-CoV-2 based on saliva samples from COVID-19 patients at Cork University Hospital. They are using a DNA Genotek preservative and extracting RNA prior to analysis. The assay works well and in they are in the process of comparing saliva and NPS samples. It is now being employed to screen students at UCC. They have trialled some POC antigen screening kits but found them only to detect high viral levels above 10,000 virus particles. They have also screened wastewater / sewage around Munster and have detected SARS-CoV-2 in samples which, considering the dilution factor, could be a useful community marker. They have developed a RT-PCR assay and sequenced UK (B1.1.7) variant.

The National Virus Reference Lab (NVRL) has done some analysis of NPS versus matched saliva samples (chemically inactivated) and anterior nasal swabs, using extracted RNA and then tested the RNA by qRT-PCR. They recently completed a comparison of >1900 community acquired samples where they found 134 positive samples by PCR using NPS samples. At low Ct values (<21), there seemed to be relatively good agreement with saliva samples (circa 75%), but this fell off at higher Ct values, with PCR from saliva failing to detect NPS-determined positives in about 50% of cases for Ct values 21-30 and 25% for Ct values ≥ 31 . Better correlations were observed between NPS and nasal swab samples, but sensitivity was reduced at high Ct values. The nasal swabs were comparable to NPS swabs up to a Ct of 30 with 84/87 (97%) of results in agreement. However weaker samples, (Ct ≥ 31) were only detected in 13/27 (48%) of samples tested. The specificity of saliva-derived data was good (with no false positives detected in a negative panel). A caveat of this study is that the exact same PCR assay was not performed on saliva-derived samples and NPS/nasal swab-derived samples. The general conclusion was that the sensitivity (in comparison to NPS standard) was higher from nasal swabs compared with saliva.

Conclusions

Collectively the work in different Irish Universities indicates that saliva is a suitable sample for SARS-CoV-2 screening or testing. It can be used in RT-PCR or LAMP assays without RNA extraction and is therefore quicker and more person friendly and likely to result in higher compliance for volunteer screening. This is supported by recent work of Turner *et al*¹⁰¹ who reported that saliva is likely a superior sample for testing and screening.

It is important to note that we are not suggesting that saliva should replace NPS as a routine diagnostic of SARS-CoV-2. Processing saliva in the laboratory can be time consuming and would not be a suitable sample type for a high throughput laboratories particularly those using liquid handlers. However, anterior nasal swabs, although less sensitive than NPS at Ct <30, could be a pragmatic and less invasive alternative to NPS for diagnostic testing as well as screening. Unlike NPS, saliva or anterior swabbing do not require swabbing centres or trained individuals to take the samples and even if they result in some loss of sensitivity, they will pick up positive cases that otherwise would not be identified, mostly in asymptomatic individuals.

¹⁰¹ Turner F, VandenBerg A, Slepnev VI, Car S, Starritt RE, Seger M V, *et al*. Post-disease divergence in SARS-CoV-2 RNA detection between nasopharyngeal, anterior nares and saliva/oral fluid specimens - significant implications for policy & public health. medRxiv. 2021 Jan 26; preprint:2021.01.26.21250523. <https://doi.org/10.1101/2021.01.26.21250523>

9. Settings where Ireland should prioritise rapid testing

“Real-world” evaluation of rapid tests in asymptomatic individuals outside of a healthcare setting is essential. There is much to learn about the deployment- logistics, reporting, acceptance, compliance, training, accuracy, utility of rapid testing and of the behavioural changes which may occur with either a positive or negative result and a false positive or false negative result. Large-scale pilots could be deployed as an opportunity to learn and improve the design of the testing programme. Continuous learning and interaction will be key to any programme. In addition to deploying rapid antigen testing in specific scenarios for Health Care Workers, the HSE and DAFM have recently undertaken a serial testing programme for the deployment of rapid antigen tests as a means of further enhancing risk mitigation for COVID-19 in the workplace in meat processing plants.

The overall aim of any programme should be to support a safe, sustainable reopening of society and the economy. Many experts advocate for widespread rapid testing with this intended goal.^{102, 103} Rapid proactive testing should be aimed at identifying asymptomatic individuals before they transmit infection to others. For all symptomatic individuals or those considered close contacts, PCR testing is the test of choice assuming that this testing is easily accessible and not at capacity, as per current Public Health guidelines.

Rapid testing policies focus on Test to protect; Test to release; Test to enable, Test to contain. Internationally, use of rapid testing varies from mass testing in cities or countries; where PCR capacity is limited; cluster/outbreak response; travel; targeted higher risk settings or “semi-closed” populations. Community settings such as nursing homes and other long term care facilities, schools, universities, sports clubs, small and large private and public office workplaces, food processing plants, manufacturing facilities, prisons and shelters, should be considered.

Logistically, widespread testing in large communities such as countries, cities and towns is challenging however there are learnings from pilot studies that have been conducted both in Ireland and internationally. Targeted (as opposed to mass) screening yields higher positivity rates, is more cost effective than mass-screening and may help block transmission in specific settings, including high-risk congregate settings. Locally driven initiatives using community networks such as Universities have been important at ensuring buy-in, accurate information and seeing real life benefit.

Programmes need to be designed together with leaders in the particular setting in which they are to be used. The purpose of rapid testing in targeted populations needs to be clearly defined. Strategies for additional proactive testing to detect asymptomatic infections and prevent spread can range from testing of individuals who are at high risk of being exposed, activities that are important to society and the economy such as education, processing plants, sports and businesses. For many of these settings, rapid testing would provide the opportunity of introducing an additional tool to support Health and Safety in a setting where testing for case detection is not normally done. Thus, there are many ‘use cases’ for tests for the presence of the virus. Specification of a ‘use case’ will include at least: a description of who will be tested, the decisions that test results influence and the motivating goal of the test programme.

Testing in “semi-closed” settings is more effective when done frequently, with the level of frequency dependent on the setting, the rates in the community at a given time and capacity of a contact tracing

¹⁰² Expert Letter for Thesis. <https://www.rapidtests.org/expert-letter>

¹⁰³ Johnson-León M, Caplan AL, Kenny L, Buchan I, Fesi L, Olhava P, *et al*. Executive summary: It’s wrong not to test: The case for universal, frequent rapid COVID-19 testing. *EClinicalMedicine*. 2021 Feb;0(0):100759. <https://doi.org/10.1016/j.eclinm.2021.100759>

programme. Proactive testing of higher exposure individuals can be employed to identify asymptomatic infectiousness and prevent spread in conjunction with all other public health measures.

9.1 Supporting long-term residential care facility visits

The current testing strategy in long-term residential care facilities (LTRCFs) is limited to residents and staff. Visitation to care homes by family and friends has been severely curtailed during the pandemic and offering testing of visitors needs to be considered. Public health interventions including vaccination of residents and infrequent controlled visits are strategies to improve protection of residents. However, the inability to have human contact with family and friends has an impact on the health & wellbeing and quality of life of residents especially during level 3 plus restrictions.

The use of rapid testing for a family member or friend of a resident combined with infection prevention and control measures could support meaningful indoor visits. This is used as an additional protection strategy. The rapid test can be administered at LTRCF before a visit. The UK and Germany are using rapid testing to this end.^{104, 105, 106} In discussion with PHE, it was stated that testing of staff in care homes has been detecting 2,000-3,000 cases per week with rapid testing using LFAT (pre-vaccine roll-out). The use of the tests on visitors is at the discretion of the facility. Although vaccine roll-out is underway, a cautious approach would need to be taken before complete lifting of restrictions given the risk of immunosenescence¹⁰⁷ in older adults which would need to be factored, whilst more data on vaccine efficacy is accumulated.

9.2 Supporting the re-opening of Higher Education Institutions

Serial and reliable testing to break chains of transmission is key in the strategy to mitigate the spread of SARS-CoV-2. Settings of large gatherings especially indoors, communal living, commuting and close contact, are associated with risk of spread. Universities constitute such an environment with faculty, staff and students. A recent SAGE report from the UK¹⁰⁸ highlights the risk of spreading in asymptomatic students living in Halls of Residence. It also highlights the detrimental effect on education and mental health of students being unable to study on campus. The safe return of students to colleges especially those living in residential settings requires an effective monitoring strategy. A specific screening test that can be administered frequently and reports quickly may allow early case detection of infectiousness thereby blunting infection. This would be an additional tool to all our Public Health measures in place in the University setting that could allow the safe return of students to campus.

Because universities have laboratory infrastructure on campus and availability of trained staff, they have been an ideal setting for testing hubs for their students and staff. As summarised previously,

¹⁰⁴ Health Protection Scotland. Coronavirus (COVID-19): adult care home visitor testing guidance. 2020.

