Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary for use of rapid antigen testing for screening or surveillance of asymptomatic individuals to limit transmission of SARS-CoV-2

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- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation.
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Evidence summary for use of rapid antigen testing for screening or surveillance of asymptomatic individuals to limit transmission of SARS-CoV-2

Key points

Overview of rapid antigen detection tests

- Rapid antigen detection tests (RADTs) refer collectively to both:
  - near-patient (or point-of-care) antigen tests administered in healthcare or other settings by an experienced trained professional
  - self-tests administered by a lay person, typically at home.
- This evidence summary specifically considers screening or surveillance of asymptomatic populations with RADTs to identify individuals infected with SARS-CoV-2. Use of RADTs was considered as an alternative to no-testing, rather the use of a different test such as RT-PCR.
- Screening or surveillance (with high frequency testing) using RADTs offers the potential for rapid identification of infectious cases of COVID-19 to enable prompt isolation and interruption of onward transmission.
  - Screening tests are intended to identify occurrence of SARS-CoV-2 infection at the individual level even if there is no reason to suspect infection, for example, where there is no known exposure.
  - Surveillance testing is used to gain information at a population level; it usually involves testing a representative group of the population as opposed to all individuals.

Regulatory status

- An increasing number of SARS-CoV-2 RADTs have been affixed with a CE (Conformité Européenne) mark and made available on the EU market since the beginning of the pandemic. Involvement of an external Notified Body is required for self-tests while those intended for use by professionals are CE-marked on the basis of manufacturers' self-assessment only.
- To date, almost all RADTs have been CE-marked as point-of-care tests for use in symptomatic individuals (within a certain timeframe from symptom onset) by professionals, with only a small number of tests authorised for use as self-tests. It is unclear how many self-tests, if any, are intended for use in asymptomatic individuals.

Investment

- As RADTs are portable and do not require laboratory analysis, they could facilitate decentralised testing at scale for screening or surveillance purposes. While the estimated cost of a professionally administered RADT is considerably

lower than that of an RT-PCR test, successful deployment of RADTs at scale, would still incur a significant total cost.

- In the context of a professionally conducted or supervised testing programme using RADTs, guidelines highlight the following resource requirements:
  - a designated area for the provision of testing including suitable facilities for sample collection, test performance, instrument storage, safe disposal of clinical waste and appropriate storage of consumables
  - personnel to conduct/supervise sample collection, process tests and store results
  - training and certification to cover all stages of the testing pathway
  - quality assurance systems to monitor the end-to-end testing process.
- In the case of a self-testing programme using RADTs, resources required include:
  - training for lay persons to improve the quality of sample collection and interpretation of test results.
  - appropriate mechanisms for reporting test results.

Diagnostic test accuracy

- Three systematic reviews of the diagnostic test accuracy of RADTs compared with RT-PCR were identified. The reviews broadly found that test:
  - sensitivity was higher in symptomatic individuals (ranging from 64%-84%) than in asymptomatic individuals (40%-74%)
  - specificity was high in both symptomatic and asymptomatic individuals (approximately 99%)
  - sensitivity was highest (ranging from 94%-96%) for cycle threshold (C_t) values on RT-PCR ≤25 (which can be considered to reflect a high viral load) compared with C_t values >25 (sensitivity 40%-50%).
- One systematic review of diagnostic test accuracy of RADTs and RT-PCR compared with viral culture (as a proxy for infectiousness) was identified. The pooled sensitivity was estimated to be 90% (95% CI 84% to 94%) for RADTs and 99% (95% CI 96% to 100%) for RT-PCR. Specificity was not estimated in this review.
- These data presented therefore suggest that RADT can reliably detect those most likely to be infectious. While C_t values provide an indication of potential infectivity, it is important to note that they only reflect viral load at the time of sampling and that there is no accepted cut-off of C_t values to eliminate transmissibility. In this context, the timing of the test is important: while a high Ct value late in the disease course may reflect detection of non-viable virus and individuals who are no longer infectious, those tested shortly after exposure are at the start of their infection and will subsequently become infectious. Identification of the latter is important to facilitate prompt isolation in order to

break the chains of onward transmission. From a public health perspective, identification of those that are no longer infectious is also still important as it allows contact tracing to be initiated to identify other potentially infectious individuals.

- To interpret the sensitivity and specificity of RADTs relative to RT-PCR, it is important to consider the context in which the test is being deployed, in particular the performance of the test in the target population and the prevalence of disease. For example, if an individual tests
    - *positive* for COVID-19 in a low prevalence (for example, 0.5%) setting, it is highly uncertain that an individual *is* infected (due to the low positive predictive value of the test, that is the numbers of false positives will be significantly higher than numbers of true positives); in these situations confirmatory RT-PCR testing has been recommended for positive test results to verify the presence of disease (or frequent serial testing using RADTs in certain settings)
    - *negative* for COVID-19 in a high prevalence (for example, 10%) setting, it is more uncertain that an individual is *not* infected (due to the reduced negative predictive value of the test); in these situations, confirmatory RT-PCR testing has been recommended for negative test results.
- The performance of RADTs can be affected by a range of other factors, including the timing of the test; the concentration of virus in the specimen; the quality and processing of the specimen collected; the precise formulation of the reagents in the test kits; and compliance with manufacturers' instructions for use. Performance of different RADTs varies and these tests should not be regarded as interchangeable. There is also evidence of batch-to-batch variation, and additionally performance can differ by variant of concern.

International guidance

- The European Centre for Disease Prevention and Control (ECDC) advises that RADTs may be of benefit in screening asymptomatic individuals in high prevalence settings (>10%), where RT-PCR capacity is limited, to control transmission in local communities or in specific settings. In a high-risk indoor occupational setting, the ECDC advises that RADTs (including self-tests), could be used to screen employees at or before arriving to the workplace, and as part of local public health prevention and control programmes.
- The United States (US) Centers for Disease Control and Prevention (CDC) reports value in conducting screening (including serial testing) with RADTs, where turnaround time is critical in identifying people with COVID-19, for example in high-risk congregate housing settings.

Ethical considerations

- There are a number of ethical considerations in relation to the use of RADTs for screening or surveillance of asymptomatic people. These include:
    - the use of less accurate tests with implications for false negative (such as providing false reassurances) and false positive test results (such as unnecessarily self-isolating)
    - the impact of existing health inequalities on uptake and participation in such testing programmes
    - whether the resources required and opportunity cost are justified
    - autonomy over healthcare decisions and reporting obligations for a notifiable disease in the case of self-testing
    - what viable alternatives to testing are available
    - the risk of severe disease in the population/setting.
- A sound ethical framework, involving stakeholder engagement, may be required to enable systematic and principled decision making with regard to screening or surveillance of asymptomatic people for COVID-19.

Effectiveness of rapid antigen testing

- Sixteen relevant studies were identified that provided evidence regarding the effectiveness of RADTs for screening of asymptomatic individuals to limit transmission of SARS-CoV-2. Eight examined the effectiveness of RADTs for mass testing, four for pre-event screening and four for serial testing in different settings (high school students, prison inmates and staff, students and staff of a university sports programme, and staff in care homes).
- No included study examined the effectiveness of RADTs for surveillance purposes, or for screening for travel-related activities or in workplaces (with the exception of those involving staff identified above).
- All included studies evaluated the use of RADTs in the context of background public health restrictions (for example, national lockdowns) or in conjunction with other public health measures (for example, face mask use).
- Overall, there is uncertainty regarding the effectiveness of rapid antigen testing for screening of asymptomatic individuals at limiting the transmission of SARS-CoV-2. This uncertainty is due to the relatively low number of studies identified, the predominantly observational and/or uncontrolled study designs used, and concerns regarding the methodological quality of these studies.
- Screening programmes were found to be resource-intensive and costly. There is currently insufficient evidence as to whether the use of RADTs for screening of asymptomatic individuals represent a good use of resources and value for money.
- While mass testing using RADTs in conjunction with public health restrictions might have some short-term effect at reducing SARS-CoV-2 transmission, it is

likely that re-testing at regular intervals would be necessary to achieve any potential sustained effect.

- Though still limited, research is being conducted on the potential role of RADTs for pre-event screening, in conjunction with other public health measures, such as face mask use, social distancing and optimising ventilation.

Conclusions

- RADTs may have an important supplementary role in testing symptomatic individuals, close contacts and in outbreak situations, particularly in high prevalence settings where RT-PCR testing is constrained, and rapid results are needed.
- While RADTs can reliably detect those most likely to be infectious at the time of testing, transmission can still occur in those with high C_t values (low viral low) with no accepted cut-off of C_t values at which risk of transmission is eliminated.
- Based on the current evidence, there is uncertainty regarding the effectiveness of RADTs for screening asymptomatic individuals (who have no known or suspected exposure to SARS-CoV-2) at limiting the transmission of SARS-CoV-2, with no evidence found regarding their use for surveillance purposes.
- The included studies were conducted in populations with limited vaccination uptake and before the emergence of the Delta variant, thus effectiveness may differ in settings where another variant of concern is dominant or where there are very high levels of vaccine uptake.
- There is uncertainty surrounding the clinical- and cost-effectiveness of RADT screening programmes at limiting the transmission of SARS-CoV-2. Any decision to introduce such screening should consider the feasibility, potential benefits and harms, ethical and social issues, regulatory aspects, and value for money of such screening relative to other available mitigation measures.

1 Background

Since the onset of the COVID-19 pandemic, large scale testing programmes have been rolled out globally, with hundreds of millions of individuals tested for SARS-CoV-2 to-date.[1] Given the unprecedented scale of testing, new tests have been developed which have the potential to assist in the control of the pandemic, alongside vaccination and other public health measures.[2] Many types of COVID-19 tests are now available for both clinical and public health use, some of which are laboratory-based, and others can be performed in pharmacies, GP clinics, schools, workplaces, airports, and at home.[3] However, it is important that the right tests are undertaken in the right people at the right time for the right purpose,[4] as testing under the wrong circumstances may cause harm to individuals and populations, and may not represent an efficient use of scarce healthcare resources.[5]

There are four main testing scenarios for SARS-CoV-2 - diagnostic, close contact (including outbreaks), screening and surveillance - each of which serve different purposes and require different approaches.[3] Diagnostic testing is intended to identify infection at an individual level and is performed when a person has signs or symptoms consistent with COVID-19. Close contact testing is also intended to identify infection at an individual level and is performed when an individual is asymptomatic, but has had recent known or suspected exposure to SARS-CoV-2; this includes outbreak situations.[6] Diagnostic and close contact testing aim to identify infected individuals, so that medical care can be initiated where appropriate, and infection prevention and control (IPC) and public health measures implemented. Screening tests are performed in asymptomatic populations (showing no signs or symptoms consistent with COVID-19) who have no known, suspected, or reported exposure to SARS-CoV-2.[6] Screening tests aim to identify infectious individuals in a population, who can be isolated to prevent the onward infection of others.[1] Testing employees in a workplace is an example of screening.[6] Surveillance testing is primarily used to gain information at a population level, rather than an individual level, and generally involves testing of de-identified specimens. Surveillance testing results are usually not reported back to the individual. As such, surveillance testing is not routinely used for an individual's healthcare decision making or individual public health actions such as isolation or quarantine. The main function of surveillance is to monitor population-level burden of disease from a public health perspective. Monitoring of waste water is an example of surveillance testing.[6]

Rapid antigen detection tests (RADTs) work by detecting viral proteins (called antigens) on the surface of the virus.[7] RADTs offer advantages over the gold

standard reverse transcription polymerase chain reaction (RT-PCR) tests in that they provide faster results, thus enabling prompt isolation of positive cases and quarantine of their close contacts.[8] It is possible that the cases identified through RADTs are potentially the most infectious cases based on viral load.[9-11] However, RADTs have significantly lower sensitivity than RT-PCR tests, particularly in asymptomatic populations, and their clinical performance is reduced in low prevalence settings. Therefore, false positives and false negatives may arise, which can affect the reliability of RADTs.[12] Use of RADTs varies considerably across countries,[13] with some countries, including Ireland, largely reserving their use in the public healthcare system to support RT-PCR in outbreak management situations [14] while other countries, including England, use them more widely such as for regular population-wide screening.[15] It has been argued that repeated use of RADTs at a population level may overcome the issue of low sensitivity, and therefore may provide an effective means of reducing SARS-CoV-2 community transmission.[16] While findings from mathematical modelling studies based on hypothetical cohorts support this hypothesis,[17, 18] including an analysis conducted by the Health Information and Quality Authority (HIQA) in the context of meat processing plants,[19] real-world evidence of effectiveness needs to be evaluated. Therefore, the aim of this evidence summary was to collate and synthesise the real-world evidence on the effectiveness of rapid antigen testing for screening and surveillance of asymptomatic individuals at limiting the transmission of SARS-CoV-2.

HIQA has developed a series of evidence syntheses to inform advice from HIQA to the National Public Health Emergency Team (NPHET). The advice takes into account expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group.

The following policy question was outlined by NPHET:

> "What is the emerging evidence with regard to the effectiveness of rapid antigen testing of asymptomatic populations, to limit the spread of SARS-CoV-2?"

The following two research questions (RQs) were formulated to inform the policy question:

> RQ1: What are the key technical characteristics of SARS-CoV-2 rapid antigen detection tests, in relation to their use for screening or surveillance in asymptomatic populations?
>
> RQ2: What is the evidence that SARS-CoV-2 rapid antigen testing for screening or surveillance of asymptomatic people, reduces onward transmission?

For the purpose of these research questions, the focus was on screening and surveillance for SARS-CoV-2, which were defined as follows in line with the United States (US) Centers for Disease Control and Prevention (CDC) definitions:[2, 20]

- **Screening** tests for SARS-CoV-2 are intended to identify occurrence of infection at the individual level even if there is no reason to suspect infection, for example, where there is no known exposure. Screening tests are intended to identify infected individuals who may be contagious, but who are without, or prior to development of, symptoms. This is performed so that IPC measures can be taken to prevent further transmission, for example, in a workplace, educational or healthcare setting. Screening may also be conducted as part of pre-admission protocols to ensure individuals who are infected with SARS-CoV-2 are identified prior to admission to events or availing of flights. Screening also includes serial testing (repeated testing) to maintain access to activities (for example elite athletes) or in settings where infection is more likely to occur despite implementation of IPC measures (for example, meat processing factories, and health and social care settings).
- **Surveillance** for SARS-CoV-2 includes ongoing systematic activities, including collection, analysis and interpretation of health-related data that are essential to planning, implementing and evaluating public health practice. Surveillance testing is generally used to monitor for community or population-level infection, for example, an infectious disease outbreak, or to look back at the level of incidence and prevalence of infection that has already occurred. Surveillance testing is used to gain information at a population level rather than an individual level - for example, to evaluate the effect on the population of public health interventions such as social distancing - and usually involves testing a representative group of the population as opposed to all individuals.

Other key definitions and concepts that are relevant for this evidence summary, in the context of diagnostic test accuracy, are as follows:

- **Target condition** refers to the disease or condition of interest. In the case of this evidence summary, SARS-CoV-2 infection is the target condition.[21] Detection of SARS-CoV-2 infection, both recent and current, is important for initiating case investigation and contact tracing to identify other infected individuals.[22] That an individual tests positive for SARS-CoV-2 does not mean that an individual is currently infectious as they may be in the early or late stages of the infection.
- **Index test** refers to the test that is being assessed,[21] for example an RADT.
- **Reference standard** is the most reliable method for determining if the target condition is present or absent, and is used to verify index tests.[21] For

SARS-CoV-2 infection the reference standard includes RT-PCR tests and established clinical diagnostic criteria.[12] There is currently no reference standard for establishing infectiousness.[12]

- **False positive** refers to a test result that detects a condition (SARS-CoV-2 infection) in someone when it is not present.[21]
- **False negative** refers to a test result that does not detect a condition (SARS-CoV-2 infection) when it is present.[21]
- **True positive** refers to a correct diagnosis of a condition (SARS-CoV-2 infection) being present.[21]
- **True negative** refers to a correct diagnosis of a condition (SARS-CoV-2 infection) being absent.[21]
- **Sensitivity** refers to the proportion of people with the target condition (SARS-CoV-2 infection) that are correctly identified by the index test (RADT).[21]
- **Specificity** refers to the proportion of people without the target condition (SARS-CoV-2 infection) that are correctly identified by the index test (RADT).[21]
- **Positive predictive value (PPV)** refers to the probability that someone who has tested positive for the target condition (SARS-CoV-2 infection) with the index test (RADT) will actually have it (that is, a true positive).[21]
- **Negative predictive value (NPV)** refers to the probability that someone who has tested negative for the target condition (SARS-CoV-2 infection) with the index test (RADT) will not actually have it (that is, a true negative).[21]
- A **self-test** requires an individual to collect a sample from their nose/throat (can be a nose swab, throat swab, saliva or a combination of all), conduct the test and interpret the results according to the instructions provided.[23]
- **Self-sampling** refers to an individual collecting their own swab, or sample, for a SARS-CoV-2 test. The sampling can be supervised or unsupervised. The SARS-CoV-2 test could be performed using a self-test or could be performed by a trained person.[23]
- **Professionally administered tests** are fully conducted by a trained professional who collects the sample and processes the test.[24]

In this evidence summary, only evidence relating to the use of SARS-CoV-2 rapid antigen testing for screening or surveillance of asymptomatic individuals as an alternative to no testing was evaluated. The use of RADT rather than another test, such as RT-PCR, was not considered. Also out of scope was the use of SARS-CoV-2 RADTs in symptomatic individuals or close contacts (including outbreaks) for the purpose of diagnosing infection. In addition, the use of laboratory-based antigen tests was not specifically evaluated, as the focus was on RADTs that are intended for use as self-tests or in near patient (point-of-care) settings. As highlighted, detection

of SARS-CoV-2 does not necessarily imply that an individual is still infectious as prolonged shedding of nonviable virus particles is possible. As noted above, there is currently no standard or agreed approach for measuring infectiousness. This issue is discussed in detail in section 3.1.4.

2 Methods

A detailed summary of the methods used for this evidence summary is provided in the protocol, which is available here.

For RQ1, a description of technology was conducted in accordance with the European Network for Health Technology Assessment (EUnetHTA) Core Model guidance.[25] The purpose of RQ1 is to provide background information as context against which RQ2 is interpreted. This section provides summary information on the use of SARS-CoV-2 rapid antigen testing in asymptomatic people under the following topics:

- overview of the technology
- regulatory status
- investments, tools and training required to use the technology
- diagnostic accuracy of the technology
- guidance on the use of the technology
- ethical considerations.

For RQ2, a systematic search of published peer-reviewed articles and non-peer-reviewed pre-prints was undertaken for all studies published up to 19 July 2021 to identify evidence on the use of rapid antigen testing for screening or surveillance of asymptomatic individuals to limit transmission of SARS-CoV-2. No language restrictions were applied. The following electronic databases were searched: MEDLINE (EBSCO), EMBASE (OVID), The Cochrane Library, Europe PMC and Google Scholar.

A grey literature search was conducted using the search string "SARS-CoV-2" AND "antigen testing" AND "screening" on google https://www.google.com/ on 19 July 2021. The first 20 citations were screened. A google alert was set up to discover new citations that could be added to the grey literature search. Government and public health agency websites as outlined in the protocol were searched on 16 July 2021. Cited references and citations (if available) from relevant papers were screened using the Web of Science Core Collection database. A citation alert was set up in Web of Science to discover new relevant references. Pubmed was also searched for recently added references, by using a similar search to the Medline

search without using proximity operators and limiting the search to articles published in the last month. An alert was created to enable identification of newly added references.

All potentially eligible papers were exported to Covidence (www.covidence.org) for single screening of titles, abstracts, and full texts for relevance based on the inclusion and exclusion criteria outlined in the protocol.

Data extraction and quality appraisal of included studies was completed by a single reviewer and checked by a second reviewer. The relevant National Institutes of Health (NIH) Quality Assessment Tool was used for the quality appraisal of included studies.[26]

For RQ2, four key epidemiological indicators were extracted for the purpose of describing the national epidemiological situation at the time the included studies took place. The epidemiological parameters of interest were the:

- 14-day notification rate of newly reported COVID-19 cases per 100,000 population
- total number of vaccination doses (counted as a single dose) administered per 100 people
- share of the population that have been fully vaccinated (as prescribed by the vaccination protocol) against COVID-19
- predominant variant in circulation.

These data were extracted from the Oxford Martin School, University of Oxford *(Our World in Data)* and CoVariants.org on 30 July 2021.

3 Results

3.1 RQ1: Description of the technology

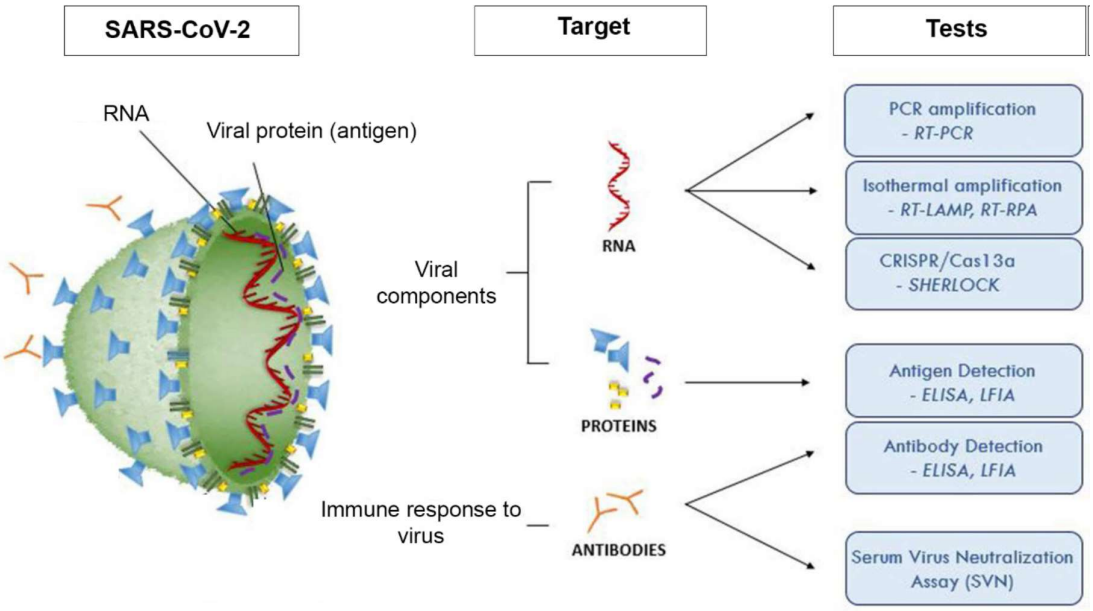
This section summarises the key characteristics of RADTs in relation to their use in asymptomatic populations in accordance with the European Network for Health Technology Assessment (EUnetHTA) Core Model guidance. Section 3.1.1 provides an overview of the technology, detailing the key features of RADTs focusing on how they work and how they differ from other tests. Section 3.1.2 reports on the current regulatory status of RADTs and focuses on RADTs that have been authorised or approved for use as self-tests or for the purposes of screening and / or surveillance in asymptomatic populations. Section 3.1.3 outlines the investment, tools and training required for the different delivery methods for RADTs. Section 3.1.4 provides an overview of published information regarding the diagnostic test accuracy of RADTs relative to reverse transcription polymerase chain reaction (RT-PCR) and viral culture in real world settings. The factors that impact accuracy, such as the choice and timing of the test, conditions of use, among others (for example, presence or absence of symptoms), are also discussed. Section 3.1.5 provides an overview of international guidance on the use of RADTs in asymptomatic populations. Finally, Section 3.1.6 discusses the potential ethical concerns regarding the use of RADTs in asymptomatic individuals not known to have been exposed to or infected with SARS-CoV-2. The information in this Technology Description section is correct as of 20 July 2021, but may be subject to change.

3.1.1 Overview of RADTs

There are two types of diagnostic tests that can determine if someone has a SARS-CoV-2 infection: molecular tests that detect viral genetic material and antigen tests that detect protein on the surface of the virus. Molecular tests amplify parts of viral genetic material (ribonucleic acid (RNA)) to detect viral infection and they include the RT-PCR test, which is considered the gold standard for detecting SARS CoV-2 infection. Antigen tests are immunoassays relying on the interaction between an antibody and an antigen to detect the presence of a viral protein on the surface of the virus.[27] Figure 1 provides an overview of COVID-19 tests that target SARS-CoV-2 specific markers at either the genetic level (RNA) or protein level (antigens or antibodies).