<https://www.gov.scot/publications/coronavirus-covid-19-adult-care-home-visitor-testing-guidance/>

¹⁰⁵ UK Government. Care home LFD testing of visitor's guidance. <https://www.gov.uk/government/publications/coronavirus-covid-19-lateral-flow-testing-of-visitors-in-care-homes/care-home-lfd-testing-of-visitors-guidance>

¹⁰⁶ Robert Koch Institut. RKI - Coronavirus SARS-CoV-2 - Nationale Teststrategie – wer wird in Deutschland auf das Vorliegen einer SARS-CoV-2 Infektion getestet?. 2020. https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Teststrategie/Nat-Teststrat.html

¹⁰⁷ British Society for Immunology. The ageing immune system and COVID-19. 2020; (November).

https://www.immunology.org/sites/default/files/BSI_Ageing_COVID-19_Report_Nov2020_FINAL.pdf

¹⁰⁸ UK SAGE Children's Task and finish Group: Paper on Higher Education Settings

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963387/S1103_Children_s_Task_and_finish_Group_Paper_on_Higher_Education_Settings_.pdf

several universities (including but not limited to TCD, NUIG and UCC) in Ireland are actively involved in the national COVID-19 effort for containing the spread of infection; testing hubs, contact tracing facilities, student and faculty testing and tracing initiatives. These universities are rolling out on-site molecular testing for varying reasons: containment of outbreaks, surveillance with early warning signals to prevent clusters, and identifying asymptomatic infection. The university infrastructure has been adapted to provide this service and could be adapted further to conduct rapid testing for both staff and students, but also for local businesses and community. This would offer valuable side-by-side comparison data. Similar efforts are underway internationally with examples including the University of Cambridge, UK,¹⁰⁹ where residential students are tested in pods. Another example is the University of Davis, US¹¹⁰ where testing has been extended to asymptomatic residents of Davis in cooperation with the City of Davis and with local businesses through the Healthy Davis initiative.¹¹¹

Internationally, there are numerous studies which have been conducted using rapid antigen tests in higher education settings. Some examples include the University of Utah,¹¹² where students took their own nasal swabs while trained non-medical operators supervised them. In Belgium,¹¹³ based on current evidence, a relatively higher increase in incidence was observed in 20–29-year-olds and was believed to be related to the re-opening of higher education institutions. There is scientific evidence, both from mathematical models and real-life experiences, that strategies of screening university students can be effective in reducing transmission and prevent outbreaks.

9.3 Supporting the Re-opening of Businesses

The pandemic has resulted in unprecedented disruption to workplaces across Ireland. Organisations such as IBEC have responded by providing frameworks and guidance for companies to assist them in managing home working, continuity of essential services, development of revised Health and Safety guidelines and COVID-19 Rapid Response Plans.

As part of this review, the Chair of the group consulted with both the IDA and Enterprise Ireland. There was strong support for the implementation of programmes to test the feasibility and impact of rapid testing. It was agreed that positioning any such testing strategy as an added Health and Safety measure was appropriate. It would be important (as for in all other settings) that rapid testing on site initially, moving to home-testing (for LFATs), would be delineated from the current clinical diagnostic tests. In addition to public health measures, rapid testing would provide further risk-reduction to employees and customers.

Given the increasing availability of rapid antigen tests on the market, it is likely that companies will seek to establish tests even in the absence of Government programmes. Therefore, the establishment of a group to provide advice on appropriate validated tests and to monitor for improvements would be beneficial. This group would provide setting-specific guidance and information on training and education, health and safety guidelines and an operational framework.

¹⁰⁹ University of Cambridge. Asymptomatic COVID-19 screening programme. <https://www.cam.ac.uk/coronavirus/stay-safe-cambridge-uni/asymptomatic-covid-19-screening-programme>

¹¹⁰ University of California. COVID-19 Testing <https://campusready.ucdavis.edu/testing-response/covid19-screening>

¹¹¹ Healthy Davis Together. COVID-19 Testing, Davis, CA. <https://healthydavistgether.org/testing/>

¹¹² Okoye NC, Barker AP, Curtis K, Orlandi RR, Snavely EA, Wright C, *et al.* Performance Characteristics of BinaxNOW COVID-19 Antigen Card for Screening Asymptomatic Individuals in a University Setting. *J Clin Microbiol* 2021;(May):1–20. <https://doi.org/10.1128/JCM.03282-20>

¹¹³ Sciensano. Recommandations sur le dépistage périodique dans des populations spécifiques. https://covid-19.sciensano.be/sites/default/files/Covid19/20210204_RAG_Advice_Testing_répété_dans_certaines_populations_FR.pdf

In the UK, PHE have run a number of pilots with many businesses including a large-scale study with John Lewis.¹¹⁴ Up to 1,000 Partners and temporary agency staff volunteered to be tested up to three-times a week. Larger companies could deploy LFATs but could also easily establish centralised LAMP-based testing.

9.4 Example of current testing approach – Combilift

Combilift¹¹⁵ employs ~650 employees in Ireland at its manufacturing site in Co. Monaghan. In January 2021, the company introduced weekly SARS-CoV-2 testing for all employees. given increases in case numbers. They opted for a saliva-based PCR test, conducted by Healthwatch.¹¹⁶ Saliva samples are collected under supervision on site on a Monday morning and results are communicated with a text message the next day. Positive cases are required to isolate and are directed to the HSE for a confirmatory test, although on occasion it has been problematic to get a GP referral in the absence of symptoms. They identified five positive tests (all asymptomatic) in January and all were confirmed following HSE testing. During January, the company was also able to provide testing for close contacts, including non-employees. Testing is not mandatory but is recommended and they have been conducting ~600 tests per week. The company is also closely monitoring any employees who are required to travel abroad for essential work. Overall, the company considers that the testing approach has provided reassurance for employees who they stated were nervous about presenting for work, and has been important for manufacturing continuity. They opted for the saliva-based testing as were concerned that NP sampling would be less conducive to serial testing. They advised that although the current approach is working well, that immediate rapid results would be optimal and beneficial and they would be amenable to setting up testing on site, such as would be required for LAMP testing or rapid antigen testing with anterior nasal sampling. They also advised that it would be helpful to have guidance in place to inform companies and suggested that this could be communicated via industry sector groups.

9.5 Supporting the Re-opening of High-Risk employment situations

Outbreaks of COVID-19 in meat processing plants (MPPs) have occurred throughout the pandemic in Ireland and internationally, presenting threats to wider society. This has been linked to the unique working conditions, although research to understand this more completely is ongoing. The US Centre for Disease Control reported on outbreaks in MPPs which had occurred in 19 states by May 2020.¹¹⁷ In Ireland, clusters of COVID-19 were investigated in 22 MPPs in which more than 1000 workers tested

¹¹⁴ John Lewis Partnership becomes one of the first UK businesses to roll out NHS test and trace rapid covid-19 testing. <https://www.johnlewispartnership.co.uk/media/press/y2020/jlp-becomes-one-of-the-first-uk-businesses-to-roll-out-nhs-test-and-trace-rapid-covid-19-testing.html>

¹¹⁵ <https://combilift.com/>

¹¹⁶ <https://healthwatch.ie/>

¹¹⁷ Dyal JW, Grant MP, Broadwater K, Bjork A, Waltenburg MA, Gibbins JD, *et al.* COVID-19 Among Workers in Meat and Poultry Processing Facilities — 19 States, April 2020. MMWR Morb Mortal Wkly Rep. 2020 May 8;69(18). http://www.cdc.gov/mmwr/volumes/69/wr/mm6918e3.htm?s_cid=mm6918e3_w

PCR positive.¹¹⁸ A major outbreak in a German MPP resulted in more than 1,400 of 6,289 employees becoming infected.¹¹⁹

Through its COVID-19 Rapid Response Call, SFI has funded a large-scale research project (led by Prof Grace Mulcahy in UCD) which aims to understand and prevent outbreaks in MPPs and similar food production facilities. In addition to evaluating testing, they are studying environmental conditions and behavioural aspects.

The Department of Agriculture, Food and the Marine (DAFM), in collaboration with the HSE, has recently conducted a large scale (>5000 asymptomatic individuals) validation study in MPPs using rapid antigen tests. In asymptomatic individuals, the sensitivity of the test using nasal swabs was 51.9% when compared with nasopharyngeal swabs analysed by PCR. When analysed by PCR cycle threshold, sensitivity was 80% for Ct ≤25, and sensitivity of 69% for Ct≤30, demonstrating greater sensitivity for higher viral loads. Notably this was a single point in time LFAT. Serial testing at least twice weekly, done days apart, has the potential for increasing the sensitivity of the test in asymptomatic workers. The HSE has recommended further studies to evaluate the potential impact of serial testing to further improve this testing strategy.