Figure 1 Molecular, antigen and antibody targets of available laboratory and near-patient tests for SARS-CoV-2

Used with permission (adapted) from D'Cruz et al 2020.[27]



Processing of specimens for both molecular and antigen tests can occur both inside and outside the laboratory setting.[1] Antigen tests that are processed outside the laboratory setting are the specific focus of this review. These can be further classified based on the setting in which the test is administered and who administers the test. Near-patient (or point-of-care) tests are administered in healthcare or other settings by an experienced trained professional, while a self-test may be administered by a lay person, typically at home.[1, 23] Near-patient antigen tests and antigen self-tests are generally referred to as antigen rapid detection tests (Ag-RDTs) or rapid antigen detection tests (RADTs). Collectively, these tests will be referred to as RADTs throughout this evidence summary.

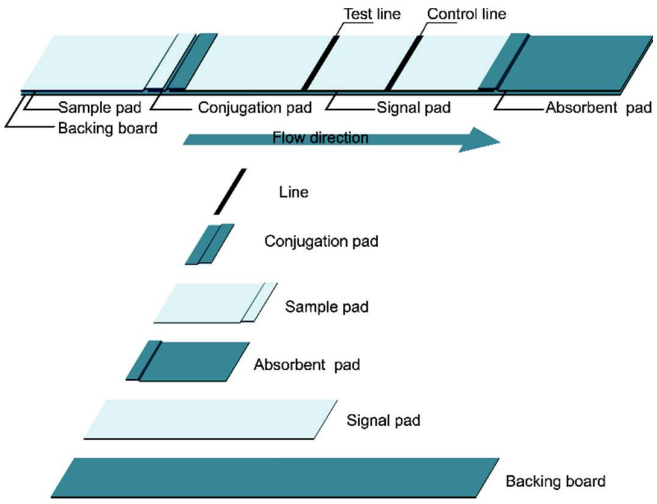
3.1.1.1 How do RADTs work?

RADTs, normally directed against the nucleoprotein of SARS-CoV-2, involve lateral flow immunoassays (LFIA). Also known as immunochromatographic assays or strip tests, LFIAs are designed to operate along a single axis. The LFIA test consists of a simple, portable lateral flow assay strip or dipstick containing immobilised test reagents, enclosed in a cassette to measure SARS-CoV-2 antigen, such as nucleoprotein (N).[27] There are two types of lateral flow devices:

- LFIA with visual read-out (qualitative; no requirement for additional instrumentation)
- LFIA with an associated reader device (quantitative or semi-quantitative; removes subjectivity from the interpretation of results).

The sample is applied at one end of the strip (sample pad), which contains buffer salts and surfactants that make the sample suitable for interaction with the detection system. The sample migrates through the conjugate release pad, which contains antibodies that are specific to the target SARS-CoV-2 antigen, and are conjugated to coloured or fluorescent particles (most commonly colloidal gold and latex microspheres).[28] The original sample, together with the conjugated antibody bound to the target antigen (if present), migrates along the strip into the detection zone - a porous membrane (usually composed of nitrocellulose) with specific antibodies immobilised in lines which react with the antigen bound to the conjugated antibody. If the antigen is detected, a response will appear on the test line.[28] A response on the control indicates proper liquid flow through the strip and the role of the absorbent pad is to absorb excess reagents and prevent backflow of the liquid.[28] Figure 2 illustrates the typical configuration of an LFIA test strip. The read-out can be assessed visually or using a device reader depending on the design of the test.[29, 30] The use of a reader standardises the interpretation of test results, reducing inter-operator variance in assay interpretation, but requires additional equipment.[30]

Figure 2 Typical configuration of an LFIA test strip



3.1.1.2 What are the differences between RADTs and other tests?

'Rapid tests', which include RADTs, are officially defined within the European Commission In-Vitro Diagnostic Medical Devices Directive as 'qualitative or semi-quantitative devices, used singly or in a small series, which involve non-automated procedures and have been designed to give a fast result'.[31] In comparison with the gold standard laboratory based RT-PCR diagnostic test for SARS-CoV-2, RADTs have a considerably faster turnaround time (from sampling to reporting of results); typically less than 30 minutes compared with 1-3 days for an RT-PCR test as the latter typically require transport to a centralised laboratory for processing. Additionally, RADTs are relatively less expensive than RT-PCR tests. However, they are also less sensitive than RT-PCR tests, with sensitivity varying depending on the timing of their administration during the course of an infection. There are alternative highly sensitive molecular tests, such as near-patient RT-PCR and reverse-transcription loop-mediated isothermal amplification (RT-LAMP) that can provide a faster turnaround of results than laboratory-based RT-PCR, however these tests are less commonly used in practice currently.[32] A summary comparison of laboratory-based RT-PCR tests, rapid near patient molecular tests, and RADTs is provided in Table 1 below.

Table 1 Summary comparison of laboratory based RT-PCR tests, rapid near patient molecular tests and RADTs*

Characteristic	Laboratory-based RT-PCR tests	Rapid near patient molecular tests	RADTs
Intended use	Detect current infection	Detect current infection	Detect current infection
Analyte detected	Viral ribonucleic acid (RNA)	Viral ribonucleic acid (RNA)	Viral proteins
Sensitivity	Varies by test, but generally high	Varies by test, but generally high. PCR generally higher than LAMP	Varies depending on the course of infection, but generally moderate-to-high at times of peak viral load, and low at other times
Specificity	High	High	High
Usability	Varies by test	Relatively easy to use	Relatively easy to use
Authorised for use at near patient test	Most are not, some are	Yes	Most are, some are not
Authorised for self-test	No	No – not in EU	Most are not, some are
Turnaround time (from sampling to reporting of results)	Days: typically 1-3 days	Minutes: 15 minutes	Minutes: typically 15-30 minutes
Place of processing	Inside the laboratory setting	In clinical settings, near patient testing	Mostly outside the laboratory setting
Cost per test	More expensive than RADTs	Comparable to lab batch PCR tests and microfluidics RADTs. Less expensive than laboratory rapid PCR tests	Less expensive than RT-PCR
Advantages	Most sensitive test method available Usually does not need confirmatory result	High sensitivity Short turnaround times Usually does not require confirmatory test	Short turnaround time Allows for rapid identification of infectious people, thus preventing further virus transmission in the community, workplace, etc. Comparable performance to RT-PCR tests in symptomatic persons and/or if culturable virus present, when the person is presumed to be infectious

Disadvantages	Longer turnaround for laboratory-based test Higher cost per test Prolonged detection of viral RNA is possible (often for several weeks) after the person is no longer infectious.	Require Near Patient Testing governance and quality management system NPT-PCR may detect remnant RNA as seen in lab based PCR. Less significant with LAMP assays.	May need confirmatory testing Less sensitive (more false negative results) compared to RT-PCR test, especially among asymptomatic people

Key: EU - European Union; RADT – Rapid antigen detection tests; RT-PCR – Reverse transcription polymerase chain reaction

*Adapted from US Centers for Disease Prevention and Control[33]

3.1.1.3 How are RADTs conducted and results reported?

Rapid antigen detection tests may be conducted (administered and processed) by a lay person, a trained professional or a combination of both as follows:

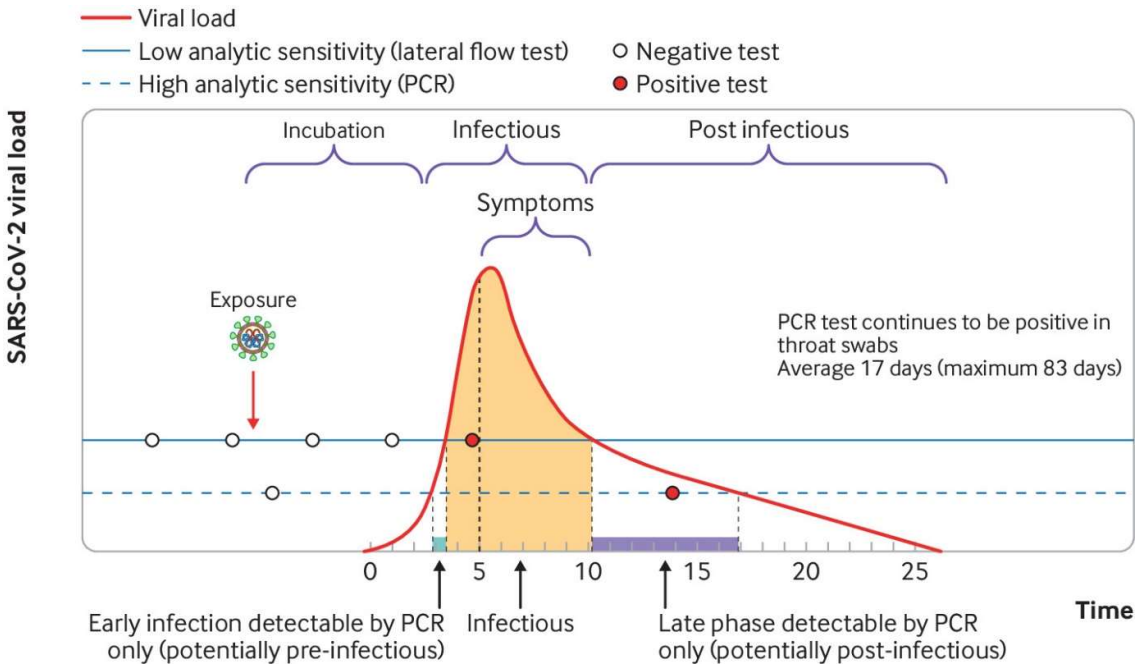
- Solely by a lay person who self-samples and processes the test without input from a trained professional (self-test).
- Fully by a trained professional who collects the sample and processes the test.
- Lay person self-samples under the supervision of a trained professional who then processes the test
- Lay person self-samples and processes the test under the supervision of a trained professional.

If healthcare personnel are involved in the testing process, additional workforce capacity is typically required given the time needed to train staff and to collect samples from individuals, administer tests and report test results to clinical staff and public health authorities, where appropriate.[7] While self-testing reduces the burden on healthcare personnel, there are potential issues when management of the end-to-end testing process rests solely with an individual. These include the potential for sub-optimal sample quality, which may affect the accuracy and reliability of results and the self-reporting of results which may lead to under- and or delayed reporting which could have an onward impact on contact tracing efforts and surveillance.[23]

3.1.1.4 What is the potential role of RADTs in screening and surveillance?

Given that RADTs are less sensitive than RT-PCR tests, they are not intended as a replacement for the gold standard RT-PCR test, but may supplement RT-PCR when diagnostic capacity is constrained. Detection of infectious individuals with an RADT is limited to an early and short-lived window compared with an RT-PCR test (Figure 3).[8] RADTs perform better in symptomatic individuals compared with asymptomatic individuals, with higher sensitivity reported for those who are symptomatic.[12, 24] Modelling studies have suggested that in the context of screening, frequency of testing and speed of reporting results should be prioritised over test sensitivity.[18] Therefore, although there is a very limited period in which to identify asymptomatic cases before they can transmit infection, it is suggested that RADTs used as part of screening or surveillance (with high frequency testing, for example every 3-4 days) for SARS-CoV-2, may offer the potential for rapid identification of the most infectious cases to enable prompt isolation and interruption of onward transmission.[16, 30]

Figure 3 Hypothetical scenario of high frequency (every 3-4 days) testing with low analytic sensitivity (RADT) versus low frequency (every 2-3 weeks) testing with high analytic sensitivity (RT-PCR). (Used with permission from Crozier et al.)[8]



Key: A person's infection trajectory (red line) is shown in the context of two hypothetical surveillance regimens (blue lines and circles) with different analytic sensitivity. Higher frequency testing is more likely to test in the infectious window. Therefore, although both testing regimens detect the infection (red circles), the high frequency (every 3-4 days) lateral flow test is more likely to detect it during the transmission window (yellow shading), despite its lower analytic sensitivity. The figure is not an accurate representation of exactly when a positive test is likely to signify that a case is infectious.

3.1.2 Regulatory status

As detailed in section 3.1.1, a range of tests are available for the purposes of detecting current infection with the SARS-CoV-2 virus. These tests are classified as in-vitro diagnostic medical devices (IVD), since they analyse a sample in-vitro (that is, outside the body) for the presence of the virus. In Europe, as elsewhere, tests used for COVID-19 must meet certain regulatory requirements in order to be placed on the market. According to the European *In Vitro* Diagnostic Medical Devices Directive (IVDD; 98/79/EC), manufacturers of professional tests for COVID-19 (SARS-CoV-2) are required to specify device performance characteristics and **self-declare** conformity with the essential requirements outlined in the Directive.[34] Manufacturers are not required to specify a setting in which RADTs should be used, but must indicate whether the device is intended for use by professionals or lay persons (that is, self-tests). Tests that fulfil these criteria are subsequently affixed with a CE (Conformité Européenne) marking and may be placed on the EU market.[34]

3.1.2.1 Self-tests

Since the beginning of the pandemic, an increasing number of RADTs have been CE-marked and made available on the EU market. Currently, there is no centralised register of CE-marked RADTs or other IVDs, so it is not possible to quantify the exact number of such devices on the EU market. However, according to the European Commission's Joint Research Centre (JRC), which has compiled a non-exhaustive list of CE-marked IVDs, a total of 373 RADTs had been CE-marked as of 20 July 2021; these include a wide range of automated and non-automated tests (for example, manual or lab-based and near-patient (point-of-care) tests).[35] Self-tests or at-home tests, which are tests that can be used by lay (or untrained) persons, additionally require manufacturers to apply to a third-party body (called a Notified Body) to examine the design aspects of the device and issue a corresponding certificate. An increasing number of tests are reportedly being CE-marked for use as self-tests, although only one such test was listed on the JRC website as of 20 July 2021.[35]

While only a small number of RADTs have been CE-marked as self-tests to date, countries can authorise the use of RADTs for purposes other than those specified under the CE marking through national derogations from Directive 98/79/EC. Upon receiving a request for a national derogation, the competent authority must assess the device to determine whether the provision of the non-CE marked device is in the interest of the protection of health as outlined in Article 14 of the IVDD. When a competent authority in a member state issues a national derogation, this derogation only applies to that individual member state.

An increasing number of countries have introduced RADTs for personal or home use (that is, self-tests). In Germany, a number of self-tests have been made available through a national derogation process for personal use.[36] These tests, which were originally CE-marked for use by professionals, can now be purchased in supermarkets, pharmacies, and shops, as well as online, by members of the public to provide reassurance prior to 'everyday situations', such as before visiting someone or going to a bar or restaurant. In the event that a positive result is obtained from a self-test, individuals are not required to confirm the result with local health authorities, but are requested to arrange a confirmatory test using RT-PCR.[37]

In France, self-tests were introduced in April 2021, but have only been made available for purchase in pharmacies, in line with the country's regulation of IVDs.[38] As in Germany, users are not required to report their results to local public health authorities, but are asked to attend for RT-PCR testing if the self-test returns a positive result.

In contrast, in Austria, positive test results must be reported to district administrative authorities, where self-tests have been available since March 2021, and the result must be confirmed by a molecular biological test such as RT-PCR.[39] The tests have been incorporated into the country's national testing strategy through a special national regulatory process; individuals with registered national health insurance may avail of five free self-tests from pharmacies in any given month. Sweden has also permitted the use of self-tests, but appears to have limited their use to certain workplaces for the purposes of routine screening.[40]

In Ireland, the Health Products Regulatory Authority (HPRA) is the Competent Authority (CA) for medical devices and IVDs, and monitors the safety of medical devices and IVDs after they have been placed on the market.[41] The HPRA has developed a regulatory derogation process for the urgent assessment of applications to facilitate the use of critical non-CE marked medical devices and IVDs in the context of the COVID-19 emergency in Ireland. Any devices that have been CE-marked as self-tests anywhere in the EU may be marketed in Ireland, but as noted, this does not apply for those that have only been authorised through a national derogation in another member state. To-date no national derogation has been issued with respect to an RADT for use as a self-test in Ireland.

3.1.2.2 Screening / surveillance

While a small number of SARS-CoV-2 RADTs have been CE-marked for use by lay persons (self-tests), the vast majority of RADTs have been CE-marked as point-of-care tests for use in symptomatic individuals (within a certain timeframe from symptom onset) by trained persons. It is unclear how many self-tests, if any, are intended for use in asymptomatic people. The manufacturer's performance evaluation is based on the test being used according to the CE-marking and manufacturers' instructions for use (IFU). The extent that these data can be replicated in real world settings depends on the pre-test probability (that is, the chance that the patient has the disease, estimated before the test result is known), and the extent that users follow the manufacturer's IFU (any deviation from this can affect the accuracy of the test, as detailed in section 3.1.4.4), although the performance of the device may be affected by other factors (for example, timing of sample). The European Commission recommended in April 2020 that, in the absence of validated data on the clinical performance of RADTs in real world settings, member states should carry out validation studies before introducing RADTs into clinical practice.[42] Countries, including Ireland, have been validating and verifying the clinical performance of RADTs in clinical settings.[43]

In recent months, countries have also extended the use of RADTs (likely beyond their CE marking; referred to as 'off-label' use) to include asymptomatic populations

for the purposes of screening and serial testing. For example, in France, the Haute Autorité de Santé (HAS) authorised the use of RADTs for diagnostic purposes, as well as for screening in certain situations, such as in a targeted population (for example, in schools, factories, collective accommodation, among other settings).[44, 45] Targeted testing (or screening) has also been permitted in asymptomatic individuals in at-risk groups or settings across a range of other EU Member States, including in, but not limited to, Belgium,[38] Denmark,[46] Italy,[47] Portugal,[48] Spain,[49] and Sweden.[40] A small number of countries have also implemented mass screening using RADTs in an effort to limit the spread of COVID-19 in the general population. As well as conducting ongoing screening and serial testing in health and other settings, Slovakia[50] conducted multiple rounds of national mass screening using RADTs, while Austria[51] and Czechia[52] undertook voluntary population-wide antigen testing. (Further details on the effectiveness of various mass screening programmes is presented in Section 3.2). While there is no legal impediment against 'off-label' use of IVDs in the EU, liability falls to the healthcare professional and/or health service using or commissioning the tests, as opposed to the manufacturer, in the case of 'off-label' usage.

RADTs have also been authorised for use in non-EU countries for screening or serial testing purposes in asymptomatic populations. In England, for example, where screening has formed a large part of the country's efforts to limit the spread of COVID-19, RADTs have been widely used, including in a pilot mass screening programme, which was conducted in Liverpool between November 2020 and April 2021.[53] (Further details on the effectiveness of mass screening in Liverpool are presented in Section 3.2). These tests are regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and have been authorised for exceptional use in asymptomatic populations by the National Health Service (NHS) Test and Trace programme.[54] Innova are the supplier of NHS Test and Trace RADTs, although the Department of Health and Social Care (DHSC) take on the responsibilities of the legal manufacturer for the products used in the UK, due to the relabelling of the Innova test for use in asymptomatic populations.[55] The Innova RADTs are originally manufactured in China, and are intended to be used in those "suspected of COVID-19 by their healthcare provider within the first five days of the onset of symptoms."[56]

In the US, as of 20 July 2021, the Food and Drug Administration (FDA) had granted emergency use authorisation (EUA) for 30 antigen detection tests (including laboratory-based and near-patients tests).[57] Of these, 12 RADTs have been authorised specifically for screening or serial testing in asymptomatic individuals.

3.1.2.3 Upcoming changes to EU regulations

The regulatory framework within which IVDs are currently regulated in the EU is in a state of transition. New regulations (Regulation 2017/746)[58] entered into force in May 2017 and will become fully applicable for IVDs from 26 May 2022 (the new regulations became fully applicable for medical devices from 26 May 2021) and replace the existing Directive 98/79/EC.[31] The regulations are aimed at strengthening the existing principles and fundamental components of the regulatory system. With respect to IVDs, the new regulations will improve the performance of Notified Bodies; enhance provisions for market surveillance; and strengthen the requirements and structures defined to provide for governance, coordination and cooperation of the regulatory system. Under the new regulations, a risk-based device classification system will be introduced, ranging from class A (low risk) to class D (high risk). The new regulations may have a significant impact on the regulation of RADTs, which will likely fall into the high risk class, meaning manufacturers will no longer be permitted to self-declare conformity with the general safety and performance requirements.[59] Further details of Regulation 2017/746 can be found in Appendix 1.

3.1.3 Investment, tools and training

3.1.3.1 The test procedure

It is recommended that nasopharyngeal and oropharyngeal samples are taken by trained healthcare providers, while anterior nasal samples can be taken by healthcare providers or by self-sampling.[60] Figure 4 illustrates an example of the rapid antigen testing procedure. The extraction tube is filled with the buffer liquid. A sample is taken using the swab. The swab with the collected sample is placed into the extraction tube and is left in the extraction solution for a specified amount of time (usually 1-2 minutes). The nozzle cap is installed tightly onto the extraction tube. Several drops are squeezed onto the specimen well on the test strip. The specified wait time designated by the manufacturer (usually 15-30 minutes) needs to be adhered to before reading the test result. One line on both of the C (control) and T (test) indicates a positive result (even if the T line is faint). One line on C indicates a negative result, while no line, or a line only at T indicates an invalid test and that the test needs to be repeated.

Figure 4 Example of the rapid antigen test procedure

3.1.3.2 Training and resource requirements for scaling up

In this evidence summary, the use of RADT for screening or surveillance was considered as an alternative to no-testing, rather than the use of a different test such as RT-PCR. Hence, while some of these resource implications may be applicable to any test (for example, RADT or RT-PCR) used at scale in asymptomatic populations, the resource implications considered in this section are from the perspective of RADT versus no-testing.

As discussed in Section 3.1.1 RADTs are portable and do not require laboratory analysis, therefore in the context of screening and surveillance, they could potentially facilitate decentralised testing at scale.[8] Costs of rapid antigen testing in particular settings, including meat processing plants and higher education institutes, have been estimated in Ireland.[19, 61] The indicative average cost in meat processing plants of an RADT test including the typical cost of the test kit, and staff time for supervising swabbing and processing the test is estimated at €10 (95% CI: €7 to €13), while an estimate cost of a RT-PCR test including the typical cost of test processing and staff time for swabbing and administration is €83 (95% CI: €68 to €99).[19]

Considering higher education settings,[61] the estimated cost per test for supervised RADT testing is €13 (95% CI: €12 to €15) carried out by a trained individual, including PPE, waste disposal, test kit costs, staff time and costs associated with confirmatory RT-PCR tests for a given level of prevalence. In this setting, supervised RADT implies supervised self-sampling of nasal specimens with staff on site to process and report the tests. For unsupervised self-administered testing, the estimated cost is €4 (95% CI: €3 to €5) per test. This includes staff costs for assembling testing packs, test pack consumables and again confirmatory RT-PCR tests.

In the case of professionally administered RADTs, these are potentially suitable for near patient testing (NPT), which occurs on site and thus tests are not transported elsewhere. All testing for SARS-CoV-2 is directly impacted by the integrity of the

specimen, which depends on specimen collection, storage and transport.[33] Guidelines for NPT highlight that a designated area for the provision of NPT should include suitable facilities for sample collection, test performance, instrument storage, safe disposal of clinical waste and storage of consumables in accordance with the appropriate conditions as defined by the manufacturer and applicable legislation. Quality assurance measures are required to monitor the ongoing "in-use" diagnostic performance of rapid antigen tests. Individual settings may need to consider their own staffing, infrastructure and culture when establishing the workflow for COVID-19 NPT.

The National NPT Consultative Group guidelines highlight the benefits of a designated operational team to provide oversight and monitoring of training and certification thereby ensuring consistency across all NPT sites.[62] The World Health Organization (WHO) emphasises that training must cover all stages of the testing pathway.[63] With respect to diagnostic testing, it notes that, given the challenges associated with adequate sample collection and the potential pre-analytical and analytical vulnerabilities associated with testing, sample collection and processing should only be performed by trained personnel.[63] Additional training requirements include:

- the use of test devices and readers (if applicable)
- systems for recording results (patient results and quality assurance)
- internal and external quality assurance systems
- troubleshooting methods and an understanding of health and safety legislation.[64]

While training requirements for the operation of some low-complexity tests are said to be minimal, training in all aspects of NPT should be provided to ensure that testing is carried out in line with best practice procedures, ensuring that results are accurate and reliable. User experience and familiarity with the device are an important consideration for achieving good performance.

Self-testing may be applicable in some settings (for example, to enable people to return to work or school). In this case, the costs and training of healthcare staff is removed, but ideally training should be arranged in order to ensure the quality of sample collection. In addition, mechanisms for reporting the test results which have resource implications, should also be in place. Internationally, self-test RADTs are in use in some sectors, for example, education, hospitality and mass gatherings where the sampling, testing and result interpretation is completed by the test-individuals

themselves.[23, 65] The main instruction with this type of usage is typically in the form of paper or electronic leaflets and/or videos demonstrating the taking of the test and interpretation of the results. The variation in test sensitivity comparing self-testing to testing by skilled professionals is discussed in section 3.1.4.4.

Some examples of implementation of testing using RADTs are given to illustrate the resource requirements that have been required in particular settings. RADTs have been used at scale in many European countries in a variety of settings. In Austria, both professionally taken and self-test RADTs are widely used. For example, since December, the Austria Centre Vienna has been hosting the nation's largest testing facility.[66] In the two weeks at the end of 2020 (between 18 and 31 December 2020), around 113,000 RADTs were conducted at the venue, with 200 people involved in running the facility each day. Self-test RADTs have been used amongst school students in Austria since February 2021.[67] The students test under supervision in the school. Each week in the period from mid-February to the end of March between 1.3 million and 1.7 million RADTs were completed in schools as the testing regime was rolled-out.[68]

As part of a mass testing pilot in Liverpool, that took place between November 2020 and April 2021, over 283,338 residents (comprising 57% of the total population) took at least one RADT (which was a supervised, self-administered swab). In each of the 48 test sites across the city, there were 20 bays each testing six people per hour from 07:00 to 19:00 each day to generate a capacity of 69,120 tests daily, which is around 14% of the population per day.[69] RADT twice weekly school testing commenced nationally in England on 8 March 2021.[70] Pupils were provided with two RADTs per week to self-test at home. In addition to school testing, since April 2021, everyone in England has been offered access to twice weekly rapid testing for COVID-19 in a huge expansion of the government's mass asymptomatic testing programme.[71] RADTs (free to the individual) can be ordered online to use at home, accessed through their workplace, or obtained from their local authority or local pharmacies. It has been suggested that the estimated spend for this national asymptomatic screening strategy, known as "Operation Moonshot" would be approximately £100bn (€117bn).[71]

RADTs have been used in one-off events with the aim of minimising infection spread amongst attendees, however this can carry substantial staffing and logistical requirements particularly if supervised testing is implemented. For example, in Barcelona, Spain, a concert was held in the Palau Sant Jordi stadium in March 2021 with RADT required of each person who was due to attend on the day of the concert.[72] On the day of the event (from 8:00 to 15:00), a team of 74 nurses performed RADTs for all attendees at three screening sites, for 5,000 attendees.[72]

A large-scale mass testing campaign comes with potential staffing and training challenges. During October and November 2020, Slovakia conducted a mass antigen testing programme among its entire population of 5.5 million, with more than 50,000 positive cases being identified.(50) In Slovakia, the need to mobilise sufficient medical personnel to conduct the nasopharyngeal swabs proved to be a major obstacle.(50) Also, the logistics of mobilising large numbers of assisting army personnel and vast amounts of testing and personal protective equipment (PPE) material proved challenging. Overall, Slovakia deployed around 20,000 medical staff and 40,000 non-medical personnel with cost estimates of €30 million for military staffing and €52 million for purchasing test kits.(73)

In summary, there are substantial staffing and logistical requirements if trained professionals are involved in the testing process (sample taking and or test processing and or reporting). While a number of RADTs are authorised as self-tests, the quality of sample collection may be reduced compared with samples taken by trained professions, leading to reduced sensitivity. When scaling up rapid antigen testing for asymptomatic populations, it is important to consider that some of the required infrastructure may already be in place from RT-PCR testing processes (for example, trained personnel, reporting systems, confirmatory tests). However, given that testing may be expanded to large sections of the population who would not otherwise be tested, it is likely that significant investment in resources would still be needed, which may be associated with a substantial opportunity cost (for example, redeployment of staff). While the individual cost of a procuring an RADT is considerably lower than that of an RT-PCR test, successful deployment of RADTs at scale, for screening and or surveillance of asymptomatic individuals or populations, would incur a significant total cost.

3.1.3.3 Reporting and confirmatory testing

The public health response to COVID-19 depends on comprehensive testing data which contribute to understanding the impact of COVID-19, positivity trends and testing coverage. All test results (positive and not detected) should be recorded appropriately in accordance with defined procedures and the General Data Protection Regulation. As COVID-19 is classified as a notifiable disease, all medical practitioners, including clinical directors of diagnostic laboratories, are required to notify the Medical Officer of Health (MOH) and or Director of Public Health of a confirmed case of COVID-19. The MOH reports the notification onwards to the Health Protection Surveillance Centre (HPSC).(74)

The HPSC states that detection of SARS-CoV-2 antigen in a clinical specimen can be considered a confirmed case. They add that an RADT should be performed within five days of onset of symptoms or within seven days from time of last exposure to a case. The sensitivity and specificity of RADTs depend on the assay used, the

personnel carrying out the test and the clinical indication or setting in which they are used. Due to this variability in test performance, antigen testing undertaken outside the governance of the public laboratory service is not recognised at present for the purpose of notification of SARS-CoV-2 infection.[75] In particular, if the RADT was undertaken outside the governance of the public laboratory service, a confirmatory RT-PCR is required before a case is notified. When community prevalence is high, and when there may be pressures on laboratory capacity for RT-PCR testing, the HPSC state that RADTs have a role in detection of symptomatic cases, particularly in settings where there is swabbing capacity on site, such as in acute hospitals.[14] In these circumstances RADTs as well as laboratory-based antigen detection tests might be used. Test results should be reported to the HPSC to ensure results obtained in non-laboratory settings are documented in the national level statistics to facilitate accurate monitoring of infection rates and trends, and to provide accurate data on the extent and setting of testing.

The new national medical laboratory information system (MedLIS) aims to deliver a complete national pathology record for all patients in Ireland including integration of NPT results.[62] Piloting of the new system commenced in Cavan General Hospital in late 2020.[76] In order to reduce reporting burdens for testing facilities and ensure that COVID-19-related test data is accurate and consistent, standardised terminology should be used (for example, SNOMED-CT) to improve the accuracy of reporting tests for the SARS-CoV-2 virus. It has been noted that it is important that the results of diagnostic and screening tests are distinguishable in the reporting system according to the type of test used (for example, RT-PCR, rapid molecular test, RADT).[77] The recording of the results from screening, using rapid tests, and laboratory confirmed RT-PCR represents a challenge for duplication of results in the reporting system that are later confirmed. Patient test results can be linked to a unique patient identifier in order to determine the total number of tests carried out, and the number of individuals tested. Electronic reporting options are favoured to reduce the administrative burden on providers reporting test results and minimise the risk of reporting errors. The HSE National Testing Programme is currently building a platform for the recording and reporting of RADT results, including onward referral for confirmatory RT-PCR.[78]

In England, students and staff self-testing at home must report their results to the contact tracing system in England run by the UK Health Security Agency either online or by telephone. They should also inform the school of the result to assist with contact tracing. Prior to 27 January 2021, positive RADTs taken under supervision needed to be confirmed by a RT-PCR test. Between 27 January 2021 and 29 March 2021, confirmatory RT-PCR testing was temporarily removed for positive RADTs taken at general public test sites due to the high level of SARS-CoV-2

infections in England. During this period, a positive RADT result triggered the start of contact tracing.[79] A confirmatory RT-PCR test for a positive RADT was re-introduced in England in 30 March 2021 when prevalence of COVID-19 was lower and hence the positive predictive value of the RADTs was lower.[80] A positive RADT result currently activates contact tracing in England. However, the contact tracing system will inform anyone self-isolating from a positive RADT to stop isolating if the confirmatory RT-PCR is negative and these individuals are then removed from contact tracing. Currently the general public are asked to report their RADT results within 24 hours of performing the test, however compliance with this measure is unclear. The requirement for confirmatory RT-PCR testing based on reduced diagnostic accuracy is further explained in Section 3.1.4.

3.1.4 Diagnostic accuracy of RADTs

Diagnostic test accuracy describes the comparison between the estimate of a disease state ('target condition'; for example, presence of SARS-CoV-2 infection) by a test of interest (the 'index test'; for example, RADT) and the current best estimate of the true disease state ('the reference standard' test; for example, RT-PCR). Key metrics of diagnostic test accuracy include clinical sensitivity (that is, the proportion of positive index tests in individuals who in fact have the disease in question) and specificity (that is, the proportion of those without the disease who are correctly classed as negative by the index test). Where an individual has a negative test result, the probability that they are truly infected with SARS-CoV-2 is a function of the sensitivity of the test and the pre-test probability of being infected. Pre-test probability depends on factors such as local COVID-19 prevalence, SARS-CoV-2 exposure history, symptoms, and potential additional risk factors for infection. For further information about the determination of diagnostic test accuracy, the reader is referred to a rapid HTA of alternatives to RT-PCR (Chapter 4), which was previously undertaken by HIQA; available here.[7]

While RT-PCR is the most commonly used reference standard for SARS-CoV-2 infection in the literature,[12] it is important to acknowledge that RT-PCR has some limitations (for example, no consensus on cycle threshold (C_t) value that defines positivity, variability across commercial kits and prolonged detection of nonviable viral particles). It has been argued that viral culture could be considered a suitable alternative reference standard specifically for infectiousness.[81] Importantly though, viral culture is generally less available in clinical settings,[82] and additionally, the lack of culture positivity does not necessarily conclude non-infectivity as analytical issues may have prevented cell culture growth.[83] For example, numerous biological (such as individual antibody status) and environmental (such as storage conditions and number of freeze-thaw cycles) variables can affect the sensitivity and outcome of viral culture.[11] For the purpose of this diagnostic test accuracy section, RT-PCR is

considered to be the reference standard for detection of SARS-CoV-2 infection as defined by the WHO.[84] The absence of an agreed reference standard for infectiousness is noted,[12] therefore the use of viral culture as an alternative to RT-PCR is also discussed.

The diagnostic test accuracy of RADTs has been the subject of a large number of independent validation studies to date. The University of Heidelberg provides a detailed overview on the data published on the performance of RADTs.[85] The website provides information about:

- the study location
- researcher independence
- sample condition (for example, fresh versus banked)
- sample type (for example, nasal versus nasopharyngeal)
- sample size
- clinical sensitivity and specificity
- a quality assessment of the risk of bias and applicability (of patients and setting to a review question) of each study using QUADAS 2 (Quality Assessment of Diagnostic Accuracy Studies).[86]

While the website provides useful information about the potential clinical sensitivity and specificity of individual antigen tests, including the potential range of sensitivity, the data are not pooled. Furthermore, pooling these data is not straightforward given the heterogeneity in the methods and characteristics in each study (such as study population (for example, symptomatic versus asymptomatic), administration and timing of test, reasons for testing, among other factors).

Three systematic reviews of the diagnostic test accuracy of RADTs relative to RT-PCR (as the reference standard) were identified, as part of RQ2 searching, and are discussed below.[12, 82, 87] One of these reviews additionally considered viral culture as the reference standard.[87] The reviews comprise a 'living' (Cochrane) systematic review by Dinnes et al.[12] which includes evidence up to 30 September 2020. The latest version was published on 24 March 2021 and a further update is expected soon with evidence up to April 2021 (personal correspondence). The two other published systematic reviews include a 'living' systematic review by Brummer et al.,[82] which was last published on 12 August 2021 with evidence up to 30 April 2021, and a systematic review (pre-print) undertaken by Parvu et al.[87] (published

on 22 May 2021) which includes evidence up to 1 February 2021; it is unclear if the latter is a living systematic review. A brief summary of the findings from each study on the diagnostic accuracy of RADTs compared with RT-PCR is provided below. It is important to note that other systematic reviews may be available, but were not identified in the search since this was not the primary purpose of RQ2.

3.1.4.1 Symptomatic versus asymptomatic populations

Table 2 provides an overview of pooled estimates of sensitivity and specificity, where available, for the three systematic reviews in symptomatic and asymptomatic individuals. According to Dinnes et al.,[12] estimates of sensitivity varied considerably between studies, however, sensitivity was higher in symptomatic individuals (72.0%, 95% CI 63.7 to 79.0%; 37 evaluations; 15,530 samples, 4,410 positive cases) than in asymptomatic individuals (58.1%, 95% CI 40.2 to 74.1%; 12 evaluations; 1,581 samples, 295 positive cases). Brummer et al.[82] observed similar findings, although sensitivity was markedly higher in symptomatic individuals (76.7%, 95% CI 70.6 to 81.9%; 38 evaluations, 17,964 samples) than asymptomatic individuals with (52.5%, 95% CI 43.7 to 61.1%; 25 evaluations, 15,228 samples). Test sensitivity in symptomatic individuals was slightly higher in Parvu et al.[87] than Dinnes et al.[12] and Brummer et al.,[82] estimated to be 80.1% (95% CI 76.0 to 83.7%, 95 evaluations, 9,351 positive cases), although broadly comparable estimates of sensitivity were observed in asymptomatic individuals with Dinnes et al.[12] and Brummer et al.,[82] at 54.8% (95% CI 48.6 to 60.8%; 23 evaluations, 1,723 positive cases). Test specificity was reported by Dinnes et al.[12] and Brummer et al.[82] and found to be high in symptomatic and asymptomatic individuals (approximately 99%), although more uncertainty was observed in Dinnes et al.[12] in asymptomatic individuals (95% CI 93.6 to 99.8%), likely due to the lower sample size.

3.1.4.2 Viral load

Detection of the SARS-CoV-2 virus is dependent on viral load. This changes during the course of disease: low shortly after exposure, highest around the time of symptom onset and declining thereafter.[88] When tested using RT-PCR, viral load is inversely correlated with the cycle threshold (C_t) value of the test – that is, the higher the viral load, the lower the C_t value.

A common finding across each of the reviews was that when compared with RT-PCR, the sensitivity of RADT was highest in those with C_t values on RT-PCR ≤25 (which can be considered to reflect a high viral load) (Table 3). For instance, Dinnes et al.[12] found that sensitivity was 94.5% (91.0 to 96.7%) in those with C_t value of ≤ 25, compared with 40.7% (31.8 to 50.3%) in those with a C_t value of ≥ 25. At a cut-off value of 32 or 33, the difference in sensitivity was substantially more pronounced; 82.5% (95% CI 74.0 to 88.6%) in those with a C_t value of ≤ 32 or 33,

versus 8.9% (95% CI 3.3 to 21.7%) in those with a C_t value of > 32 or 33. Dinnes et al.[12] and Brummer et al.[82] did not present a breakdown of sensitivity by symptom status and viral load, likely due to insufficient data. However, Brummer et al.[82] observed that median C_t values differed in symptomatic and asymptomatic individuals; where data were available, the authors observed that median C_t values ranged from 20.5 to 27.0 in symptomatic individuals and from 27.2 to 30.5 in asymptomatic individuals.

Studies have shown an approximately linear association between C_t values and transmissibility – with low C_t value (higher viral load) associated with increased transmissibility of SARS-CoV-2. The data presented therefore suggest that RADT can reliably detect those most likely to be infectious. While C_t values provide an indication of potential infectivity, it is important to note that they only reflect viral load at the time of sampling: if the sample was taken shortly after exposure, risk of infectivity may increase as the viral load subsequently rises. Conversely, positive RT-PCR results based on samples taken late in the disease course, may reflect detection of non-viable virus. However, there is evidence that individuals with a high C_t value can still transmit SAR-CoV-2 to others, with no accepted cut-off of C_t values to eliminate transmissibility.[89]

Table 2 Summary of sensitivity and specificity analyses by systematic review, stratified by symptomatic and asymptomatic groups

Study	Datasets	Samples	Positive cases	Sensitivity (95% CI)	Specificity (95% CI)
Symptomatic					
Dinnes et al.[12]	37	15,530	4,410	72.0% (63.7 to 79.0%)	99.5% (98.5 to 99.8%)
Brummer et al.[82]	38	17,964	NR	76.7% (70.6 to 81.9%)	99.0% (98.5 to 99.4%)
Parvu et al.[87]	95	NR	9,351	80.1% (76.0 to 83.7%)	NR
Asymptomatic					
Dinnes et al.[12]	12	1,581	295	58.1% (40.2 to 74.1%)	98.9% (93.6 to 99.8%)
Brummer et al.[82]	25	15,228	NR	52.5% (43.7 to 61.1%)	99.1% (98.3 to 99.5%)
Parvu et al.[87]	23	NR	1,723	54.8% (48.6 to 60.8%)	NR

Key: NR, not reported; CI, confidence interval

Table 3 Summary of sensitivity of RADTs by systematic review, stratified by viral load (based on different cycle threshold cut-offs)

Study	Datasets	Positive cases	Sensitivity (95% CI)
Dinnes et al.[12]			
C_t values of < or > 25			
High (< or ≤ 25)	36	2,613	94.5% (91.0 to 96.7%)
Low (> or ≥ 25)	36	2,632	40.7% (31.8 to 50.3%)
C_t values of < or > 32/33			
High (≤ 32 or 33)	15	2,127	82.5% (74.0 to 88.6%)
Low (> 32 or 33)	15	346	8.9% (3.3 to 21.7%)
Brummer et al.[82]			
C_t value of <20	22	741	96.5% (92.6 to 98.4%)
C_t value of ≥20	12	598	94.4% (79.2 to 98.7%)
C_t value of <25	47	3004	95.8% (92.3 to 97.8%)
C_t value of ≥25	24	987	50.7% (35.6 to 65.8%)
C_t value of <30	37	2,879	79.9% (70.3 to 86.9%)
C_t value of ≥30	29	509	20.9% (12.5 to 32.8%)
Parvu et al.[87]			
C_t value of ≤ 25	16	897	96.4% (94.3 to 97.7%)
C_t value of > 25	16	673	44.9% (33.0 to 57.4%)
C_t value of ≤ 30	37	2,536	89.5% (85.3 to 92.5%)
C_t value of > 30	37	679	18.7% (12.9 to 26.3%)

Key: C_t, cycle threshold; CI, confidence interval

While C_t values provide a useful semi-quantitative metric to reflect potential infectivity, comparisons across studies are complicated since different RT-PCR assays can yield different results. Carrol et al.[90] examined a variety of commercially available SARS-CoV-2 RT-PCR kits, used in several different laboratory sites in Ireland, and found that C_t values varied from different assays for the same calculated viral load. The authors also found that the usually assumed C_t cut-off of 34 may be insufficient in excluding SARS-CoV-2 infection, particularly in asymptomatic individuals whose potential infectivity remains broadly uncertain; instead C_t values up to 38 may be necessary. A previous rapid review also found that it is possible, though uncommon, for individuals with a high C_t value to still be infectious, though much uncertainty remains regarding the relationship between viral load and infectivity.[91] Given the issues associated with the use of C_t values, Public Health England (PHE) advises that a single C_t value in the absence of clinical context should not solely be relied upon for decision making about an individual's infectiousness (that is, the ability to transmit the virus to another person).[92]

Another important caveat in relation to viral load is that detection of viral RNA does not necessarily mean that an individual is infectious. Determination of infectivity (or

viable virus) may be accomplished by monitoring the ability of SARS-CoV-2 to replicate in laboratory-based cell culture. Viral culture, therefore, offers advantages over and above simple viral RNA detection, which could reflect non-replicative virus.[91] As such, for the purposes of determining infectivity, the sensitivity of RADTs relative to viral culture may be more informative than compared with RT-PCR, particularly in those with high C_t values. Parvu et al.[87] evaluated the sensitivity of RADTs (n=154 reference standard positive samples), as well as RT-PCR tests (n=167 reference standard positive samples), relative to SARS-CoV-2 viral culture (in varied populations of symptomatic and asymptomatic individuals, depending on the included study). From the five included datasets, the authors found that sensitivity was high for both: the sensitivity was 90% (95% CI 84 to 94%) for RADTs and 99% (95% CI 96 to 100%) for RT-PCR.

3.1.4.3 Implications of reduced diagnostic accuracy

Use of tests with suboptimal sensitivity and specificity carries a risk of misclassifying infected (or non-infected) individuals who would otherwise be detected (or excluded) using a reference standard. To correctly interpret the results of such tests, it is important to consider the context in which the test is being deployed, in particular the sensitivity and specificity of the test in the target population and the prevalence of disease. These data can be used to estimate the positive and negative predictive values (PPV and NPV, respectively) of the test, which can guide interpretation of test results and the appropriate response needed to rule out (or in) the presence of disease.

Table 4 presents potential NPV and PPV for different levels of disease prevalence (0.5%, 1%, 5%, and 10%) in a cohort of 100,000 asymptomatic individuals using pooled estimates of sensitivity and specificity from Dinnes et al. (sensitivity of 58.1% and specificity of 98.9%). The NPV and PPV are also presented for the WHO's recommended minimum performance criteria for RADTs (sensitivity of 80% and specificity of 99%) for reference. When the prevalence of SARS-CoV-2 is low, the PPV of RADTs in an asymptomatic population is similarly low, while the NPV is high, meaning an individual that tests negative for COVID-19 is unlikely to have the disease. However, if an individual tests positive for COVID-19 in a low prevalence setting, it is highly uncertain as to whether an individual is infected given the low PPV. For instance, assuming a disease prevalence of 0.5% and the sensitivity of 58.1% estimated by Dinnes et al., the PPV of an RADT in asymptomatic individuals is 21%. This would mean than of 100,000 asymptomatic individuals tested, 1,385 will test positive, of whom 291 are true positives while 1,094 individuals are misdiagnosed (false positive); that is, only approximately one in five of those with a positive test result will have COVID-19. The corresponding NPV at this disease

prevalence is 99.8%, that is, one in every 500 negative test results will be a false negative.

The ECDC recommends that in low prevalence settings, confirmatory RT-PCR testing should be undertaken for all positive test results to verify the presence of disease given the uncertainty of the results.[24] Frequent serial testing may be used in these circumstances (for example, every 2-3 days) to mitigate the reduced sensitivity of the tests and ensure infected individuals can be quickly identified. However, sufficient RT-PCR capacity for confirmatory testing would be required to ensure rapid turnaround of test results.

In contrast, in high prevalence settings, the PPV is higher (and more likely to reflect the presence of disease), while the NPV is more uncertain. In these situations, the ECDC recommends that confirmatory RT-PCR testing should be undertaken for negative test results given the increased likelihood of falsely excluding the presence of COVID-19 in infected individuals (false negatives).[24] For example, when community prevalence is 10%, based on a sensitivity and specificity of 58.1% and 98.9%, respectively the NPV is 95.5%. That is, of 100,000 asymptomatic individuals tested, approximately one in twenty of those with a negative test result will have been misclassified (4,190 infected individuals returned as false negatives; 89,010 true negative) (Table 4). The ECDC recommends that repeat antigen testing a few days later (to allow the viral load to increase) may suffice in the absence of sufficient RT-PCR capacity.[24]

Table 4 Impact of the use of RADTs in an asymptomatic population of 100,000 (for all potential C_t values) with varied prevalence of COVID-19 (0.5, 1, 5, 10%) compared against the minimum performance criteria recommended by the WHO for RADTs

Study	Prevalence	NPV	PPV	TP	FP	TN	FN	No. with disease	Positive tests
Dinnes et al.[12]	0.5%	99.8%	21.0%	291	1,094	98,406	209	500	1,385
Sensitivity: 58.1%	1%	99.6%	34.8%	581	1,089	97,911	419	1,000	1,670
Specificity: 98.9%	5%	97.8%	73.5%	2,905	1,045	93,955	2,095	5,000	3,950
	10%	95.5%	85.4%	5,810	990	89,010	4,190	10,000	6,800
WHO recommendations[30]	0.5%	99.9%	28.7%	400	995	98,505	100	500	1,395
Sensitivity: 80.0%	1%	99.8%	44.7%	800	990	98,010	200	1,000	1,790
Specificity: 99.0%	5%	98.9%	80.8%	4,000	950	94,050	1,000	5,000	4,950
	10%	97.8%	89.9%	8,000	900	89,100	2,000	10,000	8,900

Key: FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive; WHO, World Health Organization.