9.6 Example of current testing approach – Kerry Group

The Kerry Group¹²⁰ employs ~5000 people across 13 factory sites and 2 commercial offices in Ireland and the UK, and employs ~26,000 people globally. As part of its Covid-19 response plan, the company has implemented a number of stringent control measures across all of its national and international sites to ensure the safety and wellbeing of its employees and to keep the business open. These include hand-sanitisation, wearing of masks, physical distancing on the factory floor as well as guidance for employees when they have COVID-19 symptoms and/or are identified as close contacts. The company has taken the approach of evolving controls for evolving challenges and in late 2020, they also integrated SARS-CoV-2 testing into their control measures, to keep staff safe. PCR testing was implemented initially in a number of sites in Ireland in conjunction with the HSE East. All staff were tested on a monthly basis, or since January 2021, on a weekly basis. The company has also implemented rapid lateral flow antigen testing (using the Innova platform) for a number of high-risk groups. These groups encompass those individuals who are new to the site, including agency and contract staff as well as employees who are returning following long periods of leave. The company has set up test sites on the grounds of the factory and tests are administered by trained operators. Only individuals with a negative rapid antigen test are permitted on site.

This combined PCR and targeted rapid testing strategy, considered as a risk management tool, has, according to the company, provided reassurance for both employees and their families and has served to validate that their control measures are working well. The learnings from the pilots, including the need for appropriate guidance and education, that have been conducted in Ireland are now being used to inform approaches being taken across all national and international sites.

¹¹⁸ National Outbreak Control Team. Investigation into a Series of Outbreaks of COVID-19 in Meat Processing Plants in Ireland, 2020 <https://assets.gov.ie/95603/8c23ae9c-9a30-4c01-9ebf-f624f2c99702.pdf>

¹¹⁹ Guenther T, Czech-Sioli M, Indenbirken D, Robitailles A, Tenhaken P, Exner M, *et al.* Investigation of a superspreading event preceding the largest meat processing plant-related SARS-Coronavirus 2 outbreak in Germany. SSRN Electron J. 2020 Jul; <http://dx.doi.org/10.2139/ssrn.3654517>

¹²⁰ <https://www.kerrygroup.com/our-company/our-response-to-covid-19/>

9.7 Rapid Testing in Schools

Schools are institutions that should be the last to close and the first to open. Schools play an essential role in providing not just education but in identifying a wide-range of social, emotional, physical, developmental, and mental health needs whilst helping children to access appropriate supports.

Data from the UK^{121,122} suggest that transmission can occur in schools but not at a high level and mainly from staff. However, in European countries, e.g. Belgium, where schools have remained open whilst the B.1.1.7 variant first described in the UK was increasing, outbreaks in schools, including primary schools increased beyond levels previously seen with the wild-type virus and such outbreaks were almost exclusively with the B.1.1.7 variant.

Every available tool needs to be considered to safely and sustainably open schools. Non-pharmaceutical interventions, self-screening for symptoms, mask wearing, staggering of schedules and cohorting students into pods have been effective strategies. A correspondence in the *Lancet* emphasises the need for ongoing robust multi-layered mitigation measures in schools with risk of variants and concerns relating to long COVID symptoms in children¹²³. In the UK rapid testing pilots, the testing served also to provide reassurance to concerned teaching staff, students and parents. The use of rapid testing as an additional tool to protect students and staff is being considered in some countries. In the UK mass testing of staff, students and their families on return from restrictions, and twice weekly thereafter, is being implemented to detect individuals who are asymptomatic or presymptomatic thereby preventing onward transmission. Commentary on the planned rollout highlighted that implementation should happen with rigorous evaluation of the impact of rapid testing.¹²⁴ In the US, the Rockefeller Foundation have published a number of comprehensive reports providing guidance for the design and implementation of effective testing strategies in community settings, with a key focus on re-opening schools.^{125,126} These reports outline the essential elements that testing strategies should consider including adequate risk assessment, a testing regimen that factors the sensitivity of the test and the time taken to generate results, clear communication. The report describes how conducting tests of varying levels of sensitivity – for example, rapid PCR testing, LAMP testing, and antigen testing – can each yield similar reductions in the overall rate of transmission when these tests are performed frequently and with rapid turnaround times (see also Larremore *et al.*)¹²⁷. The authors also recommend the use of pilots to test the feasibility and impact of such testing, and to build best practice implementation guides in specific settings, to allow rapid scaling if these approaches prove effective. In France, which has kept its schools open throughout a surge in cases this Autumn and Winter, rolled out at least 200,000 weekly saliva PCR tests in junior schools after the February break in an effort to continue to keep schools open.

¹²¹ Flasche S, Edmunds WJ. The role of schools and school-aged children in SARS-CoV-2 transmission [Internet]. Vol. 21, *The Lancet Infectious Diseases*. Lancet Publishing Group; 2020. p. 298–9. <https://doi.org/10.1016/S1473-0>

¹²² Ismail SA, Saliba V, Lopez Bernal J, Ramsay ME, Ladhani SN. SARS-CoV-2 infection and transmission in educational settings: a prospective, cross-sectional analysis of infection clusters and outbreaks in England. *Lancet Infect Dis*. 2020;21(3):344. [https://doi.org/10.1016/S1473-3099\(20\)30882-3](https://doi.org/10.1016/S1473-3099(20)30882-3)

¹²³ Gurdasani D *et al.* School reopening without robust COVID-19 mitigation risks accelerating the pandemic. March, 2021, *The Lancet*. [https://doi.org/10.1016/S0140-6736\(21\)00622-X](https://doi.org/10.1016/S0140-6736(21)00622-X)

¹²⁴ Deeks J, Raffle A, Gill M. Covid-19: government must urgently rethink lateral flow test roll out. *BMJ*. 2021; <https://blogs.bmj.com/bmj/2021/01/12/covid-19-government-must-urgently-rethink-lateral-flow-test-roll-out/>

¹²⁵ Caitlin Rivers A, Silcox C, Associate M, Potter C, Franklin M, Ray R, *et al.* Risk Assessment and Testing Protocols for Reducing SARS-CoV-2 Transmission in K-12 Schools Funded by Risk Assessment and Testing Protocols for Reducing SARS-CoV-2 Transmission in K-12 Schools. https://www.rockefellerfoundation.org/wp-content/uploads/2020/10/Risk-Assessment-and-Testing-Protocols-for-Reducing-SARS-CoV-2-Transmission-in-K-12-Schools_Final-10-14-2020.pdf

¹²⁶ Silcox C, Anderson D, Zavodszky A, Borre E, Dentzer S, Aspinall MG, *et al.* A National Decision Point: Effective Testing and Screening for Covid-19. <https://www.rockefellerfoundation.org/wp-content/uploads/2020/09/A-National-Decision-Point-Effective-Testing-Screening-for-Covid-19-Full-Report.pdf>

¹²⁷ Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, *et al.* Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening. *Sci Adv*. 2021 Jan 1;7(1):1–11. <https://doi.org/10.1101/2020.06.22.20136309>

The CDC¹²⁸ has provided guidance on the use of rapid testing in schools, highlighting that the decision to implement testing in schools should be guided by what is feasible, practical, and acceptable. If antigen testing is used, it should be tailored to each community's needs including where public health officials are recommending expanded testing on a voluntary basis, including testing of a sample of asymptomatic individuals, especially in areas of moderate to high community transmission or as part of a cohort for whom testing is recommended (e.g., in the context of an outbreak).

In the UK, all secondary students and staff are being given the option of testing with LFAT, and this has identified clusters of students, sometimes arising from social interactions outside of school. Students will first be tested (and trained) at community test centres and in school, after which they will self-test at home, although in-school testing will remain available at all times. For primary schools, a different test strategy is being taken, in that households with primary school children are being offered home tests to detect cases in the whole household, leaving parents/guardians with the opportunity to test family members and care givers within their 'bubbles' regularly. Lower-risk contacts in schools, could also be tested daily with LFATs such that children could come to school every day if they had a negative test. This approach was not employed when prevalence was low as it was not considered essential. The UK Government recently announced in its Spring 2021 COVID-19 response plan, that all secondary school students will be offered twice weekly testing from March 2021.¹²⁹

In Northern Ireland, the Queens University of Belfast is providing weekly testing of pupils and staff in special schools using saliva sampling and the direct LAMP test platform.¹³⁰

In Belgium, a review was conducted,¹³¹ to consider the use of serial testing in certain settings. The report highlighted the need to take into account socio-economic, feasibility and acceptability as part of the decision-making and planning. They are planning pilots to examine this and plan to employ saliva / PCR-based tests of school staff in the first instance. Also, in Belgium, where increased outbreaks in schools have been associated predominantly with the more rapidly spreading UK variant (B.1.1.7), LFATs have been used successfully to screen low risk contacts, e.g., the entire class or school twice weekly to reassure parents and staff and to prevent the unnecessary closure of entire schools.