False positive refers to a test result that detects a condition (SARS-CoV-2 infection) in someone when it is not present.[21]

False negative refers to a test result that does not detect a condition (SARS-CoV-2 infection) when it is present.[21]

True positive refers to a correct diagnosis of a condition (SARS-CoV-2 infection) being present.[21]

True negative refers to a correct diagnosis of a condition (SARS-CoV-2 infection) being absent.[21]

Sensitivity refers to the proportion of people with the target condition (SARS-CoV-2 infection) that are correctly identified by the index test (RADT).[21]

Specificity refers to the proportion of people without the target condition (SARS-CoV-2 infection) that are correctly identified by the index test (RADT).[21]

Positive predictive value refers to the probability that someone who has tested positive for the target condition (SARS-CoV-2 infection) with the index test (RADT) will actually have it (that is, a true positive).[21]

Negative predictive value refers to the probability that someone who has tested negative for the target condition (SARS-CoV-2 infection) with the index test (RADT) will really not have it (that is, a true negative).[21]

3.1.4.4 Factors that impact accuracy

There are a range of factors that might affect the performance of RADTs. According to the WHO,[63] these include the:

- time from onset of infection
- concentration of virus in the specimen
- quality and processing of the specimen collected from a person, and
- precise formulation of the reagents in the test kits.

With respect to the timing of the test, Dinnes et al.[12] reported that sensitivity was high in the first seven days after symptom onset (78.3%, 95% CI 71.1 to 84.1%) compared with the second week of symptoms (51.0%, 95% CI 40.8 to 61.0%). Brummer et al.[82] observed similar findings with a sensitivity of (83.8%, 95% CI 76.3 to 89.2%) observed in the first week after symptom onset compared with testing after one week (61.5%, 95% CI 52.2 to 70.0%), while Parvu et al.[87] observed slightly higher sensitivities: 86.2% (95% CI 81.8 to 89.7%) in the first week and 70.8% (95% CI 60.7 to 79.2%) thereafter. While the timing of the test since symptom onset is important (in symptomatic populations), it is less applicable to asymptomatic populations; instead, timing relative to exposure is important. However, none of the reviews considered 'time from exposure' in asymptomatic individuals, likely due to it being poorly reported or difficult to ascertain, particularly in asymptomatic populations whose exposure may be unknown.

There is some evidence that specimen type might affect performance. Parvu et al.[87] found that test sensitivity was higher with a nasal specimen (82.7%, 95% CI 74.7 to 88.5%) compared with a nasopharyngeal specimen (73.1%, 95% CI 68.5 to 77.2; p=0.037). However, Brummer et al.[82] found no significant difference between the specimen types, while Dinnes et al.[12] had insufficient data to pool estimates by specimen. When used for self-testing or by non-trained individuals compared to use by skilled professionals, the sensitivity of RADTs has been shown to be lower. For example, in people recruited from NHS test and trace centres, mainly those with symptoms, the sensitivity was 58% (95% CI 52 to 63%) for tests taken by non-skilled individuals compared with 73% (95% CI 64 to 81%) for tests taken by trained medical staff, and 79% (95% CI 73 to 85%) for tests taken by laboratory scientists, in an evaluation carried out by the Public Health England Porton Down and the University of Oxford.[93] In a separate multidisciplinary assessment it was found that the sensitivity of the RADT (compared with RT-PCR) was 74% (95% CI 64 to 82%) for staff-collected anterior nasal swabs, while the sensitivity for self- or

parent-collected swabs was 57% (95% CI 37 to 76%).[94] Although the difference between the staff- and self-collected sensitivity was not statistically significant (p = 0.1) in this study, the lower sensitivity may be relevant for clinical management and outpatient testing strategies if confirmed in a larger cohort.

Compliance with manufacturers' instructions for use (IFU) can also affect the performance of RADTs. Brummer et al.[82] found that sensitivity was higher in studies that conformed to manufacturers' IFU (76.3%, 95% CI 73.1 to 79.2%) than non-conforming studies (65.9%, 95% CI 60.6 to 70.8%). Conformity was also explored in Dinnes et al.[12] but only for individual tests; these were not compared against non-conforming studies. Dinnes et al. also reported that the sensitivity varied between different RADTs and so these tests should not be regarded as interchangeable.[12] With regard to RADTs, there is also evidence of batch-to-batch variation,[95] and reduced performance due to variants of concern.[96]

3.1.5 Guidance and use of RADTs for screening or surveillance purposes

3.1.5.1 International guidance on the use of RADTs for screening or surveillance of asymptomatic individuals

The ECDC advises that RADTs may be of benefit in screening asymptomatic individuals in high prevalence settings (>10%), where RT-PCR capacity is limited, to control transmission in local communities or in specific settings for example staff in healthcare settings, and to identify clusters or outbreaks in specific settings.[24] Additionally, in a high-risk indoor occupational setting, RADTs (including self-test RADTs) could be used to screen employees at the workplace or before arriving to the workplace, and as part of local public health prevention and control programme for the identification of cases in conjugation with public health authorities.[97]

The United States (US) Centers for Disease Control and Prevention (CDC) report that there is value in conducting screening (including serial testing) with rapid antigen tests where turnaround time is critical in identifying people with COVID-19, for example in high-risk congregate housing settings such as long-term care facilities or correctional or detention facilities. They advise that if resources allow, serial antigen testing, in addition to other prevention strategies, has a role to play in the public health response to COVID-19.[33] However, the US CDC advise that vaccinated individuals in non-healthcare settings should be exempt from routine screening testing (type of test not specified) if feasible,[33] while fully vaccinated asymptomatic healthcare professionals may be exempt from expanded screening testing.[98]

The World Health Organization (WHO) does not currently recommend the use of RADTs in settings or populations with low expected prevalence of disease (for

example, screening at points of entry, prior to travel, elective surgery), where confirmatory testing by RT-PCR is not readily available, due to the burden presented by the high rates of false positives.[63]

3.1.5.2 Use of RADTs in asymptomatic screening and surveillance in the UK

As discussed in Section 3.1.3, in England, RADTs are offered for screening purposes to asymptomatic individuals in a range of different settings such as education providers, care homes and workplaces. Testing at these sites is assisted, where a person will take a swab test under the supervision of a trained operator who then processes the test and reads and records the result.[99] They are also offered to anyone in England and Scotland who does not have symptoms for COVID-19, with advice to self-test twice per week (every 3 or 4 days).[15, 100] Tests can be ordered online or picked up at a test centre (one pack per day with seven tests per pack). Additionally, RADTs can be obtained through education providers and employers or the test can be conducted at a test site specifically conducting RADTs for asymptomatic individuals.

In Northern Ireland, asymptomatic testing with RADTs is available to all employers for all staff. Small businesses or organisations can access testing at test sites, order test kits online or collect from a test site. Organisations with more than 10 employees work with the Department of Health to identify the most appropriate form of testing available based on their specific requirements.[101]

In Wales, RADTs for asymptomatic individuals is limited to the following:[102]

- volunteers
- those who cannot work from home
- unpaid carers
- those visiting Wales from elsewhere
- those travelling to other areas of the UK
- if a health board requires testing before hospital visits
- those (and their partners) using hospital maternity services
- parent, carer or guardian of a child in hospital
- those going to an event that requires it.

In England, most testing with RADT is now being conducted entirely by individuals themselves, where the individual takes their own test without professional assistance and reports their own result.[99] Results for RADTs should be reported within 24 hours via a web-based service or by phone. A positive result must be confirmed by an RT-PCR test.[103] In the week to 16 June 2021, 4,543,304 RADTs were conducted and registered in England through the National Testing Programme digital

infrastructure, compared with 1,154,970 RT-PCR tests. Of the 4.54 million RADTs conducted, 16,469 tests (0.36%) returned a positive result. Of the 15,727 self-reported positive test results with corresponding data, 11,239 were matched to a confirmatory RT-PCR test (71%). Of those 11,239 matched RT-PCR tests, 9,700 (86%) were positive (that is, a true positive). The remaining were either negative or void. During the same time period, a total of 45,148 (3.91%) RT-PCR tests were positive for SARS-CoV-2.[99]

3.1.6 Ethical considerations

There are a number of high level ethical considerations specifically relevant to screening or surveillance of asymptomatic people, including how widespread testing should be and whether selective testing is in accordance with principles of social justice.[104] In this evidence summary, the use of RADT was considered as an alternative to no screening or surveillance testing, rather than as an alternative to another test, such as RT-PCR. Hence, while some of these ethical considerations may be applicable to any test (for example, RADT or RT-PCR) used at scale in asymptomatic populations, the focus here is on ethical issues relevant to the perspective of testing with RADTs versus no-testing given the focus of the policy question.

Firstly, RT-PCR is considered the most accurate and reliable tool to detect the SARS-CoV-2 virus. Therefore, the use of less accurate RADTs to increase testing capacity and guide the public health response is potentially problematic from an ethical perspective.[104, 105] There are implications for false negatives (such as providing false reassurances) and false positives (such as unnecessarily self-isolating) that need to be considered when a less accurate test is scaled up and used at a population level.[23] Conversely, given the often prolonged detectability of SARS-CoV-2 RNA in upper respiratory tract specimens,[88] it has been argued that reliance on a highly sensitive test, such as RT-PCR, may result in a disproportionate number of cases, who are no longer infectious being required to self-isolate, despite no longer representing a public health risk (Figure 3).[16] From this perspective, it has been argued that a less sensitive test (such as RADT), used more frequently, could rapidly identify the most infectious individuals in the population allowing them to self-isolate, while permitting those who are post-infectious to continue engaging in society.[3]

Secondly, ethical considerations are relevant in a decision to conduct surveillance involving large numbers of people where existing inequalities will potentially impact on uptake and participation. An evaluation of social and spatial inequalities of mass testing in Liverpool highlighted that participation rates and repeat testing were lower in areas of higher deprivation, in areas that were greater distances from test sites

and areas containing populations less confident in using the internet and associated technologies.[106]

Thirdly, there may be ethical issues regarding widespread testing of asymptomatic people who are not known to have been exposed to or infected with COVID-19. If these people are considered suspected COVID-19 cases, this could potentially impact on their ability to access healthcare for reasons other than treatment for COVID-19. Additionally individuals will have to self-isolate and may lose income as a consequence of a positive test. This may be particularly problematic in the case of false positives, where these hardships may have been avoided by not taking the test, or by using an RT-PCR test instead.[69] Conversely, the use of RADTs at home can negate some of the issues people may have with accessing RT-PCR test centres (for example, transport and childcare). The pandemic has impacted greatly on non COVID-19 care and inclusion in screening or surveillance programmes should not affect an individual's ability or willingness to access required healthcare, and should not result in unnecessary financial hardship.[104]

Fourthly, the alternative to RADT needs to be considered. It is possible that screening programmes using RADTs may detect infectious cases in an asymptomatic population that would otherwise not have been detected.[16] Additionally, false negative RADT results in populations at low risk of severe disease may not be as harmful as those that might occur in populations at high risk.[107] However, RADT screening may be used to replace other mitigation measures, which may have unintended negative consequences (that is, result in superspreading events).[108]

Lastly, there are ethical considerations with regard to resource use in screening or surveillance of asymptomatic people. If testing of large numbers or repeated testing in certain settings is unlikely to contribute value in controlling the spread of the virus, and resources could be used more efficiently in other areas, then such testing may not be ethical or justified.[109]

There are also a number of ethical considerations specifically related to self-test RADTs. Where sample collection is performed by a lay person instead of a trained professional, there are potential issues in terms of sample quality which could impact on the accuracy of test results. Given that self-tests are not processed in a clean laboratory setting, there is also a risk of sample contamination, affecting the accuracy of test results. Additionally, there are concerns regarding the safe disposal of hazardous waste from self-tests conducted at home.[110] The absence of a trained professional also raises the possibility of misinterpretation of results.[111] Additionally, the absence of adequate information accompanying self-tests potentially impacts on the interpretation of results, particularly with regard to negative results which may be false-negatives.[109] Lastly, COVID-19 is a notifiable disease and in the case of

self-tests, ethical issues relating to reporting obligations on the general public require consideration.

While ethical issues associated with screening and surveillance of asymptomatic people for COVID-19 with RADTs have been identified, it is argued that in a public health crisis, decisions around who is tested need to strike a balance between individual and public health considerations.[104] Providing access to self-tests may allow individuals to assess their own level of risk in the context of an ongoing pandemic and may give a greater level of autonomy to the individual.[23] However, it has been argued that increased patient autonomy and choice within healthcare, specifically around the use of self-testing, may not best serve the patient population given the potential impact of these personal choices on others.[112]

Given the nuances of this topic, it has been suggested that a sound ethical framework, involving stakeholder engagement, is required to enable systematic and principled decision making with regard to mass testing of asymptomatic people for COVID-19.[113] Such a framework has been developed in the UK to guide testing for students in higher education institutions.[114] Table 5 lists and describes the areas of ethical consideration in that setting.

Table 5 Ethical Considerations in an Ethical Framework for asymptomatic COVID-19 testing for students in higher education institutions[114]

Ethical Considerations	Description
Design and operation of the programme	Assess if a testing programme is the right choice and whether all aspects of it can be delivered. Ensure public and legal duties will be met.
Goals of the testing programme	Identify the programme goals, explain why they were chosen, tell students about them, and keep them under review.
Properties of the test(s) selected for the programme	Assess the available testing options, considering current evidence and guidance. Acknowledge uncertainty and take action to address risks associated with the chosen test.
Enabling isolation	Provide suitable support -practical, psychological, social and educational - for students who test positive.
Choices regarding participation in testing programmes	Generally, favour the least intrusive approach to individual choice about participation.
Benefits, harms, and opportunity costs	Assess possible benefits, costs, risks and harms and be prepared to explain decisions.
Responsibilities between students and institutions	Clarify that both institutions and students have responsibilities if shared goals are to be achieved.

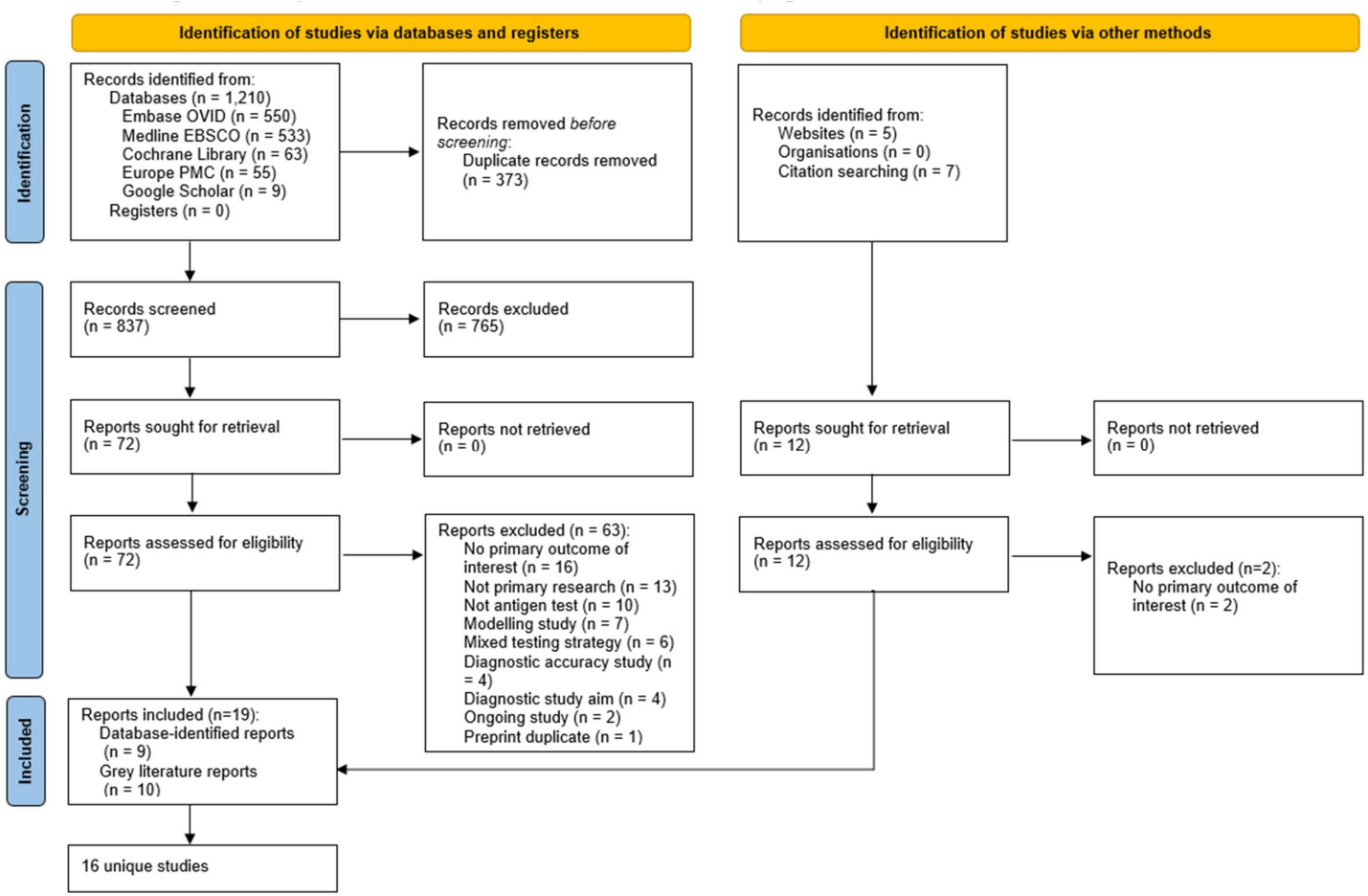
Privacy, confidentiality and data-sharing	Ensure information governance systems meet data protection and confidentiality requirements. Be clear who is informed about test results and why.
Communication	Make clear communication with students and staff a priority, and put feedback and response mechanisms in place.

3.2 RQ2: Evidence synthesis

3.2.1 Search findings

Database searches up until 19 July 2021, identified a total of 1,210 records; following removal of duplicates, the titles and abstracts of 837 records were screened for relevance, with 72 full-texts assessed for eligibility and 63 subsequently excluded. Twelve reports identified via website and citation searching were assessed for eligibility on 16 July 2021; of which two were excluded. At the end of this process, 19 reports in total were included in this evidence summary,[50, 69, 72, 73, 106, 115-126] nine of which were identified via databases[50, 73, 106, 119-121, 124-126] and ten via other methods.[69, 72, 115-118, 122, 123] These 19 included reports refer to 16 unique studies. These 16 unique studies are the focus of this review. The PRISMA 2020 flow diagram of included studies is presented in Figure 5.[127]

Figure 5 PRISMA 2020 flow diagram of included studies



3.2.2 Characteristics of included studies

Of the 16 included studies, eight examined the effectiveness of RADTs for mass testing,[50, 69, 73, 106, 116, 117, 119, 120, 122, 123, 125] four for pre-event screening,[72, 115, 118, 124] four for serial testing in four different settings (schools,[128] a prison,[129] a university sports programme for athletes and staff,[121] and in care homes) (Table 6).[126]

The eight mass testing studies referred to population-based screening programmes that occurred in England (Liverpool),[69, 106, 119] Wales (Merthyr Tydfil and Lower Cynon Valley),[116, 123] Slovakia (whole-country)[50, 73, 120] and Italy (South Tyrol).[117, 122, 125] Of note, each of these mass testing programmes had multiple studies. In the case of the Slovakian and Italian programmes each of the included studies was conducted by a different research group and so the analyses differed. However, in the case of the English and the Welsh programmes, the same research team was involved in the included studies and so the analyses overlapped, with the main report from each site generally including sub-studies which were subsequently published as discrete academic papers. For the purpose of this evidence summary, the eight mass testing studies refer to one 'study' each from England[69, 106, 119] and Wales,[116, 123] and three studies each from Slovakia[50, 73, 120] and Italy.[117, 122, 125]

While the effectiveness of RADT-based screening of staff was assessed in prisons, a university sports programme and in care homes, none of the included studies examined the effectiveness of RADTs in other workplace settings. None of the included studies examined the effectiveness of RADTs for travel-related activities. All 16 included studies used RADTs for the purpose of screening in asymptomatic populations; none used them for surveillance.

Five were retrospective cohort studies,[50, 120, 125] four studies were prospective cohort studies,[69, 122, 123, 126] three were uncontrolled before-after studies,[72, 115, 118] two were mathematical modelling studies based on ecological studies,[73, 117] one was a randomised controlled trial (RCT)[124] and one was a case series.[121] All of the eight mass testing studies, [50, 69, 73, 106, 116, 117, 119, 120, 122, 123, 125] along with the schools testing programme[128] were ecological in design, in that the data were analysed over a period of time at the population-level. For the remaining seven studies, the data were analysed at the individual-level, and usually at a specific point in time.[72, 115, 118, 121, 124, 126, 129]

Four studies were conducted in Italy,[69, 106, 115, 119, 126] three studies each were conducted in England,[117, 122, 125] and Slovakia,[72, 124] two studies each were conducted in Spain,[72, 124] and the US[121, 128] and one study each was conducted in Wales[116, 123] and the Netherlands.[118] The sample size varied substantially between included studies with the largest involving over 5.2 million RADTs conducted in

Slovakia,[50, 73, 120] and the smallest involving 188 cases across two specific outbreaks that occurred with daily antigen testing in the US.[121]

Table 6 Characteristics of included studies including 14-day SARS-CoV-2 incidence and COVID-19 vaccination status during the study period

First author (year)	Country	Dates	Study design	Setting	Aim of testing	Sample size	National 14-day incidence rate per 100,000 population	Total vaccine doses administered per 100 people nationally	Share of the national population fully vaccinated (%)	Overall quality rating†
Mass testing										
University of Liverpool (2021)	England	6 Nov 2020 – 30 Apr 2021	Prospective cohort study (Ecological study)	General population of Liverpool	Screening/serial testing (Voluntary)	283,338 participants / 739,553 RADTs	6 Nov = 465 30 Apr = 49	6 Nov = 0 30 Apr = 73	6 Nov = 0 30 Apr = 22	Fair
Public Health Wales (2021)	Wales	21 Nov – 20 Dec 2020	Prospective cohort study (Ecological study)	General population of Merthyr Tydfil and Lower Cynon Valley	Screening/serial testing (Voluntary)	55,756 RADTs	21 Nov = 482 20 Dec = 469	21 Nov = 0 20 Dec = 1	21 Nov = 0 20 Dec = 0	Poor
Pavelka* (2021)	Slovakia	23 Oct – 7 Nov 2020	Retrospective cohort study (Ecological study)	General population of whole country	Screening/serial testing (Testing voluntary, but isolation requirements mandatory)	5,276,832 RADTs	23 Oct = 385 7 Nov = 602	23 Oct = 0 7 Nov = 0	23 Oct = 0 7 Nov = 0	Poor
Kahanec* (2021)	Slovakia	23 Oct – 7 Nov 2020	Retrospective cohort study (Ecological study)	General population of whole country	Screening/serial testing (Testing voluntary, but isolation requirements mandatory)	5,276,832 RADTs	23 Oct = 385 7 Nov = 602	23 Oct = 0 7 Nov = 0	23 Oct = 0 7 Nov = 0	Fair
Frnda* (2021)	Slovakia	23 Oct – 7 Nov 2020	Mathematical modelling study based on an ecological study	General population of whole country	Screening/serial testing (Testing voluntary, but isolation requirements mandatory)	5,276,832 RADTs	23 Oct = 385 7 Nov = 602	23 Oct = 0 7 Nov = 0	23 Oct = 0 7 Nov = 0	Poor

First author (year)	Country	Dates	Study design	Setting	Aim of testing	Sample size	National 14-day incidence rate per 100,000 population	Total vaccine doses administered per 100 people nationally	Share of the national population fully vaccinated (%)	Overall quality rating†
Pagani‡ (2021)	Italy	20-22 Nov 2020	Prospective cohort study (Ecological study)	General population of South Tyrol	Screening (Voluntary)	361,781 RADTs	20 Nov = 799	20 Nov = 0	20 Nov 2020 = 0	Poor
Ferrari‡ (2021)	Italy	20-22 Nov 2020	Mathematical modelling study based on an ecological study	General population of South Tyrol	Screening (Voluntary)	361,781 RADTs	20 Nov = 799	20 Nov = 0	20 Nov = 0	Fair
Ricco‡ (2021)	Italy	20-22 Nov 2020	Retrospective cohort study (Ecological study)	General population of South Tyrol	Screening (Voluntary)	361,781 RADTs	20 Nov = 799	20 Nov = 0	20 Nov = 0	Poor
Pre-event screening										
UK Government (2021)	England	17 Apr – 15 May 2021	Uncontrolled, before-after study	9 mass gathering events	Screening (Mandatory)	58,103 participants across 9 events	17 April = 43.9 15 May = 45	17 April = 63 15 May = 83.5	17 April = 15 15 May = 30	Fair
Revollo (2021)	Spain	12 Dec 2020	RCT	1 concert	Screening (Mandatory)	1,047 participants	12 Dec = 219	12 Dec = 0	12 Dec = 0	Fair
Llibre (2021)	Spain	27 Mar 2021	Uncontrolled before-after study	1 concert	Screening (Mandatory)	5,000 participants	27 Mar = 153	27 Mar = 15	27 Mar = 5	Fair
Fieldlab (2021)	The Netherlands	27 Mar 2021	Uncontrolled, before-after study	1 football match	Screening (Mandatory)	5,108 participants	27 Mar = 566	27 Mar = 12.7	27 Mar = 3.3	Fair
Serial testing- sports programme										
Moreno (2021)	USA	Sep – Nov 2020	Case series (epidemiological investigation)	University athletics programme	Screening: athletes and staff (Mandatory)	188 positive cases across 2 outbreaks	1 Sep = 177 30 Nov = 714	1 Sep = 0 30 Nov = 0	1 Sep = 0 30 Nov = 0	Fair
Serial testing – health and social care setting										
Tulloch (2021)	England	1 Dec 2020	Prospective cohort study with	11 care homes	Screening: Care home staff	1,638 RADTs on 407 staff	1 Dec = 343	1 Dec = 0 10 Jan = 4	1 Dec= 0 10 Jan = 1	Fair

First author (year)	Country	Dates	Study design	Setting	Aim of testing	Sample size	National 14-day incidence rate per 100,000 population	Total vaccine doses administered per 100 people nationally	Share of the national population fully vaccinated (%)	Overall quality rating†
		– 10 Jan 2021	qualitative evaluation		(Mandatory, but poor adherence)		10 Jan = 1,158			
Serial testing - schools										
Lanier (2021)	USA	30 Nov 2020 – 20 Mar 2021	Retrospective cohort study (ecological study)	127 Public high schools	Screening: students, 'Test to Play' (Mandatory)	148,262 RADTs among 50,400 students	30 Nov = 714 20 Mar = 231	30 Nov = 0 20 Mar = 36	30 Nov = 0 20 Mar = 13	Poor
Serial testing - prison										
Stufano (2021)	Italy	10 Nov 2020 – 27 Jan 2021	Retrospective cohort study	1 prison	Screening: prisoners and staff (Voluntary)	1st round of testing: 426 prisoners and 367 staff 2nd round of testing: 480 prisoners and 325 staff	10 Nov = 712 27 Jan = 301	10 Nov = 0 27 Jan = 3	10 Nov = 0 27 Jan = 1	Fair

Key: RADT – rapid antigen detection test; RCT – randomised controlled trial.