An asymptomatic screening study in Switzerland in school children and teachers concluded that unrecognised virus spread within the schools was relatively low, due to the effectiveness of measures already in place¹³² further demonstrating the need for pilots to measure the impact, and for testing strategies to be agile and capable of balancing factors such as rates of viral spread and threats of variants etc. In Germany, as part of the Safe School Hesse programme, teachers conducted home-tests every 48 hours, following instruction on how to conduct the tests. The authors of this study concluded that as the prevalence was very low, that the testing may be most beneficial when applied during high local incidence or local outbreaks.¹³³

¹²⁸ CDC. Interim Considerations for Testing for K-12 School Administrators and Public Health Officials. 2020
<https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/k-12-testing.html>

¹²⁹UK Government. COVID-19 Response – Spring 2021.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963491/COVID-19_Response_-_Spring_2021.pdf

¹³⁰ <https://www.qub.ac.uk/News/Allnews/QueensplayingkeyroleinweeklyCovid-19testingforspecialschools.html>

¹³¹ Sciensano. Recommandations sur le dépistage périodique dans des populations spécifiques. https://covid-19.sciensano.be/sites/default/files/Covid19/20210204_RAG_Advice_Testing_répété_dans_certaines_populations_FR.pdf

¹³² Kriemler S, Ulyte A, Ammann P, Peralta GP, Berger C, Puhan MA, *et al.* Surveillance of acute SARS-CoV-2 infections in school children and point-prevalence during a time of high community transmission in Switzerland. medRxiv. 2020 Dec;2020.12.24.20248558.
<https://doi.org/10.1101/2020.12.24.20248558>

¹³³ Hoehl S, Schenk B, Rudych O, Göttig S, Foppa I, Kohmer N, *et al.* At-home self-testing of teachers with a SARS-CoV-2 rapid antigen test to reduce potential transmissions in schools. medRxiv. 2020 Dec 7;2020.12.04.20243410. <https://doi.org/10.1101/2020.12.04.20243410>

To date, there is no testing strategy regarding screening in schools in Ireland - in part because of the variable prevalence at a given time, potential constraints on testing and trace capacity, cost and logistics. Factors such as availability of tests, logistics and student/parent/staff buy-in are key considerations of a testing strategy in this setting. Defining the goals, i.e., 'use cases' of rapid testing in schools will be important in designing appropriate implementation programmes. Goals should include: limiting the contribution that interactions at school make to community transmission, and / or keeping teachers safe from infection, and / or keeping pupils safe from infection, and / or monitoring the effectiveness of local public health control measures, and / or providing reassurance to staff, pupils and their parents. Rapid testing should only be done in conjunction with all other available mitigation strategies as outlined above.

9.8 Supporting Sporting Activities

The pandemic has had a significant impact on the conduct of sports, affecting both competitive sports leagues and tournaments and recreational sports for all ages in Ireland. COVID-19 has posed challenges to both national and international sporting events as well as to individual physical activity and well-being (both players and spectators). With the closure of gyms, stadia, pools, dance and fitness studios and the cessation of many non-professional team sports, many individuals are struggling to keep active. Taken together with the closure of schools, this has further impacted on younger generations. There are also adverse economic impacts. The UN has highlighted these concerns and the importance of re-starting sporting events as soon as it is safe to do so, given the considerable effects on physical and well-being.¹³⁴

In the Netherlands, the Royal Netherlands Football Association (KNVB),¹³⁵ conducted longitudinal serial testing in more than 800 asymptomatic football players to allow them to play. Nasopharyngeal swabs were taken by the league's physicians and tested using the Abbott Panbio Rapid Test. Sensitivity in asymptomatic players was ~69%. The rapid tests identified 11 of 12 pre-symptomatic infections and 29 of 32 early infections. The rapid tests failed to identify 14 of 21 PCR positives, all had high Cts, indicating low viral load. A similar parallel comparison of PCR and LFAT is currently ongoing within the Irish national and regional rugby teams (across the island) involving players and support staff as part of the 'CARAT Study'; a collaboration between the IRFU and University College Dublin.

In a large-scale study in the US involving 24 universities, PCR testing was used as a means of releasing college athletes from quarantine sooner than 14 days following contact using a serial testing strategy.¹³⁶ The US National Football League (NFL) are employing ongoing monitoring of players and essential staff using PCR, rapid antigen and antibody tests¹³⁷ in order to keep sporting activities safe.

¹³⁴ UN. The Impact of COVID-19 on Sport, physical Activity and Well-Being and Its Effects on Social Development. Vol. 1, Policy Brief No 73. 2020. https://www.un.org/development/desa/dspd/wp-content/uploads/sites/22/2020/05/PB_73.pdf

¹³⁵ Winkel BMF, Schram E, Gremmels H, Debast SB, Schuurman R, Wensing AMJ, *et al.* Screening for SARS-CoV-2 infection in asymptomatic individuals using the Panbio™ COVID-19 Antigen Rapid Test (Abbott) compared to RT-qPCR. medRxiv 2020.12.03.20243311. <https://doi.org/10.1101/2020.12.03.20243311>

¹³⁶ Atherstone C, Peterson ML, Malone M, Honein MA, MacNeil A, O'Neal CS, *et al.* Time from Start of Quarantine to SARS-CoV-2 Positive Test Among Quarantined College and University Athletes — 17 States, June–October 2020. Vol. 70, MMWR. Morbidity and Mortality Weekly Report. 2021. <https://stacks.cdc.gov/view/cdc/99431>

¹³⁷ NFL-NFLPA COVID-19 testing & treatment protocols fact sheet. <https://www.nfl.com/playerhealthandsafety/resources/fact-sheets/nfl-nflpa-covid-19-testing-treatment-protocols-fact-sheet>

10. To suggest how Ireland could implement any recommendations

10.1 Start Immediately

It is very important to initiate rapid testing programmes now. The urgency to facilitate a safe, sustainable reopening of society and the economy is obvious. Importantly, with the roll out of vaccination we are moving from a virus pandemic to an endemic. The virus is not going away – if given the opportunity, it will infect susceptible people, new variants with a transmission or other advantage have already emerged and others may arise anywhere in the world and spread. Existing or new SARS-CoV-2 variants with escape mutations will necessitate vaccine modification and booster immunisation regimes, whilst normal travel and trade will mean that widespread, prolonged surveillance for the introduction of (variant) infection will be necessary for a long time in the future. UK modelling studies have shown that with the increased transmissibility of new variants, a very high percentage of the population needs to be immune to infection, either through vaccination or previous infection to keep R below 1 and hence prevent future lockdowns. Current data emerging from Israel and the UK show vaccine effectiveness at the population level at or above 60%. Importantly, vaccination seems to reduce significantly the number of deaths, ICU admissions and hospitalisations, and any infections in vaccinated individuals appear to be generally milder. This means that soon, infectiousness (i.e., possible virus transmission) and infection will diverge so necessitating more widespread testing of individuals with mild or few symptoms. Given the (perhaps unrealistically high) expectations of the public with respect to vaccination, the prospects of acceptance and adherence to another lockdown after widespread vaccination are low. The Spring and Summer months of 2021, with more outside activities and better ventilation, should help but we must prepare now, especially for next Winter with increased indoor gatherings in poorly ventilated spaces. Moreover, it is likely that as more people become vaccinated, their adherence to public health measures, e.g. mask wearing, social distancing, regular hand washing etc. will decrease and this will work against the positive effects of the vaccination campaign.

It is therefore important that some new focused messages, e.g. rapid testing, enhanced ventilation etc. are introduced now, when the infection levels are dropping and vaccination is commencing, i.e. ahead of any resurgence of infection. Moreover, when the infection levels are low, the current PCR testing system has the capacity to handle the increased workloads of confirmatory tests which will flow from widespread deployment of rapid testing.

Once the economy and society have significantly and safely reopened, the first of the current public health measures to dispense with to allow economic recovery is social distancing. Mask wearing, hand washing, respiratory etiquette, good ventilation, repeated testing can continue indefinitely with little economic impact, but prolonged social distancing will be problematic for many restaurants, pubs, hotels, theatres, cinemas, public transport, schools, colleges, universities etc. So it will be key to establish, as early as possible, if widespread, repeated, rapid testing combined with the other public health measures can allow the safe relaxation of current social distancing measures. All of the above are good reasons to act now: expect the expected. They are compounded by the fact that lots of things about the virus, the effects of global immunisation etc. are unknown so the introduction of widespread rapid testing will also allow us to prepare for the unexpected.

10.2 Make Rapid Testing A Shared Community Action and Responsibility – Across Government Departments, Agencies, Employers, Voluntary and Community Groups and Give This Programme A New Name

The population need to be empowered, given hope and a way of managing a safe, sustainable recovery as a result of collective action and responsibility. Wherever possible, we need to align incentives. Rapid testing together with vaccination, can be deployed, along with other public health measures, as a way of decreasing the risk of transmitting COVID-19 as well as maintaining the effectiveness of the current vaccination by minimising the spread of new variants. To that end it is like a Health and Safety measure, i.e. it further decreases your risk, hopefully to a low level, but it does not eliminate it. This in turn allows society and the economy to safely and sustainably reopen and it gives people control over their own health. Rapid testing can be part of the measures including mask wearing, social distancing, respiratory etiquette, hand washing, good ventilation etc. which allow you to function with a decreased risk of virus transmission or infection. Importantly, the effect of taking these additional measures is not just additive, it is multiplicative.

Widespread rapid testing should be one of these preventative measures. It will be very important to distinguish this community testing from individual diagnostic testing. By its nature, widespread, non-professionally administered, rapid testing is less accurate than a professionally administered diagnostic PCR test performed in an accredited laboratory, but rapid testing has advantages: widespread deployment, cheap, fast result, meaning important decisions can be made there and then, e.g. admittance to an event, building, plane, workplace etc, or rapid self-isolation, if positive. Intelligent deployment, e.g. repeat testing, serial testing, testing families/bubbles can greatly increase accuracy. To distinguish such a widespread testing programme where the benefits are predominantly for the community, from individual diagnostic testing and to facilitate public education, we recommend calling it something different, e.g. community testing, public health testing, infectious/contagion testing, enabling testing, have all been suggested but one can think of disadvantages for each of these names. Alternatively, it could be called something neutral which does not attempt to signify its aim, e.g. Ireland Testing. Rapid tests are most useful as a single point in time result to inform you whether you have a respiratory viral load that is likely to be infectious to other people. It is highly likely that the specificity and sensitivity of rapid tests will improve, that more convenient and person friendly sampling, e.g. saliva, nasal swab, exhaled air will emerge and that ways of enhancing the accuracy of reading the result, e.g. AI function on a mobile phone, will all progress rapidly in the next months. So establishing the logistics, public awareness and monitoring infrastructure for widespread testing should take place now, to allow that such future advances be easily deployed at scale. A quotation from a recent article by Tom Whipple (The Times, 13th February 2021 “We’ll get our lives back, even without a VE Day for Covid’) sums it up, “Most of us have still not used a lateral flow test. By this time next year, it is likely that few of us will not have.”¹³⁸

Setting expectations, building cooperation and engagement, aligning incentives, monitoring behavioural responses and getting widespread engagement from across society is key to the success of widespread testing. Most, if not all of it, will be voluntary and the UK have developed useful ethical guidelines for mass testing (see Section 4.13). Particular attention should be paid to ensuring that advice, support, facilities and services are in place to allow those who test positive to do the right thing and self-isolate. This means paying attention to wage supports, dependant supports, facilities (e.g. free isolation hotel room) for those who cannot properly self-isolate at home. Failure to do so will

¹³⁸ The Times, UK, 13th February 2021 “We’ll get our lives back, even without a VE Day for Covid’.

both decrease the value of any programme (by creating incentives for individuals to avoid testing) and exacerbate inequalities. Testing on its own does not stop virus transmission. It is the subsequent behaviour, i.e. isolation, contact tracing and testing that helps break the transmission chains. Those who either cannot afford the price of a test or cannot afford the consequences of a positive result (either through loss of income or inability to self-isolate) are unlikely to volunteer for a test. To be effective, widespread testing should be decentralised but coordinated with widespread engagement and responsibility from different government departments and agencies, employers, community groups etc. This means that many actors, e.g. employers, sports clubs, Department of Education, Department of Business, Enterprise & Employment, Department of Agriculture, Food & the Marine, Department of Health, Department of Transport, Department of Further & Higher Education, Research Innovation & Science, Department of Social Protection, Higher Education sector etc. need to be engaged in effective widespread deployment. In turn this means that some core principles / guidance must be provided, e.g. up to date listing of validated test products, guidance and training on deployment, logistics, interface with public health, capture of surveillance data and integration e.g. with genomic sequencing for viral variants. Initially an outline plan for deployment needs to be put in place, across Government and in cooperation with employers and community groups. This has already started in a small way, e.g. with validation studies for screening of meat plant workers and testing of lorry drivers going to France. Consideration should be given to how the State would deploy rapid testing within its areas of control / interest, e.g. distributed testing facilities, mobile testing facilities etc. This could involve collaboration with private / community-based testing centres, established in local halls / schools / companies / buildings.

In the UK House of Commons Public Accounts Committee Report on COVID-19 Test, Track and Trace (part 1) published on 10th March 2021 , the NHS Track and Trace said that their biggest lesson learnt in the last year was that “you can only deliver this sort of service as an integrated team of all the different organisations, institutions and individuals in the country”.¹³⁹ Indeed, the committee were critical of the early roll out particularly in schools where there was apparently lack of engagement with school heads and education stakeholders and insufficient collaboration with local authorities and NHS primary care bodies in the testing and tracing activities. We should learn from this UK experience which emphasises the importance of establishing clear goals for the testing programme, ongoing analysis, evaluation and learning and widespread engagement and education of the community. The Department of Foreign Affairs may become involved in the work on widespread cheap testing through Irish Aid. Rapid cheap widely deployable tests are of great importance in many developing countries where Irish Aid have effective operations. Organisations such as FindD_x are leading on the development and deployment of widespread cheap tests in such developing countries. This is a topic where advances in research, development and deployment are mutually beneficial.

10.3 Establish An Agile Rapid Test Knowledge Group Who Will Provide Easy Access To Lists of Test Suppliers That Meet Certain Standards And Who Will Monitor New Rapid Test Developments and Their Validation / Revalidation Internationally

Many new rapid tests are in development and new products enter the marketplace on a weekly basis. New performance standards will emerge, e.g. detection of a minimum amount of protein (NIBSC / WHO standard in development). Countries are validating commercial tests deployed in various

¹³⁹ UK House of Commons Public Accounts Committee; COVID-19: test, track and trace (part 1). March 2021. <https://committees.parliament.uk/publications/4976/documents/50058/default/>

settings. Lists of validated tests are made available by various countries, e.g. UK, The European Commission Joint Research Centre (JRC) and bodies e.g. US CDC etc. Availability / production of tests vary. This is a rapidly developing and changing field. Over 2,500 new tests are in development and summarised lists are available, e.g., FindD_x, University of Arizona, 360D_x, NIH RAD_x, etc. A group should be established perhaps in NSAI, the national standards agency or in Department of Health (e.g. HPRA or HIQA) or in DFHERIS to actively monitor these developments and provide an easily accessible and up to date list of ‘recommended validated’ tests. The European Commission, through the JRC, provide such a listing where rapid tests have been validated and deployed in more than three member states and meet certain minimum standards. Such information is vital to ensure that employers, community groups etc. have access to the appropriate knowledge without having to wade through lots of reports / papers and without having to believe the latest sales pitch. This listing will be dynamic e.g. a test validated today may not be recommended tomorrow because it fails to detect a new variant. An evolving (and increasing) standard should be set for all tests to meet before they are included on the list, e.g. specificity, sensitivity, accuracy and ease of reading, CE marked, detect variants, easy specimen sampling etc. The group would compile information on batch variation and testing so that users can easily ensure that they are using a ‘good’ batch of tests. The group should monitor tests in advanced research / development to anticipate rapid deployment of better rapid tests. This group would be where everyone (employers, community groups, Government) would go for up to date, reliable information and advice. The group would compile standard training videos and information leaflets for effective training on the use of such tests. The UK NHS has provided useful training videos on YouTube¹⁴⁰ and instruction booklets in many languages¹⁴¹ on how an individual can sample, use and read a lateral flow antigen test at home and these publicly available materials are already being referred to by employers in Ireland. If properly established and functioning, such a group together with widespread development of testing pilots would make Ireland attractive for new innovative tests and the companies developing them – Ireland is an ideal test bed – small enough to pilot, large enough to scale, English speaking, EU member etc. This could assist not only with the rapid availability of such useful new technology to the Irish population, but also act as a magnet for such companies to locate some of their operations in Ireland.