†Quality can be rated as Good, Fair or Poor in accordance with the National Heart, Lung, and Blood Institute's Study Quality Assessment Tools.

*All three studies evaluating the Slovakian mass testing programme conducted unique analyses of the same dataset.

‡All three studies evaluating the Italian mass testing programme conducted unique analyses of the same dataset.

3.2.3 Public health measures and restrictions

All four population-based screening programmes (from eight included studies)[50, 69, 73, 106, 116, 117, 119, 120, 122, 123, 125] that occurred in England (Liverpool),[69, 106, 119] Wales (Merthyr Tydfil and Lower Cynon Valley),[116, 123] Slovakia (whole-country)[50, 73, 120] and Italy (South Tyrol),[117, 122, 125] along with the school-based serial testing programme that occurred in Utah (USA),[128] were initiated in the context of high SARS-CoV-2 incidence and relatively stringent background public health restrictions. Mass testing coincided with the implementation of lockdown in Liverpool (6 and 5 November 2020, respectively) and Slovakia (23 and 24 October 2020, respectively), while the South Tyrol region of Italy had been upgraded to a red zone (maximum risk) on 6 November 2020, prior to the commencement of mass testing on 20 November, and so strict measures were already in place.[130] Conversely, public health restrictions had eased considerably in Wales when mass testing commenced on 21 November 2020 due to a previous 17-day 'firebreak' lockdown which ended on 9 November. Restrictions were eased in Liverpool, Slovakia and South Tyrol shortly after commencement of the mass testing programmes. However all four regions had re-imposed lockdown within several weeks thereafter (by 19 December in Slovakia,[131] 20 December in Wales,[132] 6 January 2021 in England,[133] and 17 January in South Tyrol),[134] in light of the rapidly deteriorating epidemiological situation and the emergence of variants of concern across Europe.[135] From 9 November 2020, statewide COVID-19 restrictions were ordered in Utah, including a cessation of most extracurricular activities for high school students, in light of the deteriorating epidemiological situation. Beginning on 30 November, 'Test to Play' (a serial antigen testing programme) was mandated for all high school students who wanted to partake in extracurricular activities.[128] The incidence rates at the time these programmes were conducted are discussed in Section 3.2.4.1.

The range of public health measures implemented in each of the seven remaining studies is outlined in Table 7. The number and intensity of measures implemented varied across studies, however, no study relied solely on RADT for mitigation. Besides antigen testing, the most commonly implemented public health measures among these seven studies were health screening (that is, temperature, symptom, or close contact screening)[72, 115, 118, 121, 124, 126] contact tracing,[72, 115, 118, 121, 124, 126] and wearing of face masks (though the requirement to wear a mask varied depending on the ERP pilot).[72, 115, 118, 121, 124, 126]

The four pre-event screening studies used once-off rapid antigen testing,[72, 115, 118, 124] the prison testing programme conducted two whole-of-prison testing campaigns 30 days apart (plus on entry for all new prisoners),[129] the serial testing studies for college athletes and staff involved daily rapid antigen testing,[121] for staff in care

homes testing was undertaken twice a week,[126] while for the schools testing programme it was undertaken every 14 days.[128] The interval between testing and event admission varied between nine hours/same day for the Barcelona and Fieldlab events[72, 118, 124] to 24 to 36 hours depending on the pilot (of which there were nine) for the UK Events Research Programme (ERP).[115]

Table 7 Overview of public health measures implemented in the seven included non-mass population testing studies

Public health measure	UK Government (ERP)	Revollo	Llibre	Fieldlab	Moreno	Tulloch	Stufano
Pre-event/serial testing	✓ (once off) <24-36 hours	✓ (once off) <9 hours	✓ (once off) same day	✓ (once off) same day	✓ (daily)	✓ (twice a week)	✓ (2 tests 30 days apart, plus on entry for all new prisoners)
Pre-event quarantine	-	-	-	-	-	-	✓
Health screening	✓	✓	✓	✓	✓	✓	✓
Face masks	Va	✓	✓	✓	✓	✓	✓
Ventilation	Va	✓	✓	**O**	-	-	-
Excluded vulnerable populations	-	✓	✓	✓	-	-	-
Hand sanitiser	✓	✓	✓	✓	-	✓	✓
Reduced numbers	✓	✓	✓	✓	-	-	-
Physical distancing	**Va**	-	-	-	✓	✓	✓
Congestion control	**Va**	✓	✓	✓	-	-	✓
Cohorting	**Va**	-	✓	✓	-	-	✓
Contact tracing	✓	✓	✓	✓	✓	✓	✓
Post-event testing	✓	✓	✓	✓	NA	**NA**	NA
Restrict movements/quarantine post event	-	-	-	✓	-	-	**NA**

Key: NA = not applicable. ERP = Events Research Programme. O = Outdoors; Va = Varied; study trialled these measures to different intensities

3.2.4 Study findings

3.2.4.1 Mass testing

Eight mass testing studies were identified, that evaluated four different RADT population-based screening programmes in England (Liverpool),[69, 106, 119] Wales (Merthyr Tydfil and Lower Cynon Valley),[116, 123] Slovakia (whole-country)[50, 73, 120] and Italy (South Tyrol).

3.2.4.1.1 Liverpool community testing pilot

Four studies conducted by the same research team were identified that evaluated the Liverpool Covid-SMART community testing pilot that occurred between 6 November 2020 and 30 April 2021.[69, 106, 119, 126] The main evaluation report, led by the University of Liverpool, was published on 7 July 2021.[69] In addition to the main evaluation report there were three published sub-studies, two of which are described as part of the community testing pilot here,[106, 119] and one which is described separately as part of serial testing within care homes (Section 3.2.4.3.2).[126]

The Liverpool Covid-SMART community testing pilot was a public health intervention, open to everyone aged over five years old without symptoms in the city of Liverpool. Testing was voluntary, free, and people were encouraged to return for repeat testing. The targets for this project were threefold:

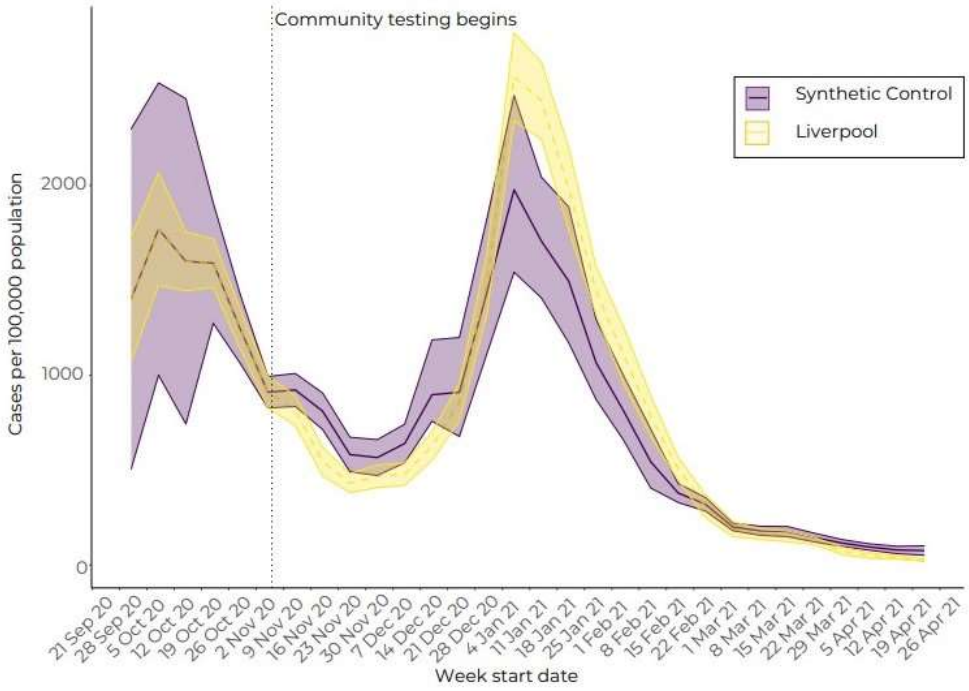
- test-to-protect (vulnerable individuals/settings/services)
- test-to-release (sooner from quarantine)
- test-to-enable (safer return to key activities for society and the economy).

Between 6 November 2020 and 30 April 2021, 283,338 Liverpool residents, comprising 57% of the eligible population, took an RADT (Innova SARS-CoV-2 rapid antigen lateral flow device (LFD)) based on a supervised, self-sampled swab. A total of 739,553 RADTs were conducted, of which 6,300 were positive (0.9%). The pilot commenced during a period of high incidence and ended when incidence was low (national 14-day notification rate per 100,000 was 465 and 49 on 6 November and 30 April, respectively). COVID-19 vaccination programmes had not commenced in UK at the time of pilot initiation, however by 30 April 2021, 22% of the UK population were fully vaccinated. While no cost data were provided for the pilot, there was an acknowledgement of "significant multi-agency involvement, including at least 2,000 army personnel," highlighting the substantial resource requirements to facilitate the pilot.

A synthetic control group, where mass testing was not undertaken, was developed for this study, to estimate the effect of mass testing in Liverpool. To construct this synthetic control group, calibration weights were derived to match areas outside Liverpool to those within Liverpool across the five-week period prior to the intervention, in terms of deprivation, ethnicity, population density, age profile, prevalence of chronic conditions and prior trend in cases. As Liverpool entered less stringent Tier 2 restrictions on 2 December compared with most of England which entered more stringent Tier 3 restrictions, the researchers made adjustments to remove the estimated 24% relative reduction in case numbers that would be seen in a Tier 3 region (that is, the synthetic control group) compared with a Tier 2 region (that is, Liverpool).

Compared with the synthetic control (using a log linear Poisson regression model), the authors estimated that the community testing pilot was associated with an 18% (95% Confidence Interval (CI), 7% to 29%) increase in case detection equivalent to an additional 4,766 cases (95% CI, 1,878 to 7,940) of SARS-CoV-2 being identified between 6 November 2020 and 30 April 2021 that would not have been identified without RADT-based community testing. Based on the authors' pessimistic model, they estimated that 850 (95% CI, 500 to 1,350) infections were prevented, whereas their optimistic model suggested that 6,600 (95% CI, 4,840 to 9,070) infections were prevented by interrupting the chains of transmission. The authors additionally estimated that the testing pilot was associated with a 21% (95% CI, 12-27%) reduction in cases up to 17 December (Figure 6). However, beyond 17 December, the authors found no statistically significant difference in case rates (compared with the synthetic control group) as the Alpha variant surged through England and a national lockdown was implemented.

Figure 6 The trend in average COVID-19 case rates in Liverpool compared with a synthetic control group without community testing (used with permission from University of Liverpool)[69]



The authors estimated the trend in terms of the COVID-19 hospital admission rate in Liverpool, before and during community testing compared with the predicted counterfactual trend based on the Bayesian structural times series model. The counterfactual was adjusted for the effect of stricter Tier 3 conditions introduced in December 2020.This counterfactual comprised a group of ten lower tier local authorities that did not undergo similar testing, but that had similar trends in COVID-19 admissions and cases prior to the introduction of the pilot. Of note, the authors used a different synthetic control group to estimate the potential impact on hospitalisations. The estimated overall effect over that period is a non-statistically significant reduction in admissions (16%, 95% Credible Interval, 53% reduction to 15% increase).

The researchers' estimated impact of the pilot on case detection, transmission and hospitalisation needs to be viewed with some caution as these estimated effects are relative to a retrospectively developed synthetic control group, and are based on particular assumptions that are uncertain. Confirmatory RT-PCR uptake was variable throughout the study period. Uptake was low (19%) initially when the pilot was conducted through self-testing at home (during the period of 6-22 November), improving to 79% after moving to a dedicated testing site (during the period of 23

November-12 December), although a reduction in uptake was observed from the end of January. Additionally, significant changes to public health restrictions occurred throughout this period, making it challenging to disentangle the effect of RADT mass testing from other measures. Moreover, it has been argued that even if mass testing by RADTs reduced cases by 21%, as estimated in this study, this may not be enough to stem an epidemic that is in exponential growth.[136] The surge of the highly transmissible Alpha variant throughout December resulted in a third nationwide lockdown in England on 6 January 2021.[133]

In a quality assurance study conducted during the pilot by García-Fiñana et al., the clinical performance of the Innova SARS-CoV-2 rapid antigen LFD in an asymptomatic population was compared with that of RT-PCR.[119] Of 5,869 paired samples, and excluding the void results, the sensitivity of the RADT was found to be low (40%, 95% CI, 28.5% to 52.4%). When the void samples were assumed to be negative, the sensitivity of the RADT was found to be even lower (37.8%, 95% CI, 26.8% to 49.9%). However, the sensitivity of the RADT in participants with a C_t value of <18.3 (assumed to be very high viral load) was found to be high (90.9%, 95% CI, 58.7% to 99.8%). This study highlighted the difference in clinical performance of this RADT in general asymptomatic populations compared with those with a low C_t value at the time of testing.

Another linked study by Green et al. aimed to explore social and spatial inequalities in uptake and case-detection of RADTs during the community testing pilot.[106] The study found that uptake was highest in November, peaked again in the week preceding Christmas and was sustained into the national lockdown, though at a lower rate. Overall uptake was lower among males, ethnic minorities and in the most deprived areas. These population groups were also more likely to have received positive test results for COVID-19. Uptake and repeat testing was found to be lower in areas located further away from test sites and in communities less confident in using internet technologies. Thus highlighting the potential for use of RADTs to impact on inequalities that exist during the COVID-19 pandemic.

3.2.4.1.2 Whole-country testing in Slovakia

Three studies conducted by three different research teams were identified that evaluated the impact of multiple rounds of population-wide rapid antigen testing in October and November 2020 in Slovakia.[50, 73, 120] Coinciding with the introduction of a national lockdown, a pilot took place between 23 and 25 October in the four most affected counties in Slovakia, followed by a round of national mass testing on 31 October and 1 November (round 1). High prevalence counties were again targeted with a subsequent round of testing on 7 and 8 November (round 2). Testing was voluntary, although those who did not undergo testing were mandated to quarantine

for 10 days. Additionally, those who tested positive by RADT along with their household members and self-traced recent contacts (within the previous two days) were required to quarantine for 10 days, and were instructed not to participate in the next testing round. While a third round of testing occurred in high prevalence areas on 22 November, there was no associated requirement to quarantine, and uptake was found to be poor.[137] The results from the third round of mass testing were not discussed in any of the included studies. The pilot commenced during a period of high incidence (national 14-day notification rate per 100,000 was 385 on 23 October 2020), and COVID-19 vaccination programmes had not commenced in Slovakia at this time. The mass testing programme involved over 20,000 medical staff and 40,000 non-medical personnel.[50] An estimated €30 million was spent on military staffing and €52 million on rapid antigen test kits.[73]

Nasopharyngeal samples were sampled and processed by trained medical personnel using SD-Biosensor Standard Q RADTs. In total, 5,276,832 RADTs were conducted across the three phases of testing (pilot, rounds 1 and 2). This corresponded with 87%, 83% and 84% of the eligible population of the target areas within Slovakia (10-65 year olds plus older adults in employment), respectively for each testing phase. A total of 50,466 individuals tested positive. No confirmatory RT-PCR testing of positive cases was undertaken. Based on an overall total cost of €82 million for this programme, a crude estimate of cost per test and cost per positive case is €15.50 and €1,625, respectively, though this is likely an underestimate of the total cost for this programme.

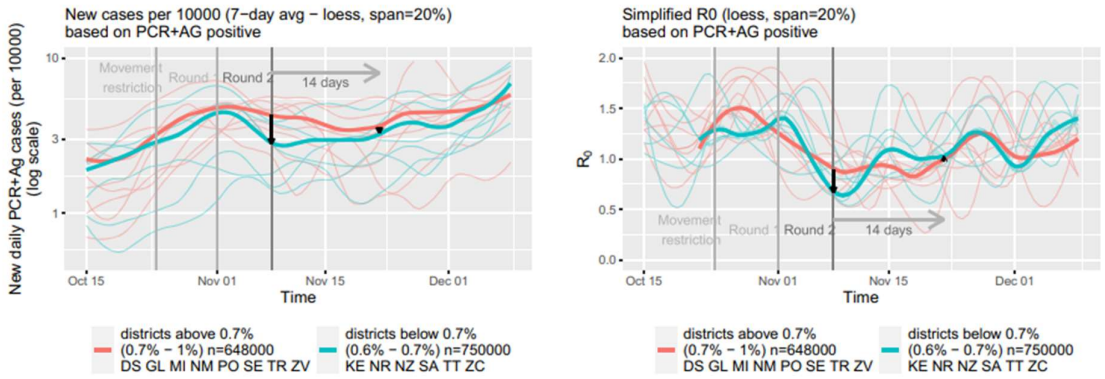
Pavelka et al. published the first evaluation of the Slovakian mass testing programme. The researchers conducted a retrospective cohort analysis and estimated changes in prevalence based on changes in RADT positivity between rounds of testing.[50] As noted, 50,466 participants tested positive of 5,276,832 completed tests (0.96%). The positivity rate was 3.91% in the pilot, 1.01% in round 1 and 0.62% in round 2. The authors estimated that the test positivity (assumed to be a proxy for prevalence) decreased by 58% (95% CI, 57 to 58%) within one week in the 45 counties that were subject to at least two rounds of mass testing, after controlling for attendance rates, reproduction number and prevalence in previous rounds. The authors further estimated that in the four counties that underwent three rounds of testing, observed infection prevalence decreased by 82% (95% CI, 81 to 83%) between the pilot and round 2. Assuming an epidemic growth of 4.4% (95% CI, 1.1% to 6.9%) per day preceding the mass testing campaign, the authors estimated that the decrease in prevalence compared with a scenario of unmitigated growth was 70% (95% CI, 67% to 73%). Modelling conducted by the authors indicated that this decrease could not be explained solely by infection control measures, but required the addition of the isolation and quarantine of household

members of those testing positive by RADT. Among the multiple intervention scenarios tested, the authors reported that only the scenario that assumed a substantial impact of both the additional contact reducing measures (that is, lockdown) and the mass testing campaigns was able to generate reductions in test positivity rates between testing rounds that were similar to those observed.

However, there have been several criticisms of this study, which significantly reduce the confidence in its findings.[138] The most fundamental critique has centred on the use of RADT positivity to measure changes in SARS-CoV-2 prevalence between rounds. Given that individuals who tested positive and all of their household and close contacts were instructed to quarantine and not to participate in the next round of testing, this may have caused a significant underestimation of prevalence in subsequent rounds. Secondly, the use of mass RADT as both an intervention and as an outcome measure can introduce significant bias into the study as they cannot be independent of each other. Thirdly, the model assumed that the RADT was 100% sensitive for currently infectious individuals, in contradiction with previous research which finds high, but not complete, sensitivity for those with a low C_t value (who are assumed to be highly infectious).[12] Fourthly, while the model assumed an epidemic growth of 4.4% prior to the round 1 of nationwide testing, it is not evident that this was the case as the lockdown introduced on 24 October may have impacted on controlling the epidemic prior to round 1 of testing on 31 October. Finally, the epidemiological situation deteriorated rapidly shortly after round 2 of testing, with cases peaking on 13 January (14-day incidence of 766 per 100,000 population).

Kahanec et al. conducted a retrospective cohort study of the mass testing programme.[120] These researchers used a difference-in-differences model to compare changes in incidence (using passive surveillance as opposed to RADT results) and the reproductive number between counties who underwent one round of testing (control group) and those who underwent two rounds of testing (treatment group). This study excluded the four counties that underwent pilot testing, which may have introduced a selection bias into this study. The authors found that the second round of mass antigen testing was associated with a reduction of the 7-day average in infections measured 14 days after round 2 by approximately 2.3 daily cases per 100.000 inhabitants (36% reduction), and decreased the reproductive number (R_0) by 0.28 (31% reduction), more than control groups (Figure 7). However, the authors found that after reaching the maximum reduction in cases 15 days after round 2, the effect diminished towards a zero effect, and that about three weeks after the second round of mass testing, the estimated impact of repeated mass testing on R0 was statistically indistinct from zero.

Figure 7 Changes in incidence and reproductive number in counties with two rounds (red) compared with one round (blue) of mass testing (used with permission from Kahanec et al. under a Creative Commons Attribution 4.0 International License)[120]



The authors concluded that while mass antigen testing coupled with quarantining of positive cases and their contacts may have an important effect on mitigating the epidemic in the short term, mass testing conducted only irregularly and after long time intervals is unlikely to sustainably suppress the epidemic.[120]

A mathematical modelling study based on data from the mass testing programme in Slovakia was conducted by Frnda et al.[73] In this study, models were developed to estimate the impact of self-isolation for antigen test-positive cases who may not have otherwise been tested by RT-PCR due to their asymptomatic status. The authors estimated that based on a prevalence of 5% in the four worst affected counties (using antigen test positivity), the pilot round of testing identified 36% to 68% of all infected individuals in the population. The authors estimated that RT-PCR could only trace about 11% of these infected individuals at this time (due to capacity issues). The authors estimated that this prevented 70-149 hospitalisations and 5-11 ICU admissions (within 2-3 weeks after the pilot testing). During the nationwide testing, the authors estimated that antigen testing identified 40% to 76% of all infected cases at the time (assuming a prevalence of 1.5%), compared with 12% by RT-PCR. The authors estimated this prevented 557-1,111 hospitalisations and 42-85 ICU admissions (within 2-3 weeks after the mass testing). The authors concluded that mass antigen testing in areas of high prevalence can flatten the curve of daily newly reported cases significantly, but in low prevalence regions, the benefit of such testing is questionable. However, there are significant concerns regarding the underpinning assumptions specifically that the sensitivity of RADT was not

considered in the model and the data (that is, use of antigen positivity as a proxy for prevalence) used in this modelling study. In addition, given the surge of cases that occurred in Slovakia shortly after round 2 of mass testing, associated with the emergence of the Alpha variant, it is unclear whether the modelled effects outlined in this study were observed.

3.2.4.1.3 Whole-area testing pilot in South Wales

Two studies that evaluated the impact of whole-area testing in a region of South Wales were identified.[116, 123] The main evaluation report, led by Public Health Wales was published on 22 March 2021.[123] The main report, of prospective cohort design, additionally includes one published sub-study, an economic evaluation, which is also discussed here.[116]

A whole-area testing pilot, using RADTs, was conducted in the Merthyr Tydfil and lower Cynon Valley areas of South Wales from 21 November until 20 December 2020. These two areas have a combined population of approximately 86,000 people and are among the most deprived areas in Wales, with high levels of COVID-19 cases and associated deaths. At the time of pilot commencement, Wales had just exited a 17-day 'firebreak' lockdown on 9 November 2020 and public health measures had eased somewhat. Locally the 7-day notification rate was around 150 per 100,000 by late November, while COVID-19 vaccination programmes had not yet commenced in Wales. The Innova SARS-CoV-2 rapid antigen LFD was used in this pilot, however it is unclear whether self- of professional-sampling occurred. Testing was voluntary, but free, and people were encouraged to return for repeated testing. The pilot was open to everyone without symptoms who was 11 years and older. A total of 810 staff were required for the implementation of this month-long pilot, with an estimated total cost of £1.25 million (excluding military costs).

In total, 55,765 RADTs were performed with uptake rates of 49% and 56% observed in Merthyr Tydfil and lower Cynon Valley, respectively. However, there was lower uptake in males, younger people (11-29 years) and those living in the most deprived quintiles of the population. There was notably low uptake in groups with high positivity rates (such as males, younger people, those living in the most deprived areas and in close contact occupational groups).[123]

The authors estimated that 353 cases (95% CI, 306 to 409) (both asymptomatic and symptomatic), 24 hospitalisations (95% CI, 16 to 36), five ICU admissions (95% CI, 3 to 6) and 14 deaths (95% CI, 11 to 19), that would have otherwise occurred without the implementation of the pilot, were prevented. This represents a reduction in mean daily incidence rate of 13.6 (95% CI, 11.8 to 15.8) cases per 100,000 per day. These 353 estimates cases prevented represents 2.2% (95% CI, 10.6-14.1%)

of cases that would have occurred in a six week period, which the authors translated into a predicted 6-12% reduction in burden on the healthcare system.[123]

The estimated impact of the pilot was based on the effective reproduction number (R_t) in Merthyr Tydfil at the time. By applying a series of assumptions on the natural history of the infection and the performance of the test, and then applying these estimates to a time-lagged regression model, the number of hospitalisations, ICU admissions and deaths prevented were estimated. However, there are some concerns regarding the use of the reproduction number as the basis for estimating cases prevented given that estimation of R_t is inherently challenging and any temporal inaccuracy may have over- (or under-) estimated the growth of the epidemic at the time.[139] In addition, some of the assumptions underpinning the model are questionable, such as assuming that all RADT positive cases will fully self-isolate, as well as the assumed case-hospitalisation and case-fatality rates of 6.7% and 4%, respectively, given that the age distribution of cases prevented is not outlined. By comparison, the observed case-fatality rate of COVID-19 across all of the UK (since the start of the pandemic) is estimated to be 2.2%,[140] though caution is advised when comparing case-fatality rates as these are influenced by many different factors such as the level of testing and demographics of those infected.

The average cost per test of community testing was £20, of school testing was £21 and of home testing was £38, with the average cost per positive RADT estimated to be £895 and £5,753, in non-school and school settings, respectively. The cost differential reflects the low positivity rates in schools. An economic evaluation of the Merthyr Tydfil component reported that the pilot was highly cost-effective with an incremental cost effectiveness ratio (ICER) of £2,143 to £2,292 per quality-adjusted life year (QALY). Net monetary benefit for the intervention, which is cost savings, plus the value of QALYs gained was estimated to be £5.8 million to £6.2 million.[116] It is important to consider that all of the expected benefits (cases, hospitalisations, ICU admissions and deaths prevented) from the economic evaluation were modelled, based on questionable assumptions, and were not observed outcomes. Additionally, there was no comparator in the economic evaluation and hence the ICER is based on the potential cost savings and QALY gains arising from mass testing versus doing nothing, which may be an oversimplification.

Though the authors concluded that mass testing using RADTs is effective in preventing cases, hospitalisations and deaths and is cost effective as an intervention, there is uncertainty regarding these findings, and they should be treated with caution. Importantly a national lockdown was reinstated in Wales on 20 December coinciding with a surge in the Alpha variant.[132]

3.2.4.1.4 Mass testing in North-Eastern Italy

Three studies by three different research teams evaluated the impact of a mass testing programme in South Tyrol (also known as the Autonomous Province of Bolzano) in North-Eastern Italy between 20 and 22 November 2020.[117, 122, 125] At the time of the mass testing, South Tyrol was classified as a Red Zone (maximum risk) by the Italian authorities, and significant restrictions were in place (such as curfews, regional travel bans, prohibition on gatherings, closure of non-essential retail, hospitality and middle to high schools).[130] All residents were invited to participate in the mass antigen testing programme, which was voluntary. The exceptions to testing were children below the age of five, people with COVID-19 symptoms, those on sick leave, those who had tested positive within the last three months, and those who were in quarantine or self-isolating. Residents were tested once using SD-Biosensor Standard Q and Abbot Panbio rapid antigen tests with testing conducted by trained medical personnel, using nasal and throat swabs. The 7-day moving average of case numbers in South Tyrol was 103.4 per 100,000 inhabitants (95% CI, 95.4 to 111.4) for the time period 1 November 2020 to 20 November 2020, and COVID-19 vaccination programmes had not yet commenced in Italy.

In total, 361,781 RADTs were conducted, which equated to a 72.3% uptake rate among the eligible population (500,607). There was an RADT positivity rate of 1% (n=3,619 positive tests). The mass testing programme involved almost 2,000 staff and cost an estimated €4.5 million.

Pagani et al. conducted a retrospective cohort study and estimated that the basic reproduction number (R_0) decreased from a peak of approximately 1.8 on 3 November to a low of 0.6 by 24 November and plateauing at around 0.7 until 6 December.[122] The 7-day moving average of daily positive cases decreased from a peak of around 600 from the 5-10 November, to a low of around 250 on 6 December. Between 24 November and 11 December 2020, the observed number of COVID-19 cases in the region fell in:

- general hospital beds from 323 to 239 (26% reduction)
- ICU beds from 38 to 31 (18% reduction)
- other hospital areas from 148 to 138 (7% reduction).

The authors estimated that 612 deaths were avoided during this time period. Importantly, the data are truncated and no additional information is provided beyond 6 December, despite a rise in case numbers over the Christmas period, in

line with the surge in the Alpha variant. Therefore, any potential benefits, whether due to mass testing or the underlying public health restrictions, or both, were likely short-lived.

Ferrari et al. conducted a mathematical modelling study based on data from the mass testing programme in South Tyrol.[117] By embedding a semi-parametric growth model into a synthetic control framework, the authors estimated that the mass test campaign decreased the growth rate of the epidemic by 39% (95% CI, 29 to 49%), which corresponds to a reduction in the total additional cases of 14%, 18%, 30% and 56% within 7, 10, 20 and 40 days from the intervention date, respectively (assuming that the post-intervention transmission growth rate remained constant). Given the use of a retrospectively derived synthetic control group and uncertainty regarding the underpinning assumptions, caution is urged in its interpretation.

Ricco et al. conducted a retrospective cohort study, comparing South Tyrol and neighbouring provinces, Trentino (in Italy) and Tyrol (in Austria).[125] During November 2020, South Tyrol experienced a surge of COVID-19 cases (7-day moving average of 103.4 cases per 100,000 inhabitants, for the time period 1 November to 20 November), which was double the rate of the bordering Italian region of Trentino (42.8 cases per 100,000 inhabitants), and the Austrian State of Tyrol (40.1 cases per 100,000 inhabitants). The authors found that after mass testing in South Tyrol, the 7-day average of daily notification rates dropped from 110.9 (on 20 November) to 31.5 cases per 100,000 inhabitants (on 23 December), and was then comparable to those of Trentino (on average: 34.5 per 100,000, 95% CI 32.0 to 36.9 for South Tyrol, versus 35.0 per 100,000, 95% CI 33.1 to 37.0, for Trentino), but still higher than that for Tyrol (10.5 per 100,000 inhabitants, 95% CI 9.7 to 11.2). However, after daily rates were percent normalised to their respective maximum values in order to adjust for different diagnostic strategies, epidemic curves of the three regions substantially overlapped until the end of December 2020, thus sharing a common trend. The authors concluded that the available data cannot unambiguously confirm the effect of mass antigen testing on the epidemic in South Tyrol. Caution is urged in the interpretation of this study by Ricco et al. given that it is unclear how the comparator provinces were selected and whether this introduced bias into the study. Additionally, the usefulness of the normalisation of the daily notification rate by maximum percent value as an outcome measure is unclear.

3.2.4.2 Pre-event screening

Four included studies examined the effectiveness of RADT for pre-event screening.[72, 115, 118, 124] These studies were conducted in England,[115] Spain[72, 124] and the Netherlands.[118]

3.2.4.2.1 UK Events Research Programme

The findings from the first phase of the ongoing UK Events Research Programme (ERP) were published on 25 June 2021.[115] Between 17 April and 15 May 2021, a total of 58,103 participants attended nine pilot events that were conducted as part of Phase 1 of the ERP. Some of these pilots were delivered across multiple days, in a variety of indoor and outdoor settings, with variations of seated, standing, structured and unstructured audience styles, and a range of participant numbers (ranging from 149 to 18,720). The pilots occurred during a period of low incidence of SARS-CoV-2 infections (national 14-day notification rate per 100,000 was 44 and 45 on 17 April and 15 May, respectively). COVID-19 vaccination programmes were being rapidly rolled out throughout this period, with the proportion of the UK fully vaccinated doubling from 15% to 30% between the 17 April and 15 May. Importantly, while the Alpha variant was dominant at the start of these Phase 1 pilots (accounting for over 95% of sequenced samples in the UK), the more transmissible Delta variant had become more prevalent by the end of these pilots (accounting for a third of all sequenced cases). The nine pilot events were as follows:

- World Snooker Championship in the Crucible Theatre, Sheffield (17 April - 3 May)
- Emirates FA Cup Semi Final in Wembley Stadium, London (18 April)
- Carabao Cup Final, in Wembley Stadium, London (25 April)
- The Good Business Festival Presents 'Change Business for Good', in ACC Exhibition Centre, Liverpool (28 April)
- Circus Presents 'The First Dance', in Circus Nightclub (warehouse club), Liverpool (30 April - 1 May)
- Sefton Park Pilot (Outdoor music event), in Tented Stage in Sefton Park, Liverpool (2 May)
- BRIT Awards, at the O2, London (11 May)
- Emirates FA Cup Final, in Wembley Stadium, London (15 May)
- Reunion 5k, in Kempton Park, Surrey (15 May).

All events required a negative RADT for entry. The time interval between test and entry was initially 24 hours, but was extended to 36 hours for later pilots due to logistical issues. While professionally administered RADTs conducted at Asymptomatic Testing Sites (ATS) were a requirement for entry for seven of the nine

pilots, the two final events (Reunion 5K and FA Cup Final) permitted self-testing at home. Participants were also asked to take voluntary RT-PCR tests, before the event (on the same day) and five days after the event, for research purposes, however these were not a requirement for entry.

Across all nine pilot events, a total of 28 RT-PCR positive cases were identified. Of these, 11 were identified as potentially infectious at an event and a further 17 were identified as potentially infected at or around the time of an event. No substantial outbreaks were identified by public health teams and their surveillance teams around any of the events. However, RT-PCR test return rates were very low with only 15% of participants completing both pre- and post-event RT-PCR tests. RT-PCR return rates improved when tests were provided to attendees, compared with when attendees had to order them online. Events offering incentives, such as the chance to win future festival tickets, saw also higher return rates than those that did not offer an incentive. No information on resource use or costs were provided in this report.

Exploratory modelling of transmission risks at nightclubs that was undertaken to complement the pilot studies suggests that primary transmissions in nightclubs were reduced by 53% through testing on the day (between 37% and 71% depending on scenario), by a further 13% through the use of face coverings (10% to 29%), and by a further 41% through social distancing (11% to 41%). The modelling did not fully account for aerosol and fomite (surface) transmission; is limited by the lack of direct evidence on transmissions in nightclubs; and did not cover onwards transmissions, hotspots, or cross-community infections.

Caution is urged with regard to the interpretation of this study given that SARS-CoV-2 was not circulating widely in the community at the time, the very low uptake (15%) of pre- and post- event PCR tests, along with the limited scale, scope and design of these Phase 1 pilots. However, findings from Phase 2 and 3 of the ERP, which involve larger events, may provide more evidence regarding means to mitigate the risk of SARS-CoV-2 transmission at mass gatherings, through the use of RADTs and other measures (such as proof of vaccination or recovery from COVID-19).

3.2.4.2.2 Barcelona concerts

Two studies by the same research group were conducted in Barcelona, Spain to evaluate the effectiveness of pre-event RADT screening, plus face mask usage and adequate ventilation, at preventing SARS-CoV-2 transmission at live indoor music concerts.[72, 124] The first of these studies was an RCT conducted on 12 December 2020, involving 1,047 participants (of which 472 attended the event),[124] and the

second study took place on 27 March 2021, involving 5,000 participants (of which 4,992 attended the event) with an uncontrolled, before-after design.[72]

The aim of the RCT by Revollo et al. was to assess the effectiveness of a range of public health measures at preventing SARS-CoV-2 transmission at an indoor live concert. This study was conducted when the national 14-day notification rate of newly reported COVID-19 cases in Spain was 219 per 100,000 population. COVID-19 vaccination programmes had not commenced in Spain and the Alpha variant accounted for <1% of all sequenced samples nationally. The main measures included pre-event RADT (using Panbio COVID-19 Ag Rapid Test) (and Transcription Mediated Amplification [TMA] testing), mandatory wearing of N95 face masks and 'adequate' air ventilation. Healthcare staff (45 nurses and one physician) collected nasopharyngeal swabs from all eligible participants in a screening structure set up outdoors in front of the concert venue. All study participants with a negative antigen test (tested within nine hours prior to the event) were randomised 1:1 to the experimental arm (who attended the concert) or to the control arm (who did not attend the concert). No physical distancing was required in the concert room, however, N95 mask wearing was compulsory throughout. All study participants were followed up by RT-PCR, antigen and TMA testing 8 days post-event.

A total of 1,047 participants with a negative pre-event antigen test were randomised, however complete data are only available for 960 of these, and only these data were analysed. At follow-up none of the 465 people in the experimental arm became infected with SARS-CoV-2 (observed incidence 0%; Bayesian estimated incidence 0.14%; 95% credible intervals [CrI]: 0% to 0.61%) versus 2 out of 495 controls (0.31%; 95% CrI: 0.04% to 0.73%). The Bayesian estimate for the difference in incidence between the experimental and control groups was reported to be -0.15% (95% CrI: 0.72 to 0.44). However, this study may not have been sufficiently powered to detect a statistically significant difference given that there were substantially fewer participants than the planned number of 1,000 per arm.

A follow-on study was conducted by Llibre et al. on 27 March 2021 with a larger sample size (n=5,000), but using a before-after study design without a control group.[72] At the time of the event, the age-standardised 14-day cumulative incidence rate in Barcelona was 259.5 cases per 100,000 inhabitants, nationally 5% of the population had been fully vaccinated against COVID-19, and the Alpha variant accounted for approximately 85% of all sequenced cases. Same-day pre-event RADT screening was performed by a team of 74 nurses (Panbio COVID-19 Ag Rapid Test) for all 5,000 attendees at three different screening sites. No physical distancing was required in the concert room, however, FFP2 mask wearing was compulsory and ventilation was optimised throughout the event. Of the 5,000 people screened by

RADT, six were found to be positive and two were close contacts of these positive cases, and so a total of eight people were not allowed to enter the music event. Of the 4,992 individuals who attended the event, 4,584 (92%) were included in the 14-day follow-up analysis. The authors found that six attendees none of whom were vaccinated, were diagnosed with COVID-19 within the two weeks after the concert. Of these six infected individuals, three were identified through contact tracing from known index cases who had not attended the concert; therefore, their infection was unlikely to have occurred during the event. One of the six individuals had mild symptoms at the time of the event and is thought to have attended during their incubation period. The transmission source of the two remaining cases could not be identified. Importantly, the uncontrolled nature of this study prevents direct comparisons between the incidence rate observed among attendees and that of the background population.[72]

3.2.4.2.3 Fieldlab events (the Netherlands)

A comprehensive national event pilot programme called Fieldlab events was conducted in the Netherlands.[141] As part of the first phase of pilot events, four reports were published online as technical reports, each examining different types of mass gatherings (for example, a business conference, a theatre, a football match, and outdoor festival). All of these initial events used RT-PCR for pre-event testing, except for one of the later events, a football match, which used RADT, hence only data from this single event is examined here. In the second phase of the Fieldlab events, RADTs replaced RT-PCR testing, though these reports have not yet been published. All four Phase 1 Fieldlab events have previously been reviewed as part of a HIQA evidence summary of public health measures to limit the transmission of SARS-CoV-2 at mass gatherings.[142]

The included Fieldlab study examined the use of RADT in conjunction with other public health measures (for example, temperature screening and face mask use) at a football match that took place on 27 March 2021, which involved 5,108 participants altogether.[118] Same-day antigen testing was required for entry. This study was conducted when the national 14-day notification rate of newly reported COVID-19 cases in the Netherlands was 566 per 100,000 population, the proportion of the population fully vaccinated was 3.3%, and the Alpha variant was dominant (accounting for approximately 92% of all sequenced cases). Of the 5,108 participants tested with an RADT, 18 were positive (0.35%) and so were excluded from attending the football match. Seventy three percent (3,718) of attendees underwent post-event testing with an RADT taken five days after the match, resulting in three positive cases (0.08%). The research team were notified of three other positive cases via the national contact tracing service, however these three cases were not believed to have been infectious during the event. Given the loss to

follow-up of over 25% for post-event testing, along with the high community incidence of SARS-CoV-2 infection and low vaccination coverage at the time of these studies, it is likely that the number of positive cases identified is an underestimate, though importantly, not all cases would necessarily have contracted SARS-CoV-2 at these events.

3.2.4.3 Serial testing

Four studies were identified that evaluated the effectiveness of RADT serial testing in different settings. One study examined the effectiveness of serial antigen testing in athletes and staff in a sports programme,[121] one study used serial antigen testing among staff in a care home setting in England,[126] one study examined the effectiveness of serial antigen testing in high school students,[128] and one study examined the effectiveness of serial testing in a prison setting.[129]

3.2.4.3.1 US intercollegiate sports programme

Moreno et al. conducted an epidemiological investigation of two SARS-CoV-2 outbreaks that occurred among US intercollegiate university athletic programmes while they were undertaking mandatory directly observed daily antigen testing using Quidel's Sofia SARS Antigen Fluorescent Immunoassay.[121] The researchers used genomic sequencing to investigate transmission dynamics in these outbreaks. No information was provided on the specific location, or the timing of these outbreaks other than 'Fall 2020'. The study authors stated that no students or staff had received a COVID-19 vaccine at the time of the outbreaks, as these were not yet widely available.

In the first outbreak, 32 confirmed cases occurred within a university athletics programme after the index patient attended a meeting while infectious, despite a negative RADT on the day of the meeting. In the second outbreak, 12 confirmed cases occurred among athletes from two university programmes that faced each other in an athletic competition, despite receipt of negative RADT results on the day of the competition. Overall, the first outbreak infected 133 individuals and the second outbreak infected 55 individuals.

Contact tracing during outbreak 1 identified interactions among individuals that may have contributed to at least 21 of the 32 confirmed cases in the sports programme. Notably, the team continued to have physically distanced (6-feet-apart) in-person meetings with cloth masks, until such point as the positive case was identified, and then all in-person team activities were suspended to prevent further spread. Unvaccinated attendees in these meetings were not quarantined, despite potentially becoming infected. Additionally, roommates and household contacts of the infected athletes were not required to quarantine. The authors suggest that these actions in

conjunction with the limitations of RADTs may have contributed to onward transmission during this outbreak. In outbreak 2, genomic sequencing identified that SARS-CoV-2 transmission likely occurred between the two teams during athletic competition even though all members of both teams received negative antigen results immediately before the competition.[121] The authors concluded that antigen testing alone, even when mandated and directly observed, may not be sufficient as an intervention to prevent SARS-CoV-2 outbreaks in congregate settings. An important limitation of this study was its small sample size and incomplete contact tracing data. Therefore, undocumented exposures between athletes and staff may have occurred outside of organised activities that may have led to infections.

3.2.4.3.2 Liverpool care homes

This study by Tulloch et al., was conducted as part of the Liverpool Covid-SMART community testing pilot (as discussed in Section 3.2.4.1.1).[126] This prospective cohort study, with a qualitative evaluation via semi-structured interviews, was conducted in 11 care homes in Liverpool from 1 December 2020 until 10 January 2021. This was a period of rapidly deteriorating epidemiological situation with the national 14-day incidence rate per 100,000 population increasing from 343 at the start of this study to 1,158 by the end, in line with the domination of the more transmissible Alpha variant in the UK (which accounted for 75% of all sequenced samples by 10 January). The roll out of the COVID-19 vaccination programme was only just commencing around this time, though care home residents were prioritised. An estimated 1% of the UK population were fully vaccinated by 10 January.

According to the study protocol, care home staff were to be tested twice a week using self-administered RADTs (Innova SARS-CoV-2 rapid antigen LFD). An RT-PCR test was performed simultaneously alongside the second test each week as part of the existing testing regime in care homes. During the study, 1,638 RADTs were performed on 407 staff, of whom five tested positive. However, protocol adherence was poor with only 8.6% of staff achieving >75% protocol adherence, and 25.3% achieving ≥50 adherence. Of note, all 11 care homes were SARS-CoV-2 outbreak-free at the start of the study, however by the end of the study period, six of these care homes had outbreaks. Compared with a sample of 71 non-pilot care homes in the region, there was no evidence of significant differences in the proportion of homes with outbreaks, or the size of the outbreaks, highlighting the deteriorating epidemiological situation affecting all care homes at that time. The researchers also found no apparent trend between testing protocol adherence and outbreak status.

The qualitative findings highlighted the challenges of implementing rigorous bi-weekly rapid antigen testing in an already over-burdened care home environment. In particular, staff found there was excessive administration associated with the testing

procedure which was very time consuming. In addition, some staff did not feel confident in performing the test due to perceived weaknesses in the training programme. A critical issue for some care home staff was the lack of standardised processes, in part due to inadequate designated testing areas. Performing the RADTs, on top of the RT-PCR tests, for both staff and visitors, required significant planning and increased the pressures on staff, adding to an already saturated workflow, exacerbated by the various COVID-19 public health measures.