10.4 Launch a Major Series of Testing Programmes in Different Settings and in Collaboration with Appropriate Private Sector / Public Sector / Community Groups

The overall aim of any programme should be to allow a safe, sustainable reopening of society and the economy. We have much to learn about the deployment, logistics, acceptance, accuracy, utility of rapid testing and of the behavioural changes which may occur with either a positive or negative result and a false positive / false negative result. Testing on its own is not enough – we need to have effective isolation of positive cases, good contact tracing and public health monitoring, e.g. for clusters, variants etc. Moreover, testing is only one of a suite of measures for safe sustainable reopening – vaccination, mask wearing etc. are also part of the mix. Currently there are lots of opinions about the relative importance of sampling, test sensitivity and specificity, reading accuracy, guidance and training, positive and negative behavioural changes but there are few comprehensive studies providing data and evidence. We need these. We need to learn collectively, iterate, and innovate to an optimal deployment regime. We need to move on from the present where there appear to be differences between testing as imagined, as prescribed, as reported and as performed, to a time where we know

¹⁴⁰ <https://www.youtube.com/playlist?list=PLvaBZskxS7tzQYIVg7lwH5uxAD9UrS2GJ>

¹⁴¹ <https://www.gov.uk/government/publications/instructions-for-covid-19-self-test>

how to effectively execute useful widespread rapid testing. Given that rapid tests are developing fast, positive change is likely for the foreseeable future. If the use of self-testing (with LFAT) is established, the system would be embedded and would have an immediate effect in curtailing transmission in any future pandemic. We should plan and capitalise on that.

Various complimentary approaches can be taken to the deployment of widespread testing. This could be achieved by collaboration with and, where appropriate, (co) funding from various sectors, e.g. employers (e.g. by sector: hospitality, office, construction, factories etc.), schools, colleges and universities, public sector, public transport, air and ferry transport etc. It could also be deployment by function, e.g. attending a funeral, wedding, restaurant, sporting event, concert, theatre, cinema etc. It could be by local community, e.g. villages, towns, GAA clubs etc. Young people are a high priority for widespread testing – they have high percentages of mild / asymptomatic cases, are most affected by the lockdown, will be the last group to be vaccinated and are amongst the first to want to socialise in a responsible way. In any of these pilots, it should be remembered that increased frequency of rapid testing significantly improves the accuracy of the result. Deployment of widespread rapid testing could equally be categorised by the function of the test. Targeted rapid testing has recently¹⁴² been classified into a number of groups:

Test to protect – e.g. regular testing of high-risk settings – care homes, prisons, hospices, meat plants or making the workplace a safer environment as is normal with any health and safety protection.

Test to release – to reduce harms from unnecessary quarantine, e.g. of asymptomatic contacts, critical workers, international travellers etc.

Test to enable – to allow a safer return to restricted activities, e.g. playing sport, visiting a care home, attending school, attending a funeral/wedding etc. Covid free bubbles could be created by vaccinated friends / family with regular rapid testing.

Test to contain – to offer targeted testing to low risk contacts in an outbreak cluster, e.g. the primary high-risk contacts may be screened by PCR testing, but the low-risk contacts e.g. entire company / school / village may be screened by rapid testing. This has the potential to find cases early, reduce onward transmission in the community and has been successfully deployed in other countries, e.g. Belgium.

To ensure the capture of appropriate learnings from widespread testing, some should be established as research pilots. This would involve the collection of important data on voluntary uptake, ease and accuracy of sample collection, accuracy of the test, behaviours observed following all test results etc. This will yield important information and guidance for the future widespread deployment of such rapid testing in various settings. Such an approach is in line with the recently published UN Research Roadmap for COVID-19 specifically the 5 science strategies for a better recovery namely: Data Infrastructure, Implementation Science, Rapid Learning Systems, Knowledge Utilisation, Science of Science.¹⁴³

One way of executing this would be to immediately establish a new research fund - called 'Safe Sustainable Recovery' to be administered in a coordinated way between all of the existing funders (agencies and government departments) but under a single lead agency application process with a minimum set of eligibility criteria, e.g. must involve industry / community collaboration / co-funding,

¹⁴²Crozier A, Rajan S, Buchan I, McKee M. Put to the test: use of rapid testing technologies for covid-19. BMJ 2021;n208. <http://dx.doi.org/10.1136/bmj.n208>

¹⁴³ United Nations. Leveraging the Power of Science for a More Equitable, Resilient and Sustainable Future. 2020. <https://www.un.org/en/pdfs/UNCOVID19ResearchRoadmap.pdf>

monitoring of test accuracy, behaviour etc. This would be analogous to the Rapid Response Call which SFI led on behalf of all of the agencies (SFI, HRB, IRC, IDA, EI etc), early in the pandemic. However, substantial new funding should be allocated immediately. International collaboration and mutual learning should be encouraged. Collaboration and significant co-funding from the private sector should be strongly encouraged to facilitate widespread deployment by them. Sectoral / community / societal champions should be included to ensure the findings of such pilots are rapidly disseminated and utilised within the appropriate industries / communities. Most of the rapid testing would take place outside the HSE / Department of Health, e.g. in universities, companies etc. so as to maintain the focus of the HSE / Department of Health on testing symptomatic individuals, and those in a healthcare setting, where much of the testing will be by PCR (but rapid testing could also be used by them, e.g. if PCR capacity was overwhelmed (as recently when testing of close contacts had to be temporarily stopped), for low risk contacts, or serial testing of healthcare workers. Ultimately the objective should be for widespread self-testing at home with immediate self-isolation if positive.

10.5 Interaction with Public Health Surveillance / Systems

The deployment of such widespread community mild/asymptomatic testing by multiple actors raises the question of how these results can be captured and utilised by the existing public health reporting system CIDR. A simple immediate action would be to mandate that anyone who tests positive on a rapid screening test should immediately self-isolate and report to their doctor who would order an individual diagnostic PCR test. Testing positive on a rapid test, no matter how/by whom administered could be made an additional inclusion criteria for GPs to refer someone for PCR testing. Such PCR diagnostic testing would inform us about, and rule out, any false positive rapid test results. The true positive cases would be dealt with in the established way by contact tracing etc., i.e., the confirmatory PCR test would bring the individual within the procedures and governance of the current health system. An increased PCR testing load would result, but if the programmes are established immediately – when the levels of infection are low and decreasing as a result of the current lockdown – then the PCR testing capacity exists as it is under reduced pressure from symptomatic cases. This principle of retesting an individual with a positive self-administered test result within the health system is already used, e.g. in pregnancy testing.

Whilst this is a simple and easily executed first step, it does result in the Public Health system missing a lot of useful information, e.g. number of tests performed, number of negative tests, geographic distribution of sampling etc. As the rapid tests and their deployment become more accurate, the necessity for, and logic of, a confirmatory diagnostic PCR test decreases. So, in parallel, programmes should be established now to determine how information from such widespread testing using validated tests could be effectively and usefully incorporated within public health systems. Currently in Ireland only results of tests conducted in the HSE testing system can be linked to CIDR and counted. In the UK, all rapid test results, even if self-administered, are captured within the public health system. This is facilitated by having each lateral flow test device barcoded by the manufacturer. The individual tested then scans this barcode into a smart phone and uploads the test result which is recorded centrally. A further development of this is planned whereby the user will take a photograph of the test result on the LFAT and the barcode adjacent to it. An AI interface within the smart phone app will assist in reading the result more accurately and both will be sent centrally to data collection as well as being reported immediately to the user. Perhaps in the first instance, the COVID-19 app could be upgraded to allow individuals to scan the barcodes of LFATs and upload the results. The app might also allow individuals to upload / record their vaccination status and which vaccine they were

administered and when. Certainly, some technology solution to the collation of widespread testing data needs to be deployed. For example, we also note that a UK commercial company already markets COVID-19 test management software which allows for GDPR and NHS compliant collection of data from rapid testing in schools and its subsequent reporting to public authorities. Use of similar compatible software systems may allow for the rapid, efficient, and effective collection of such widespread rapid testing data. Unless centrally recorded, the widespread use of rapid tests will interfere with the analysis and interpretation of surveillance data, as only positive tests will enter the HSE system, with no indication of the total number of tests performed (this is currently the situation for commercial tests, e.g. at the airport, or in companies in Ireland). Moreover, genomic sequencing will become increasingly important for monitoring of new variants, including escape mutations following vaccination or those introduced to the country through international travel. We note that in the veterinary management of pandemics, e.g. foot and mouth disease, rapid lateral flow test devices are deployed on the farm by the farmer but following a positive result, the virus within the device is inactivated by immersing the device in citric acid, and the device sent to a centralised laboratory for whole genome viral sequencing, using the DNA extracted from the membrane within the lateral flow device. Similar strategies could be deployed with widespread rapid tests for COVID-19, allowing in the future for integration of the genomic data with the data collected from the widespread screening. This is being piloted in the UK. In essence we need to build a distributed but coordinated system.