3.2.4.3.3 Utah high schools

Lanier et al. described the implementation of a RADT screening programme in high schools in Utah, USA between November 2020 and March 2021.[128] When the programme was initiated, the incidence of SARS-CoV-2 was high, with a national 14-day incidence rate of 714 per 100,000 population, the COVID-19 vaccination programme had not yet been rolled out and the Alpha variant was not in circulation. By the end of the programme, the 14-day incidence had declined to 231 per 100,000, an estimated 13% of the population were fully vaccinated and the prevalence of the Alpha variant had increased to 36% (20 March 2021).

The 'Test to Play' programme, which was implemented on 30 November 2020, was mandatory for high school students who wanted to undertake extracurricular activities. This programme involved antigen testing (Abbott BinaxNOW rapid antigen assay) every 14 days, using nasal swabs that were sampled and processed by trained school staff. Parental permission was required for students to undergo school-based testing. Schools were required to report all test results to the Utah Department of Health. Students could opt to undergo testing elsewhere (for example, community testing), but required a negative test to continue participation in extracurricular activities. Students who received a positive test result were required to isolate for 10 days, and their close contacts were required to quarantine for 10 or 14 days (the quarantine policy changed during the study period).

Between 30 November 2020 and 20 March 2021, 142,262 'Test to Play' RADTs were conducted in 50,400 high school students attending 127 (of 193) Utah public high schools representing an estimated two thirds (67%) of all high school students participating in extracurricular activities. Of the 50,400 students, 1,771 (3.5%) had a positive result. For the other third of students for whom test results are not available, these students may have undergone testing elsewhere, or schools may have underreported in some cases. It is also possible that some of these students did not undertake any testing, yet participated in activities. From January to March 2021, the test positivity declined, consistent with decreasing incidence in Utah among school-aged children during this period. The authors estimated that 'Test to Play' enabled approximately 95% (n=10,812) of the 11,379 scheduled competition

events for high school extracurricular winter athletics to occur. However, since there was no comparator group/period for this study, it is unclear how effective or otherwise this testing programme actually was, compared with similar schools who did not participate.

A separate testing programme called 'Test to Stay' was also implemented in 13 Utah high schools. This antigen testing programme involved school-wide testing to continue in-person instruction as an alternative to transitioning to remote instruction if a school crossed a defined outbreak threshold. However, since 'Test to Stay' involved testing for outbreak management as opposed to screening asymptomatic individuals, it is not discussed in the context of the current evidence summary.

3.2.4.3.4 Italian prison

Stufano et al. conducted a retrospective cohort study of a comprehensive mitigation plan (including serial antigen testing) in a prison in Bari, Italy.[129] When the study started, the national incidence of SARS-CoV-2 was high (14-day incidence rate 712 per 100,000 population) and the Alpha variant accounted for 0.01% of all sequenced samples. By the end of the study, the national 14-day incidence was 301 per 100,000 and the Alpha variant accounted for 59% of the sequenced samples. The roll out of the COVID-19 vaccination programme in Italy commenced during the study period, and an estimated 1% of the population were fully vaccinated by the end of the study.

This study evaluated two whole-of-prison testing campaigns that were conducted 30 days apart, on top of stringent background public health measures (for both prisoners and staff) that had been in effect since March 2020. These measures included an entry protocol for all new prisoners (quarantine plus antigen testing after 72 hours and again after 7 days), health screening, face masks, hand sanitiser, physical distancing, congestion control, cohorting and contact tracing. Nasopharyngeal samples were collected and subsequently processed by trained healthcare personnel (using fluorescence immunoassays (FIA)). These two voluntary testing campaigns were carried out in the period 10 November – 09 December 2020, and 10 December 2020 – 27 January 2021, respectively, enrolling all prisoners and staff. The second test was performed at least 30 days after the first test. A total of 426 and 480 prisoners partook in rounds 1 and 2 of testing, respectively, and 353 detainees participated in both rounds (participation rates of 100% in round 1 and >99.5% in round 2, among the various subgroups of prisoners). Two prisoners tested positive in round 1 and none testing positive in round 2 or outside of the testing campaign. In total, 367 staff were tested at the first round and 325 at the second round (participation rates >89.2% in round 1 and >59.5% in round 2, among the various subgroups of staff). In the first round, six staff tested positive,

and none tested positive in the second round. An additional two staff tested positive outside of the testing campaigns, after developing symptoms at home. All close contacts of the 10 positive cases were further tested – none of whom subsequently tested positive.

The authors concluded that the comprehensive mitigation measures that were in place, including serial antigen testing, prevented SARS-CoV-2 outbreaks in the prison. While no outbreaks were detected in this congregated setting during this study period, indicating that the layered mitigation approach was protective, the lack of comparator group/period prevents ascertainment of the added benefit of the testing campaign to the existing measures.

3.2.5 Quality appraisal

Quality appraisal was conducted using the National Institutes of Health (NIH) Quality Assessment Tools. The quality appraisal of the 11 cohort studies,[50, 69, 73, 117, 120, 122, 123, 125, 126] the three uncontrolled before-after studies,[72, 115, 118] the single RCT[124] and the single case series[121] are described in Tables 8-11, respectively. Overall 10 of the 16 studies were rated as "fair" quality[69, 72, 106, 115, 117-121, 124, 126, 129] and six were rated as "poor" quality.[50, 73, 116, 122, 123, 125, 128] No study was rated as "good" quality (the highest quality rating). Across all studies, there were important methodological concerns, which affected the internal validity of the studies.

With regard to the cohort studies, there was high participation rates[50, 69, 73, 117, 120, 122, 123, 125] and clear objectives[50, 69, 73, 117, 120, 123, 125, 126] across most included studies, with exposure measured prior to outcome in all included studies (Table 8).[50, 69, 73, 117, 120, 122, 123, 125, 126] However, there were concerns regarding the selection of participants from the population,[50, 69, 73, 117, 120, 123, 125] the lack of sample size justification,[50, 69, 73, 117, 120, 122, 123, 125, 126] choice of outcome,[50, 122, 123, 125] the lack of blinding of outcome assessors,[50, 69, 123, 126] loss to follow-up,[69, 123, 126] and insufficient controlling for confounders.[73, 122, 123, 125, 126] Of particular concern among included ecological studies, were the inferences made by the researchers between antigen testing and outcomes without sufficiently controlling for secular trends and other public health measures and restrictions (such as national lockdowns).[50, 69, 73, 117, 122, 125] Notably, some of these studies did not adequately address the subsequent epidemiological deterioration that occurred in December/January, despite the mass testing programmes.[50, 69, 73, 122, 123]

Table 8 Quality appraisal of included cohort studies

Quality appraisal criteria	Ferrari (2021)	Frnda (2021)	Kahanec (2021)	University of Liverpool (2021)	Pagani (2020)	Pavelka (2021)	Ricco (2021)	Tulloch (2021)	Public Health Wales (2021)	Lanier (2021)	Stufano (2021)
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	✓	✓	✓	x	✓	✓	✓	x	✓	✓
3. Was the participation rate of eligible persons at least 50%?	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x	x	x	x	✓	x	x	✓	x	✓	✓
5. Was a sample size justification, power description, or variance and effect estimates provided?	x	x	x	x	x	x	x	x	x	x	x
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓
8. For exposures that can vary in amount or level, did the study	NA	NA	NA	NA	NA	NA	NA	x	NA	NA	NA

Quality appraisal criteria	Ferrari (2021)	Frnda (2021)	Kahanec (2021)	University of Liverpool (2021)	Pagani (2020)	Pavelka (2021)	Ricco (2021)	Tulloch (2021)	Public Health Wales (2021)	Lanier (2021)	Stufano (2021)
examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?											
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓
10. Was the exposure(s) assessed more than once over time?	x	✓	✓	✓	x	✓	x	✓	✓	✓	✓
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	NA	✓	✓	x	x	x	✓	x	x	✓
12. Were the outcome assessors blinded to the exposure status of participants?	NR	NA	✓	x	NR	x	NR	x	x	x	x
13. Was loss to follow-up after baseline 20% or less?	✓	✓	✓	x	✓	✓	✓	x	x	x	✓
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	✓	x	✓	✓	x	✓	x	x	x	x	x
Quality Rating†	**Fair**	**Poor**	**Fair**	**Fair**	**Poor**	**Poor**	**Poor**	**Fair**	**Poor**	**Poor**	**Fair**

†Quality can be rated as Good, Fair or Poor. ✓Yes. **x** No. NA = not applicable. NR = none reported.

All three uncontrolled, before-after studies, were assessed to have clearly stated the study objectives and eligibility criteria, and delivered the intervention consistently to all participants (Table 9).[72, 115, 118] However, there were concerns regarding the lack of blinding of outcome assessors,[72, 115, 118] loss to follow-up,[115, 118] and the statistical analysis.[72, 115, 118]

Table 9 Quality appraisal of included uncontrolled, before-after studies

Quality appraisal criteria	Fieldlab (2021)	Llibre (2021)	UK Government (2021)
1. Was the study question or objective clearly stated?	✓	✓	✓
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	✓	✓	✓
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	✓	✓	✓
4. Were all eligible participants that met the prespecified entry criteria enrolled?	**NR**	✓	✓
5. Was the sample size sufficiently large to provide confidence in the findings?	**x**	✓	**x**
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	✓	✓	**x**
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	✓	✓	✓
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	**x**	**x**	**x**
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	**x**	✓	**x**
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	**x**	**x**	**x**
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	**NA**	**NA**	**NA**
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	**NA**	**NA**	**NA**
Quality Rating†	**Fair**	**Fair**	**Fair**

†Quality can be rated as Good, Fair or Poor. ✓Yes. **x** No. NA = not applicable. NR = none reported.

While the selection bias and allocation bias were minimised in the single RCT by Revollo et al, there are concerns regarding the inconsistent testing regime and outcome assessment, insufficient sample size and the lack of intention-to-treat analysis (Table 10). Additionally there was insufficient information to determine whether outcome assessors were blinded, whether the groups were similar at baseline, and whether there was high adherence to the intervention protocols.[124]

Table 10 Quality appraisal of included randomised controlled trial

Quality appraisal criteria	Revollo (2021)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	✓
2. Was the method of randomisation adequate (i.e., use of randomly generated assignment)?	✓
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	✓
4. Were study participants and providers blinded to treatment group assignment?	**x**
5. Were the people assessing the outcomes blinded to the participants' group assignments?	**NR**
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	**NR**
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	✓
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	✓
9. Was there high adherence to the intervention protocols for each treatment group?	**NR**
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	**x**
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	**x**
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	**x**
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	**NA**
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	**x**
Quality Rating†	**Fair**

†Quality can be rated as Good, Fair or Poor. ✓Yes. **x** No. NA = not applicable. NR = none reported.

With regard to the included case series study, it had clearly stated objectives and intervention, comparable subjects, appropriate outcome measurement and follow-up, and the results were well-described. However, the population and analysis were not well described and the cases were not consecutive.[121]

Table 11 Quality appraisal of included case series study

Quality appraisal criteria	Moreno (2021)
1. Was the study question or objective clearly stated?	✓
2. Was the study population clearly and fully described, including a case definition?	**x**
3. Were the cases consecutive?	**x**
4. Were the subjects comparable?	✓
5. Was the intervention clearly described?	✓
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	✓
7. Was the length of follow-up adequate?	✓
8. Were the statistical methods well-described?	**x**
9. Were the results well-described?	✓
Quality Rating†	**Fair**

†Quality can be rated as Good, Fair or Poor. ✓Yes. **x** No. NA = not applicable. NR = none reported.

Of the 16 included studies, two are published as preprints, so they have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.[117, 122] Additionally, a further four studies are published as technical reports.[69, 115, 118, 123] It is unclear whether these reports were subject to peer review.

4 Discussion

4.1.1 Summary of main findings from the review of effectiveness

This evidence summary collated and synthesised the real-world evidence on the effectiveness of rapid antigen testing for screening and surveillance of asymptomatic individuals at limiting the transmission of SARS-CoV-2. Specifically, studies were only included if they evaluated the impact of using RADTs in people with no symptoms and no known exposure to SARS-CoV-2 at the time of testing, on SARS-CoV-2 transmission. Limited evidence was found regarding the use of rapid antigen testing for screening of asymptomatic individuals, with only 19 articles referring to 16 unique studies identified.[50, 69, 72, 73, 106, 115-126] No studies were identified regarding the use of rapid antigen testing for surveillance of asymptomatic individuals. The 16 included studies examined a diverse range of settings and each study used different testing protocols. Specifically, of the identified 16 studies, eight examined the effectiveness of RADTs for mass testing,[50, 69, 73, 106, 116, 117, 119, 120, 122, 123, 125] four for pre-event screening,[72, 115, 118, 124] four for serial testing in different setting (schools,[128] a prison,[129] a university sports programme,[121] and in a care home setting).[126] With the exception of three studies that included staff in a university athletics programme, a prison and in care homes, respectively, no included studies examined the effectiveness of RADTs in workplaces. Additionally, no included study examined the effectiveness for RADTs for travel-related activities.

Overall, there is uncertainty regarding the effectiveness of rapid antigen testing for screening of asymptomatic individuals at limiting the transmission of SARS-CoV-2. This uncertainty is due to the relatively low number of studies identified, the predominantly observational and/or uncontrolled study designs used, and concerns regarding the methodological quality of these studies.

While mass testing using RADTs was reported by study authors in seven of the eight included studies, to be effective at reducing SARS-CoV-2 transmission,[125] it is important to note that the ecological design of these studies makes it very challenging to disentangle the contribution of mass testing from the ongoing background public health measures and restrictions. The estimated effect on transmission varied from minimal change in one study[125] to an 82% reduction in prevalence after three rounds of testing in another study,[50] highlighting the significant uncertainty regarding the effectiveness of this intervention. However, the counterfactual groups in these studies were largely modelled and hypothetical, sometimes based on questionable assumptions, such as limited or no mitigation or 100% sensitivity of the RADT for infectious cases.[50, 69, 73, 116, 117, 123] While estimates of effectiveness may vary, there was evidence from one included study that re-

testing at regular intervals would likely be necessary for any potential sustained effect.[120] Moreover, it was evident that these mass testing programmes were resource intensive,[73, 116, 122, 123] with uncertainty regarding their cost-effectiveness.[116] Better quality studies are needed to determine the effectiveness of mass testing programmes, and whether such interventions represent value for money. Such a study may involve randomising by geographical area, the offer of repeated testing in asymptomatic people versus no offer of testing, alongside the conduct of an economic evaluation.[5]

Though still limited, research is being conducted on the potential role of RADTs for pre-event screening, in conjunction with other public health measures, such as face mask use, social distancing and optimising ventilation.[72, 115, 118, 124] Of the four studies that examined their effectiveness for pre-event screening,[72, 115, 118, 124] one was an RCT. However, there were important methodological limitations associated with all of these studies, not least the relatively small sample sizes[72, 115, 118, 124] and the substantial loss to follow-up in the largest of these studies.[115] Research into the hosting of mass gatherings in the context of the COVID-19 pandemic is ongoing, and these studies may provide additional evidence on the use of RADTs in mitigating transmission risk at these events.[115, 141, 143]

Two included studies reported on SARS-CoV-2 outbreaks that occurred during the implementation of serial antigen testing protocols, among intercollegiate athletes[121] and care home staff,[126] respectively. These studies highlight the complex nature of SARS-CoV-2 outbreaks in congregated settings. In relation to the care home study, it was evident that there was poor adherence to the RADT protocol due to implementation and feasibility issues locally. This study highlights the significant challenges in terms of implementation even in high risk settings where motivation to protect residents is likely to be high, but competing demands on time can be overwhelming particularly during times of high prevalence. Of note, this study took place during a period of rapid epidemiological deterioration, where other care homes in the region (control group) also experienced high levels of outbreaks. Conversely, in the sports programme study, the outbreaks occurred despite mandated and directly observed daily antigen testing, suggesting that in congregated settings, antigen testing alone may not suffice and a layered mitigation approach may be necessary to prevent outbreaks.[121] The schools[128] and the prison[129] serial testing programmes reported that RADTs helped to ensure the completion of the majority (95%) of planned extracurricular activities in schools and prevented SARS-CoV-2 outbreaks in the prison, respectively. However, it is important to acknowledge that other measures were in place simultaneously (for example, face masks and physical distancing during extracurricular activities, and strict testing protocols for all new prisoners). Therefore, it is difficult to disentangle the effect of RADTs from other

mitigation measures. Additionally, the lack of comparators in both of these studies limits any determination of relative effectiveness.[128, 129]

4.1.2 Findings in context

As illustrated in RQ1, rapid antigen testing is a complicated process and many factors need to be considered to ensure that the right test is undertaken in the right person at the right time for the right purpose.[4] With regard to RADTs, it is important to consider how they work, how they differ from other tests, what they might be used for, their diagnostic accuracy, their regulatory status, the implications of a test result, the various modalities of test delivery, the associated resource requirements, as well as guidance and ethical considerations relating to their use.

In comparison with the gold standard laboratory based RT-PCR diagnostic test for SARS-CoV-2, RADTs have a considerably faster turnaround time (from sampling to reporting of results) and are relatively less expensive.[33] However, they are also less sensitive than RT-PCR tests, particularly in asymptomatic individuals. Three different systematic reviews compared the diagnostic accuracy of RADTs with RT-PCR for the detection of SARS-CoV-2 infection.[12, 82, 87] The three included reviews broadly found that test sensitivity was higher in symptomatic individuals (ranging from 64%-84%) than in asymptomatic individuals (40%-74%). A common finding across each of the reviews was that sensitivity was highest in those with C_t values on RT-PCR ≤25 (which can be considered to reflect a high viral load). The viral load is expected to be highest around symptom onset (or within a few days of exposure to a positive case for asymptomatic contacts).[88] From a public health perspective, it is still important to identify cases even when the viral load is low, as these individuals may be at the start of their infection and potentially infectious and so prompt isolation can break the chains of onward transmission.[144] Additionally, for those that are no longer infectious, case detection is still important as it can initiate contact tracing and identify other potentially infectious individuals.[22] However, as the epidemiological landscape changes due to the rollout of COVID-19 vaccination programmes, the management of contact tracing and outbreaks may change, though much uncertainty remains regarding the emergence of new variants of concern and how these might impact on pandemic control measures.[145]

The use of RADTs for diagnostic or close contact/outbreak testing was not the subject of the current evidence summary. However, it is noted that given the relatively high sensitivity of RADTs when the viral load is high, RADTs can be used to supplement RT-PCR when diagnostic capacity is constrained.[63] In Ireland, the Health Service Executive (HSE) is currently using RADTs for diagnostic purposes to support RT-PCR testing during outbreak management, with HPSC guidance recommending that RADTs should be performed within five days of onset of

symptoms or within seven days from time of last exposure to a case.[75] In England, RADTs are also being trialled for close contacts of COVID-19 cases in schools as an alternative to self-isolation.[146]

As part of screening and surveillance (with high frequency testing) for SARS-CoV-2, it has been argued that RADTs offer the potential for rapid identification of infectious cases to enable prompt isolation and interruption of onward transmission.[16] However, this evidence summary found uncertainty regarding the effectiveness of rapid antigen testing for screening of asymptomatic individuals at limiting the transmission of SARS-CoV-2, with no studies found regarding their use for surveillance purposes. While there is some evidence that repeated mass testing using RADTs may have a short-term effect on limiting SARS-CoV-2 transmission, none of the four included mass testing programmes (Slovakia, Liverpool, South Wales and North-Eastern Italy) were able to mitigate the surge of cases that occurred during December 2020 – January 2021.[50, 69, 73, 116, 117, 120, 122, 123, 125] This finding suggests that any potential transmission-limiting effect of these mass antigen testing programmes may have been insufficient to counter the increased transmissibility associated with the Alpha variant, which became the most dominant strain during this period, or perhaps that these mass testing programmes were ended prematurely.[147] These studies reiterate that RADTs supplement, rather than replace, other public health measures and restrictions as a part of a potential mitigation strategy.

In relation to pre-event screening, HIQA conducted an evidence summary of public health measures to limit the transmission of SARS-CoV-2 at mass gatherings.[142, 148] The report found evidence from 11 studies (involving approximately 30,482 participants) that implementing a range of measures may reduce the risk of SARS-CoV-2 transmission at mass gatherings. However, it is unlikely that this risk can be eliminated entirely. Though in light of the vaccine rollout, what is considered an acceptable level of risk has changed, with the recommencing of mass gatherings illustrating an acceptance of some level of transmission risk.[142] All included studies adopted a layered mitigation approach involving multiple measures. The number and intensity of measures implemented varied across studies, with most implementing resource intense measures. Two of the 11 included studies used pre-event rapid antigen testing, and were included in the current evidence summary.[118, 124] Given the multi-faceted nature of the measures implemented, it was not possible to determine the effectiveness of any single measure, though it is likely that a layered mitigation approach may be more effective than relying on any single measure. The importance of implementing multiple mitigation measures was also highlighted in another study included in the current evidence summary that examined outbreaks

among intercollegiate athletes that occurred despite mandatory daily observed rapid antigen testing.[121]

Though RADTs may be relatively inexpensive and easy to administer at an individual level,[16] real-world evidence from included studies highlights the significant resource, implementation and social issues associated with using RADTs at scale.[69, 72, 73, 115, 116, 118, 122-124, 126] For example, the largest of the included mass testing programmes that took place in Slovakia involving over 5 million RADTs, cost over €82 million,[73] and involved over 60,000 personnel.[50] Tulloch et al. described barriers to the implementation of a bi-weekly RADT protocol in care homes in Liverpool, which included inadequate training, insufficient capacity and lack of suitable areas to conduct the testing, which culminated in poor adherence to the testing protocol.[126] In the mass testing pilots conducted in Liverpool and South Wales, there was evidence of lower uptake rates in certain populations, such as those living in deprived areas, ethnic minorities, males, and young people, and in those with the highest positivity rates.[69, 106, 123] Fear of income loss due to the need to self-isolate was one of the main reported barriers to testing in the Liverpool pilot.[69] Given uncertainty surrounding the clinical- and cost-effectiveness of mass testing programmes, as well as their feasibility, it is important that the introduction of such programmes does not divert resources from other important health and social care services (for example, ensuring symptomatic individuals get tested and are supported to self-isolate) as this could exacerbate health inequalities.[106, 149]

As outlined in RQ1, there are many factors that can reduce the performance of an RADT, such as use in asymptomatic populations, poor quality of specimen collection and processing (for example, by an untrained person)[63] and lack of compliance with manufacturers' instructions for use (IFU).[82] Of the 16 included studies, self-testing using RADTs was only permitted in limited circumstances in the UK ERP (two of the nine pilot events)[115] and in one study involving care home staff who were trained to use the tests.[126] The remaining studies used either professionally administered or observed, self-sampled tests,[50, 69, 72, 73, 106, 116-125, 128, 129] hence the findings from these studies may not be transferable to settings where these tests are self-administered or used in an unsupervised nature. It is important to consider the potential implications of using self-administered RADTs at scale in untrained, asymptomatic individuals. It is possible that the sensitivity of the test will be negatively impacted by these factors, resulting in a relative rise in the number of false negative results, potentially providing false reassurance to infectious individuals.[150] It is also important to note that the PPV of a test depends on the prevalence of infection, and that there are negative consequences for false positive results in terms of work and school attendance, as individuals must await results of confirmatory RT-PCR to exit isolation.[151] There are also regulatory issues regarding

the usage of RADTs for self-testing in asymptomatic people, given that RADT usage beyond the CE marking and manufacturers' IFU, is considered 'off-label', and while there is no legal impediment to this act, liability falls to the healthcare professional and/or health service using or commissioning the tests, as opposed to the manufacturer. Additionally, reporting obligations on the general public for a notifiable disease need to be carefully considered, as it may not be possible for a positive test obtained by a self-administered RADT to initiate contact tracing processes.[23]

4.1.3 Evidence gaps

The following were the main evidence gaps identified on this topic:

- the effectiveness of rapid antigen testing for surveillance of asymptomatic individuals to limit transmission of SARS-CoV-2.
- the effectiveness of RADTs in third-level educational institutions, childcare facilities, workplaces, and for travel-related activities.
- RCTs examining the effectiveness of different test strategies at limiting transmission of SARS-CoV-2 (randomised at the regional level).
- the cost-effectiveness of mass testing and pre-event screening programmes using RADTs.