10.6 Educating and Engaging the Public

From the preceding discussion the need for clear communication with the public is evident at many levels: nature, limitations and advantages of the new testing / screening programme, what to do if test positive or negative, false positives and false negatives etc. Much work has been done on the effective communication of screening, tests and treatment choices by the Winton Centre for Risk and Evidence Communication at the University of Cambridge. They are currently working on appropriate infographics and public information resources for rapid COVID-19 tests which will be deployed widely in the UK by the NHS, schools etc. Government communications professionals in Ireland should consider learning from their experience / working with them. Equally the CDC has guidance on its website for home COVID-19 testing whilst voluntary rapid testing community groups are forming on the internet to share experiences, e.g. www.rapidtesting.org.

10.7 Collaboration with Northern Ireland / UK

To effectively manage living with COVID-19 and maintaining a successful, sustained opening of society and the economy, collaboration and coordination with Northern Ireland, with whom we share an open border and with our nearest neighbour, mainland UK, with whom we have extensive trade and travel, is important.

Every effort should be made to include collaboration with Northern Ireland. If everyone involved in planning, executing, and analysing the pilots are working together from the beginning, it will likely be easier to obtain political agreement on coordinated deployment in the future. Collaboration is often easiest in a situation of widespread infection and crisis but more challenging when the disease is at a lower severity and prevalence. This makes it all the more important for learnings from widespread

testing to be rapidly shared between NI, UK and ROI and wherever possible and sensible, for collaborative co-funded pilots to be established. This follows from the collaboration and co-funding between the NI authorities and SFI in the previous COVID-19 Rapid Response Call and is in keeping with a complementary proposal for an All Island of Ireland Infectious Diseases Research Centre.

Likewise, it is important that Ireland collaborate with our EU partners and shares information and mutual learning through the existing mechanisms.

10.8 Establish a Red Team for Agile Monitoring, Pivoting and Decision Making

When managing such a complex population programme, with many unknowns, that could quickly develop into a crisis requiring further restrictive measures on society and the economy, evaluating options and making wise decisions quickly are important. Researchers, public servants, politicians, employers and the public must interact closely, but have different responsibilities and perspectives. Constructive criticism and agile changes of direction are often inappropriately portrayed as weaknesses or incompetence in an adversarial public (political) arena which can inhibit rapid learning and effective decision making. People may become risk adverse, defensive, siloed in their thinking or simply ignorant of important information / alternatives. The need to rapidly respond to new information and to make important decisions is common in the military who use the concept of red teams as an alternate form of analysis, both in planning and in response management.^{144,145} The process of red teaming involves standing up a group of senior experts who have confidential access to all the data, are not involved in the management or accountability streams and having them peer review proposed decisions in real time, offer insights, suggest alternatives and so greatly improve the chances of making a wise choice.

¹⁴⁴Seger CD, Wang L, Dong X, Tebon P, Kwon S, Liew EC, *et al.* A novel negative pressure isolation device for aerosol transmissible COVID-19. *Anesth Analg.* 2020 Sep;131(3):664–8. <https://doi.org/10.1213/ane.0000000000005052>

¹⁴⁵ Zenko M. *Red team: how to succeed by thinking like the enemy.* New York: Basic Books; 2015. 336 p.

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12. Appendix 1 - Details of testing approaches

12.1 Viral RNA detection - PCR testing

Detection of viral RNA by real-time reverse transcription polymerase chain reaction (rRT-PCR) is the most sensitive method for testing for SARS-CoV-2 and confirming diagnosis of COVID-19. These tests are also known as quantitative reverse transcription polymerase chain reaction (RT-qPCR). PCR testing can also efficiently detect SARS-CoV-2 infection in asymptomatic individuals. The test takes hours to perform and requires specialized reagents, equipment, and highly trained individuals. The test is usually performed on samples taken by nasopharyngeal and/or oropharyngeal swabs but can also be carried out on anterior nasal swabs or saliva. The test usually requires extraction of the viral nucleic acid (RNA) from the samples, reverse transcription to obtain cDNA, followed by PCR to amplify that DNA, creating enough to be analysed. However, some assays utilise a 1-step RT-PCR protocol in a single tube with mastermix reagents. The test can be performed using commercial platform technologies, with linked instrumentation and reagents. At the outset of the pandemic, bottlenecks resulted owing to reagent availability, however this is no longer a problem.

The primer binding followed by amplification process confers high sensitivity to the test, which is considered to have a sensitivity of $\geq 99\%$. False negatives can occur following inadequate sample due to discomfort of the procedure. However, it is specific ($\geq 96\%$) and can distinguish SARS-CoV-2 from other coronaviruses, and different SARS-CoV-2 strains dependent on the nature of the differentiating mutation.¹⁴⁶

There are a number of assays coupling RT-PCR assays to DNA sequencing technologies to enable higher throughput screening of samples (e.g. Swab-seq¹⁴⁷) that leverages next-generation sequencing to massively scale up testing capacity with no loss in sensitivity compared to RT-PCR.

12.2 Viral RNA detection - LAMP testing

SARS-CoV-2 RNA can be detected using isothermal amplification approaches, that do not require thermocycling used in RT-PCR. These include loop-mediated isothermal amplification (LAMP) and recombinase polymerase amplification (RPA). Reverse transcription loop-mediated isothermal amplification (RT-LAMP) combines LAMP with a reverse transcription step to allow the detection of RNA. Unlike RT-PCR, which is based on a series of alternating temperature cycles, RT-LAMP is carried out at a constant temperature, therefore does not require a thermal cycler. It is a simple assay with either a colorimetric readout where the result is pH dependant (amplification of product results in pH drop to 6.0-6.5 and a visual colour change from red to yellow) or where amplification is detected by a change in fluorescent signal. The only equipment required is an oven or a heat block for the colorimetric assay and an additional plate reader for the fluorescent assay. The test does not require extraction of viral RNA prior to running the test. It can be performed on samples from swabbing or saliva. Multiplex versions of the fluorescent assay are available for simultaneous detection of SARS-

¹⁴⁶ Skittrall JP, Wilson M, Smielewska AA, Parmar S, Fortune MD, Sparkes D, *et al.* Specificity and positive predictive value of SARS-CoV-2 nucleic acid amplification testing in a low-prevalence setting. *Clin Microbiol Infect.* 2020;0(0). <https://doi.org/10.1101/2020.08.04.20167874>

¹⁴⁷ Bloom JS, Jones EM, Gasperini M, Lubock NB, Sathé L, Munugala C, *et al.* Swab-Seq: A high-throughput platform for massively scaled up SARS-CoV-2 testing. medRxiv. medRxiv; 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7480060/>

CoV2, influenza A and influenza B within a single tube/well¹⁴⁸ and multiplex versions for simultaneous detection of SARS-CoV2 variants of interest are in final stages of validation/EUA assessment. RT-LAMP assays have been used for many years as in validated tests for the detection of a variety of RNA viruses including influenza, Zika, Ebola, and MERS. The sensitivity of the tests is less than that of RT-PCR but greater than that of antigen testing.

12.3 Viral RNA detection - CRISPR-based testing

SARS-CoV-2 RNA can be detected using assays that combine isothermal amplification and CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) - based technology. CRISPR-based diagnostic platforms combine nucleic acid amplification with the genome editing ability of the CRISPR-Cas system allowing for simple, portable, and ultra-sensitive detection of RNA or DNA from clinically relevant samples.

In CRISPR-based tests, Cas13 (RNA-specific) and Cas12a or Cas9 (works with DNA) nucleases programmed with specific RNA guides are used to specifically detect target viral RNA (or cDNA). When the RNA guide targets SARS-Cov-2 cDNA (sequence specific) it activates non-specific “collateral” RNase activity of Cas that can be measured via fluorescence or colorimetric signals on a lateral-flow device. As both the nucleic acid amplification step and the CRISPR–Cas detection step require sequence specificity to trigger signal amplification, CRISPR diagnostic methods are highly sensitive and highly specific. CRISPR technology is capable of single-molecule detection in 1 µL sample volumes of both DNA and RNA targets. RNA purified from patient samples can be analysed for the presence of SARS-CoV-2 in 30-60 min without special equipment.

The Specific High Sensitivity Enzymatic Reporter unlocking (SHERLOCK) platform has recently been developed for the detection of SARS-CoV-2¹⁴⁹ and was 100% specific and 97% sensitive with a lateral-flow readout. CRISPR-based tests can be used to differentiate viral strains. CRISPR-based tests can be deployed with basic lab equipment (e.g. low-end basic PCR machines) and are also being developed as lateral flow devices.

12.4 Antigen testing

Viral protein antigens, the SARS-CoV-2 spike (S) or nucleocapsid (N) proteins can be detected in nasal swabs or saliva during the pre-symptomatic and early symptomatic phase of infection when the viral load is high. Antigens can be tested by enzyme-linked immunosorbent assays (ELISA) or lateral flow assays. Antigen testing does not involve amplification steps so is less sensitive than testing for RNA using RT-PCR, RT-LAMP or CRISPR based tests. However, recent studies have suggested that as the tests detect viral proteins, rather than RNA, they are effective at detecting high viral loads.¹⁵⁰ Antigen tests have high specificity at typically ~99%. Commercial kits typically indicate analytical sensitivity of

¹⁴⁸ Turner F, VandenBerg A, Slepnev VI, Car S, Starritt RE, Seger M V, *et al.* Post-disease divergence in SARS-CoV-2 RNA detection between nasopharyngeal, anterior nares and saliva/oral fluid specimens - significant implications for policy & public health. medRxiv. 2021 Jan 26, 2021;pre-print:2021.01.26.21250523. <https://doi.org/10.1101/2021.01.26.21250523>

¹⁴⁹ Patchesung M, Jantarug K, Pattama A, Aphicho K, Suraritdechachai S, Meesawat P, *et al.* Clinical validation of a Cas13-based assay for the detection of SARS-CoV-2 RNA. Nat Biomed Eng. 2020 Dec 1 ;4(12):1140–9. <https://doi.org/10.1038/s41551-020-00603-x>

¹⁵⁰ Crozier A, Rajan S, Buchan I, McKee M. Put to the test: use of rapid testing technologies for covid-19. BMJ. 2021 n208. <http://dx.doi.org/10.1136/bmj.n208>

~96%, although *in-field* tests, including those already done in Ireland, have lower reported sensitivities when compared to RNA detection by RT-PCR, which is discussed further in the body of this report. As antigen tests detect viral protein, they may be a better indicator of live virus, i.e., infectious individual, than nucleic acid-based tests.

12.5 Antigen testing by ELISA

The ELISA technique utilizes monoclonal antibodies specific for SARS-CoV-2 antigen (S or N proteins) bound to the wells of plastic tissue culture plates to capture the antigen and a different monoclonal antibody specific for the same protein to detect the bound viral antigen. The second antibody is labelled with a fluorochrome to allow automated quantitative readout of the antigen concentration in the sample.

12.6 Antigen testing by Lateral flow antigen tests

Lateral flow antigen tests, also known as lateral flow immunochromatographic assays or lateral flow immunoassay can be used to detect SARS-CoV-2 viral antigens (S or N protein) in nasal swabs or saliva samples. It utilizes the same immunoassay principle as the ELISA, the liquid sample is placed on a pad/strip and if antigen is present it will bind to the antibody resulting in a colour change. The test is not quantifiable and gives a negative or positive result only. Lateral flow tests do not require instrumentation and therefore lend themselves to point-of-care, point-of-need and home-testing.

Summary Table of High-Level Advantages, Disadvantages and Overall Assessment

Detection	Viral RNA	Viral RNA	Viral RNA	Viral antigen	Viral antigen
Test Type	RT-PCR testing	RT-LAMP testing	CRISPR-based testing	ELISA testing	Lateral flow antigen testing (LFAT)
Advantages	Highly sensitive and highly specific.	Rapid (<1 hr) simple, low-cost test, with limited reagent or equipment required, can be adapted for high throughput near patient testing. More sensitive than antigen testing.	Rapid (<1 hr), low-cost test, suitable for repeated near patient or self-testing. Low lab and reagent requirements allow decentralised testing setups. Can be adapted for high throughput labour-efficient automation. Same sensitivity as RT-PCR, higher than RT-LAMP or antigen testing.	High specificity, relatively low cost, high throughput testing approach, probably less affected by saliva sample pH or contamination that can interfere with RT-LAMP tests. Detects SARS-CoV-2 Antigen and therefore indicates that the individual is infectious.	Rapid, low cost, suitable for repeated near patient or self-testing. Detects SARS-CoV-2 Antigen and therefore indicates that the individual is infectious.

Detection	Viral RNA	Viral RNA	Viral RNA	Viral antigen	Viral antigen
Test Type	RT-PCR testing	RT-LAMP testing	CRISPR-based testing	ELISA testing	Lateral flow antigen testing (LFAT)
Disadvantages	<p>Sample transportation needed.</p> <p>Laboratory needed.</p> <p>Unless automated, the RNA extraction steps are laborious and relatively slow to perform.</p> <p>Can be constrained by reagent availability when using single commercially available platforms.</p> <p>Reagents and equipment are costly.</p> <p>All steps are not amenable to automated high throughput testing, although sample pooling strategies can be used to develop higher throughput systems.</p> <p>Does not discriminate between an active infection or resolved infection with persistent RNA.</p>	<p>Not as sensitive as RT-PCR, require basic laboratory and basic equipment. Subject to false positives with colorimetric assay if used with saliva samples as up to 10% are naturally more acidic and will generate an instant colour change if not pre-treated, so positives need to be confirmed.¹⁵¹</p> <p>Does not discriminate between an active infection or resolved infection with persistent RNA.</p>	<p>Basic lab equipment required.</p> <p>The technology is relatively novel with clinical validation ongoing.</p>	<p>Not as sensitive as RT-PCR, RT-LAMP or CRISPR-based tests for detecting COVID cases but probably as sensitive for the detection of infectious individuals. Requires lab and basic equipment (ELISA plate reader).</p>	<p>Lower sensitivity than RT-PCR, or RT-LAMP for detecting COVID cases but probably as sensitive for the detection of infectious individuals.</p> <p>Commercially available tests require confirmatory clinical and in field validation.</p>

¹⁵¹Meyerson NR, Yang Q, Clark SK, Paige CL, Fattor WT, Gilchrist AR, *et al.* A community-deployable SARS-CoV-2 screening test using raw saliva with 45 minutes sample-to-results turnaround. medRxiv. 2020 Nov 23. <https://doi.org/10.1101/2020.07.16.20150250>

Detection	Viral RNA	Viral RNA	Viral RNA	Viral antigen	Viral antigen
Test Type	RT-PCR testing	RT-LAMP testing	CRISPR-based testing	ELISA testing	Lateral flow antigen testing (LFAT)
Overall Assessment	<p>Should remain a key test for confirming the presence of SARS-CoV-2 RNA.</p> <p>However, changes to reporting algorithms are required to focus on those individuals who are potentially infectious (low Ct values).</p> <p>Medium/high-throughput RT-qPCR screening and surveillance using saliva sampling combined with pooling strategies (www.salivascreen.org) or coupled to next generation sequencing (2-10,000 samples per 24 hrs) could be a pragmatic and less invasive alternative to NP swabs.</p> <p>Extraction-free methods developed to circumvent bottleneck in equipment/reagents required for extraction have been shown to work well but are less sensitive than results using purified RNA. Merit for consideration of use in screening programs.</p>	<p>A low-cost slightly less sensitive than PCR testing for high throughput surveillance screening¹⁵² and screening/testing in certain settings e.g. higher education institutes, large schools, hospitals and large or medium-risk workplaces or in mobile testing vans.</p>	<p>A highly sensitive and specific assay with significant potential for high throughput repeated (every 3-4 days) testing in range of settings e.g. workplaces, airports etc,</p> <p>Not yet commercially available in EU; accelerated regulatory approval needed in EU / Ireland. Sherlock Biosciences received FDA EUA for the Sherlock™ CRISPR SARS-CoV-2 kit.</p>	<p>A useful adjunct to RT-PCR or CRISPR-based testing but not as sensitive as RT-LAMP, which may have applications in tests with mid-range sensitivity.</p>	<p>Suitable for high throughput repeated (weekly or biweekly) screening of relatively large numbers of individuals in certain settings e.g. schools, small-medium sized businesses, in the home by the general population.</p> <p>Potential for self-testing</p> <p>Use only commercially available, validated tests.</p>

¹⁵² Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, *et al.* Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening. *Sci Adv* . 2021 Jan 1;7(1):1–11. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7775777/>