4.1.4 Strengths and limitations

The main strength of this evidence summary is its comprehensiveness, combining a technical description of RADTs in relation to their use for screening and surveillance in asymptomatic populations, with evidence of effectiveness of these tests from 16 studies. This evidence summary therefore provides an up-to-date overview on the role of RADTs in asymptomatic populations in the context of the COVID-19 pandemic. Another strength is the focus on the clinical effectiveness of RADTs in real world situations rather than diagnostic test accuracy. In this way, primacy is given to outcomes that are of greater relevance to the public and to policymakers (such as infection and hospitalisation rates), rather than technical performance issues (such as sensitivity and specificity).[81]

A number of limitations need to be considered when interpreting the findings of this evidence summary. Studies evaluating the effectiveness of RADTs in asymptomatic populations may be subject to publication bias. This is where studies with favourable outcomes are more likely to be published in the academic literature, than those with negative findings.[152] An example of this are the most recent Fieldlab events that occurred in the Netherlands, reports of which have not yet been published by the

researchers. For these large pilot events, which took place when the Delta variant was dominant, a negative rapid antigen test taken up to 40 hours prior to the event, was required for entry, but face mask and physical distancing measures were relaxed. However, the National Institute for Public Health and the Environment of the Netherlands (known as the RIVM) have reported that at a two-day festival (3-4 July) attended by over 20,000 individuals in Utrecht, at least 1,000 people are known to have become infected.[153] In another event involving 650 attendees at a disco that took place in Enschede on 26 June, it has been reported in the media that at least 180 are known to have become infected.[108] Due to these superspreading events, the Dutch government have banned all multi-day events, as well as one-day events without fixed seating, until 1 September.[154, 155] The Dutch Government have also reduced the maximum time between taking a RADT and entry at permitted events to 24 hours.[155]

Additionally, there is an acknowledgement that RADTs are in widespread use for screening purposes in many different countries (for example, the UK, the Netherlands and Austria).[130] While a comprehensive grey literature search was undertaken to identify all relevant reports, without any language restrictions, it is possible that some reports were missed. However, it is also possible that many of these rapid antigen testing programmes were never evaluated and/or publicly reported. More data is required from countries that have implemented large scale antigen testing programmes, to enable effective knowledge translation.

In this evidence summary, the use of RADT was considered as an alternative to no-testing, as is currently the situation in most settings in Ireland for asymptomatic individuals with no known or suspected exposure to SARS-CoV-2. It is likely that many of the feasibility, resource, social and ethical challenges identified would be similar, if RT-PCR was being considered for screening and surveillance purposes in asymptomatic individuals.

Given the emergence of variants of concern, it is important to consider their potential impact on the performance of RADTs, as some mutations may reduce the ability of the test to detect the target antigens on the surface of the virus.[96, 156] Additionally, the effectiveness of screening using RADTs in vaccinated populations may be different to that in a population with limited immunity. The utility of RADTs must therefore be considered in the context of:

- widespread vaccination which interferes with transmission dynamics and may result in lower viral loads,[157] though this is less clear with regard to infection with the Delta variant in vaccinated individuals[158]
- more asymptomatic infections (relative to symptomatic infections)[159] among vaccinated individuals.

Hence the findings of the included studies may have limited transferability to settings where a different variant of concern is dominant, or where there are very high levels of vaccine uptake.

5 Conclusions

Testing is a complicated process and many factors need to be considered to ensure that the right test is undertaken in the right person at the right time for the right purpose. While RADTs can reliably detect those most likely to be infectious at the time of testing, transmission can still occur in those with high C_t values (low viral low) with no accepted cut-off of C_t values at which risk of transmission is eliminated. The timing of the test is important: while a high Ct value late in the disease course may reflect detection of non-viable virus and individuals who are no longer infectious, those tested shortly after exposure are at the start of their infection and will subsequently become infectious. Identification of the latter is important to facilitate prompt isolation in order to break the chains of onward transmission. From a public health perspective, identification of those that are no longer infectious is also still important as it allows contact tracing to be initiated to identify other potentially infectious individuals.

Background prevalence must be considered when interpreting RADT results in asymptomatic populations as this informs the need for confirmatory RT-PCR testing. Specifically, consideration may need to be given to confirmatory RT-PCR following a positive RADT result in a low prevalence setting, due to the lower likelihood that a positive test result is a true positive.

This evidence summary collated and synthesised empirical evidence on the effectiveness of rapid antigen testing for screening and surveillance of asymptomatic individuals at limiting the transmission of SARS-CoV-2. Overall, there is uncertainty regarding the effectiveness of RADTs for screening in asymptomatic individuals, with no evidence found regarding their use for surveillance purposes. This uncertainty is due to the relatively low number of studies identified, the predominantly observational and/or uncontrolled study designs used, and concerns regarding the methodological quality of these studies. The included studies were conducted in populations with limited vaccination uptake and before the emergence of the Delta variant, thus the findings may have limited transferability to settings where a different variant of concern is dominant, or where there are very high levels of vaccine uptake. There is insufficient evidence at present to determine whether the use of RADTs for screening or surveillance of asymptomatic individuals is effective at limiting transmission of SARS-CoV-2, and whether such interventions represent a good use of resources and value for money.

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Appendix 1 Summary of key upcoming changes to EU regulations

As indicated on the Health Products Regulatory Authority (HPRA) website, the key aspects specific to the in-vitro Diagnostics Regulation (IVDR), outlined in Regulation 2017/746, include, but are not limited to:[160]

- **Classification system** – the IVDR introduces a rules-based classification system for IVDs. IVDs will now be classified into four different classes based on risk from class A (low) to class D (high). This will mean that regulation and assessment for each class of device can be tailored accordingly.
- **Changes to conformity assessment procedures** – IVDs will now be subject to conformity assessment based on the classification of the device. Classes B, C and D IVDs will all require assessment and certification by a notified body for medical devices (appropriately designated for IVDs) prior to being placed on the market. This represents a significant change in the system today where many IVDs are self-declared devices rather than being assessed by a notified body.
- **Performance evaluation and clinical data requirements** – the requirements for performance evaluation of IVDs are defined in much greater detail in the new Regulations. Specific requirements are also defined in relation to the use of clinical data for IVDs and the conduct of clinical performance studies.
- **Changes to requirements for in house manufacturing of IVDs** – under the existing legislation IVDs which are manufactured within a healthcare institution and for use within that health institution are exempted from the Directive. Such tests may be developed due to the lack of a commercially available alternative e.g. for rare diseases. The new Regulation places requirements on 'in-house' IVDs and the healthcare institutions which manufacture them and allows the introduction of additional requirements at national level by individual member states.

Appendix 2 Characteristics of included studies

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
Mass testing studies					
England					
University of Liverpool **England** **Prospective cohort study (Ecological study)** **https://www.liverpool.ac.uk/coronavirus/research-and-analysis/covid-smart-pilot/** **(Technical report)** **[Linked peer-reviewed papers https://www.bmj.com/content/374/bmj.n1637 and https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00084-3/fulltext]**	**Sample size:** 283,338 participants aged over 5 years (57% of all residents) took 739,553 LFTs **Demographics:** *Sex:* Female: 150,573 (53.4%) Male: 132,765 (46.5%) *Age:* 0-14 years: 33,353 (11.8%) 15-34 years: 109,179 (38.5%) 35-69 years: 118,146 (41.7%) 70+ years: 22,660 (8%) *Ethnic group:* Asian: 11,529 (4.1%) Black: 8,196 (2.9%) Mixed: 4,886 (1.7%) Other: 3,732 (1.3% White: 254,995 (90%) *Deprivation quintiles:*	**Setting:** General population of Liverpool, England. **Aim of testing:** Screening/serial testing; Mass testing (Voluntary). The 3 targets were: ▪ test-to-protect (vulnerable individuals, settings and services) ▪ test-to-enable (safer return to work, school and social activities) ▪ test-to-release (sooner from	**Public health restrictions:** Liverpool in Tier 3 on 14 October. National lockdown in England from 5 November until 2 December 2020, with some relaxing of measures of over the Christmas period, with Liverpool in Tier 2. Liverpool moved into Tier 3 with all surrounding areas in Tier 4 on 31 December. England re-entered national lockdown on 6 January and lockdown officially ended on 19 July 2021 (with various easing of restrictions from 8 March 2021).	**National (UK) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 6 Nov 2020 = 465 30 Apr 2021 = 49 Peaked on 11 Jan 2021 = 1,165 **Total number of COVID-19 vaccine doses administered per 100 population:** 6 Nov 2020 = 0 30 Apr 2021 = 73	**Testing process:** Antigen testing followed by confirmatory PCR testing for positive results. Supervised, self-administered swab. **Platform:** Innova SARS-CoV-2 rapid antigen LFD **Frequency:** Serial testing was encouraged. 47% (n = 132 375; 26.6% of residents) of people who got tested had more than one test.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	Least deprived: 63,786 (22.5%) Quintile 2: 69,390 (24.5%) Quintile 3: 58,359 (20.6%) Quintile 4: 46,754 (16.5%) Most deprived: 45,049 (15.9%) **Timing:** 6 November 2020 – 30 April 2021 **Staff:** Significant multi-agency involvement, including at least 2,000 army personnel. Unknown number of healthcare staff involved. **Cost:** NR	quarantine after close contact).		**Proportion of population fully vaccinated (%):** 6 Nov 2020 = 0 30 Apr 2021 = 22 **Local epidemiology:** The 14-day COVID-19 notification rate peaked early Oct 2020 at ~1,750 cases per 100,000 population, falling to a low of~440 cases per 100,000 late Nov 2020. 14-day notification rate then spiked rapidly peaking at ~2,550 cases per 100,000 early Jan 2021. **Variants:** A steep rise in S-gene drop out RT-PCR results (proxy for Alpha variant) in late Dec coincided with a large surge in COVID-19 cases. On the 1 Dec approx. 5% of RT-PCR positive cases had S-gene dropout, and by the 31 Dec, this	

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
				proportion had increased to approx. 50%. By 4 Feb 2021, over 90% of RT-PCR positive samples has S-gene dropout. WGS at a UK-wide level supports these findings with Alpha comprising 12% of samples sequenced between 23 Nov and 7 Dec 2020, and increasing rapidly to 92% of samples sequenced between 25 Jan and 8 Feb 2021.	
Wales					
Public Health Wales **Wales** **Prospective cohort study (Ecological study)** **https://cwmtafmorgannwg.wales/Docs/Publications/FINAL_V2_Whole%20Area%20Testing%20Evaluation%20Full%20Report%20202103 25.pdf** **(Technical report)**	**Sample size:** 55,756 total LFTs undertaken *Community testing (n=49,799):* Merthyr Tydfil: 35,001 tests undertaken (49% uptake) Lower Cynon Valley: 14,798 tested undertaken (56% uptake). *Schools (n=4,064):* Merthyr Tydfil: 3,588 Lower Cynon Valley: 476	**Setting:** General population of Merthyr Tydfil and Lower Cynon Valley, Wales. **Aim of antigen testing:** Screening/serial testing; Mass testing (Voluntary)	**Public health restrictions:** **23 Oct 2020:** Welsh National Fire Break commenced (lockdown). Stay-at-home order. **9 Nov 2020:** Firebreak ended with significant easing of measures **20 Dec 2020:**	**National (UK) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 21 Nov 2020 = 482 20 Dec 2020 = 469 Peaked on 21 Nov 2020 = 482 **Total number of COVID-19 vaccine**	**Testing process:** Antigen testing followed by confirmatory PCR testing for positive results. Unclear if professionally sampled or self-sampled. **Platform:** INNOVA SARS-CoV-2 Rapid Antigen test **Frequency of testing:** Serial testing encouraged. 65.5% of

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
[Linked economic evaluation report https://www.medrxiv.org/content/10.1101/2021.05.10.21256816v1 (pre-print)]	*Home testing (n=1,893):* Merthyr Tydfil: 1,096 Lower Cynon Valley: 797 **Demographics:** Merthyr Tydfil: Women, 55.5% Men, 44.5%. The mean age of women in the tested population was 45.3 years (SD 19.6) and men 46.0 years (SD 20.4). Lower Cynon Valley: Women, 55.1% Men, 44.9% The mean age of women in the tested population was 44.4 years (SD 19.0) and men 45.7 years (SD 20.0) Eligibility = 11 years and older. **Timing of study:** 21 Nov – 20 Dec 2020. Merthyr Tydfil: 21 Nov - 18 Dec 2020. Lower Cynon Valley: 5 -20 Dec 2020 **Resources:** *Total = 810 staff*		National lockdown re-imposed. Stay at home measures.	**doses administered per 100 population:** 21 Nov 2020 = 0 20 Dec 2020 = 1 **Proportion of population fully vaccinated (%):** 21 Nov 2020 = 0 20 Dec 2020 = 0 **Local epidemiology:** Locally cases peaked in October before the firewall was implemented. For example, in Merthyr Tydfil, 7 –day rolling average of ~400 cases were reported mid-October. By the time the mass testing was implemented in late Nov-early Dec, case numbers have troughed. (7-day average of ~150 cases were reported late November). This was followed by a rapid rise throughout December and into January,	Merthyr Tydfil and 76.8% of Lower Cynon Valley residents only had one LFT.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	Mass population sites: 570 local authority staff plus 96 military personnel required. Additionally, 117 staff required to deliver 4,060 LFTs for once-off mass testing in 7 schools. 17 staff required for home testing resource 10 staff required for confirmatory PCR testing **Cost:** *Total cost = £1,250,181* (excluding military costs) Mass testing (non-schools) = £996,527 Merthyr Tydfil = £515,688 Lower Cynon Valley = £480,839 Schools testing cost £86,301 (excluding costs of test kits as assumed funded by UK Gov) Confirmatory PCR testing costs = £95,419			peaking at about a 7-day average of 800 cases a day in Merthyr Tydfil. **Variants:** UK-wide WGS found that the Alpha variant comprised 12% of samples sequenced between 23 November and 7 December 2020, and increased rapidly to 92% of samples sequenced between 25 January and 8 February 2021.	

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	Home-testing LFTs costs = £71,934 (excluding postage costs)				
Slovakia					
Pavelka **Slovakia** **Retrospective cohort study (Ecological study)** **https://science.sciencemag.org/content/372/6542/635** **(Peer-reviewed)**	**Sample size:** 5,276,832 antigen tests were conducted across 3 phases of testing. This corresponded with 87%, 83% and 84% of the age-eligible population of Slovakia (10-65 year olds plus older adults in employment) respectively for each testing phase. **Demographics:** NR **Timing:** October-November 2020 Pilot round – 23 Oct Round 1 – 31 Oct Round 2 – 7 Nov Round 3 – 22 Nov* *A third round of testing was implemented in 447 municipalities on Nov 22-23 in areas with a positivity rate >1% in previous rounds. Testing in this round was	**Setting:** General population of Slovakia **Aim of testing:** Screening/serial testing; Mass testing (Testing voluntary, but isolation requirements mandatory).	**Public health restrictions:** **1 Oct 2020:** ▪ Gatherings >50 banned ▪ Wedding receptions banned. **15 Oct:** ▪ Gatherings of >6 people banned ▪ Indoor dining and leisure activity banned. ▪ Secondary schools closed **24 Oct:** ▪ Lockdown introduced ▪ Non-essential movement banned. ▪ Non-essential outdoor activities banned.	**National epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 23 Oct 2020 = 385 7 Nov 2020 = 602 31 Jan 2021 = 487 Peaked on 13 Jan 2021 = 766 **Total number of COVID-19 vaccine doses administered per 100 population:** 23 Oct 2020 = 0 7 Nov 2020 = 0 31 Jan 2021 = 2.7 **Proportion of population fully vaccinated (%):** 23 Oct 2020 = 0 7 Nov 2020 = 0 31 Jan 2021 = 0.2	**Testing process:** *Three testing phases:* **Pilot** took place 23-25 Oct in the 4 counties with highest incidence. **Round 1** National testing took place (all 79 counties) 31 Oct-1 Nov **Round 2** Mass testing in 45 counties with prevalence >7 in 1,000 population. **Platform and conduct of test** SD-Biosensor Standard Q rapid antigen tests were conducted by trained medical personnel. Nasopharyngeal samples obtained by trained personnel. **Frequency of testing:** 4 counties (5%) had 3 rounds of testing.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	voluntary and no additional measures were imposed on untested individuals. The findings from this round are not discussed in this paper. **Staff:** 20,000 medical staff and 40,000 non-medical personnel **Cost:** Approx. €30 million for military staffing and €52 million to purchase test kits.		**2 Nov:** ▪ Lockdown eased ▪ Gatherings of >6 people banned ▪ Indoor dining and leisure activity banned ▪ Secondary schools closed ▪ Second half of primary schools closed. **16 Nov:** ▪ Additional activities (e.g. churches, theatres) were permitted. **19 Dec:** ▪ National lockdown re-imposed. **Measures for those testing positive:** Mandatory 10 days quarantine (for them, their household members and their close contacts <2 days prior)	**Variants of concern:** During the three mass testing dates (23 Oct, 31 Oct, 7 Nov) there was no sequenced VOC in Slovakia. However, the Alpha variant which was first detected on a sample sequenced between 23 November and 7 December, accounted for 75% of all sequenced samples between the 28 December 2020 and 11 January 2021. This coincided with a period of rapid growth in COVID-19 case numbers.	41 counties (52%) had 2 rounds of testing. 34 counties (43%) had 1 round of testing.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
			Measures for those not tested: Mandatory 10 days quarantine		
Kahanec **Slovakia** **Retrospective cohort study (Ecological study)** **https://link.springer.com/article/10.1007/s00148-021-00856-z** **(peer-reviewed)**	**As above**	**As above**	**As above**	**As above**	**As above**
Frnda **Slovakia** **Mathematical modelling study based on Ecological study** **https://www.mdpi.com/2036-7449/13/1/7** **(peer-reviewed)**	**As above**	**As above**	**As above**	**As above**	**As above**

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
Italy					
Pagani **Italy** **Prospective cohort study (Ecological study)** **https://www.quotidianosanita.it/allegati/allegato9528306.pdf** **(online presentation)**	**Sample size:** 361,781 tests for all 536,667 residents, 67.4% participation rate (but 72.3% of all 500,607 eligible participants). All residents were invited to participate, with the exception of children below the age of 5, people with Covid-19 symptoms, those on sick leave, those who had tested positive and isolated in the last 3 months, and those who had recently tested positive or were in quarantine or self-isolating. **Demographics:** *Available for 350,848 participants.* *Sex* Men: 177,029 (50.4%) Women: 170,286 (48.6%) NR: 3,533 (1%). *Age* 0-6 years: 4,589 (1.5%). 7-18 years: 45,301 (13%) 19-65 years: 239,670 (68.5%) 66 years+: 57,753 (16%).	**Setting**: General population of South Tyrol (Autonomous Province of Bolzano) in North Italy. **Aim of testing:** Screening; Mass testing (Voluntary).	**Public health restrictions:** Autonomous Province of Bolzano was deemed a Red area (maximum risk) on 6 November 2020. ▪ Curfew ▪ Inter-regional travel prohibited ▪ Gatherings prohibited ▪ Later years of middle school and high school closed ▪ Non-essential retail and hospitality closed. From 5 Dec 2020, Bolzano was deemed an Orange (high risk) area ▪ curfew ▪ gatherings prohibited ▪ limited opening of non-essential retail ▪ hospitality closed ▪ high school closed. **17 Jan 2021**	**National (Italy) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 20 Nov 2020 = 799 31 Jan 2021 = 284 Peaked on 20 Nov 2020 = 799 **Total number of COVID-19 vaccine doses administered per 100 population:** 20 Nov 2020 = 0 31 Jan 2021 = 3.3 **Proportion of population fully vaccinated (%):** 20 Nov 2020 = 0 31 Jan 2021 = 1 **Local epidemiology** The 7-day moving average of case numbers was 103.4/ 100,000 inhabitants,	**Testing process:** Mass testing of population. **Platform and conduct of test** SD-Biosensor Standard Q and Abbot Panbio rapid antigen tests were conducted by trained medical personnel once only, using nasal and throat swabs. **Frequency of testing** Once off

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	NR, 3,535 (1%) **Timing of study:** 20-22 Nov 2020. (It was also possible to be tested at some pharmacies and GPs in the period 18 to 25 November) **Staff:** 1,937 healthcare professionals: 1,289 public healthcare personnel 327 external healthcare personnel 321 white and red cross personnel **Costs** Approx. €4.5 million		Re-classified as red (maximum risk) zone. **Measures for those testing positive:** ▪ Follow home isolation measures (10 days) without confirmatory PCR. ▪ For those who developed symptoms during the isolation period, they were asked to contact their GP or paediatrician. ▪ Close contacts were not traced.	(95%CI 95.4–111.4) for the time period 1 Nov 2020 to 20 Nov 2020. Peaking at 120.3 on 14 Nov 2020, and dropping to a low of 20.7 on 24 Dec and rising again to 48.7 on 9 Jan 2021. **Variants of concern:** During the mass testing dates (20-22 Nov) there were only 2 sequenced samples of Alpha variant in Italy accounting for <0.01% of all sequenced cases. However, the Alpha variant accounted for 29% of all sequenced samples between the 28 Dec 2020 and 11 Jan 2021. This coincided with a period of rapid growth in COVID-19 case numbers, nationally.	
Ferrari **Italy**	**As above**	**As above**	**As above**	**As above**	**As above**

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
Mathematical modelling study based on an Ecological study **https://arxiv.org/abs/2104.14813** **(pre-print)**					
Ricco **Italy** **Retrospective cohort study (Ecological study)** **https://www.journalofinfection.com/article/S0163-4453(21)00034-7/fulltext** **(peer-reviewed)**	**As above**	**As above**	**As above**	During Nov 2020, Italian province of South Tyrol experienced a surge of daily notification rates for SARS-CoV-2 cases (7-days moving average of 103.4/100,000 inhabitants, 95% CI 95.4–111.4 for the time period 1/11/2020 to 20/11/2020), which was over double that of the bordering Italian region of Trentino (42.8/100,000 inhabitants, 95%CI 42.8–44.6), and the Austrian State of Tyrol (40.1/100,000 inhabitants, 95%CI 38.0–42.2).	**As above**
Pre-event screening					

<table>
<tr><th>First author
Country
Design
URL</th><th>Sample size

Demographics

Timing of study

Resource use</th><th>Setting

Aim of antigen testing</th><th>Public health measures and restrictions in place</th><th>Epidemiological situation vaccination coverage</th><th>Testing process

Platform

Frequency of testing</th></tr>
<tr><td colspan="6">England</td></tr>
<tr><td>UK Government, 2021

England

Uncontrolled, before-after study.

https://www.gov.uk/government/publications/events-research-programme-phase-i-findings/events-research-programme-phase-i-findings

(technical report)</td><td colspan="3">Table A: Details of the Events research Programme Pilot events
<table><tr><th>Pilot events and timing of study</th><th>Sample size</th><th>Setting</th><th>Mitigation measures in place</th></tr><tr><td>World Snooker Championship
Venue: Crucible Theatre, Sheffield
17 April - 3 May</td><td>10,147</td><td>Indoor seated</td><td>Social Distancing in seats for first five days, then reduced social distancing, then no social distancing for the final; No food and drink available; Face coverings mandated at all times; LFT at Asymptomatic Testing Site(ATS).</td></tr><tr><td>Emirates FA Cup Semi Final
Venue: Wembley Stadium, London 18 April</td><td>2,728</td><td>Outdoor seated</td><td>Social distancing rules applied within the venue and attendees seated one seat (0.9m+) apart regardless of if in the same household; Alcohol, food and limited hospitality available indoors; Face coverings mandated at all times; LFT at ATS.</td></tr><tr><td>Carabao Cup Final
Venue: Wembley Stadium, London
25 April</td><td>7,737</td><td>Outdoor seated</td><td>Social distancing rules applied within the venue and attendees seated one seat apart (0.9m+) regardless of if in the same household; Alcohol, food and limited hospitality available indoors; Face coverings mandated at all times; LFT at ATS.</td></tr></table></td><td>National epidemiological situation:

14 day incidence of COVID-19 per 100,000 population:
17 April 2021 = 43.9
15 May 2021 = 45

Peaked on 23 April 2021 = 54

Total number of COVID-19 vaccine doses administered per 100 population:
17 April 2021 = 63
15 May 2021 = 83.5

Proportion of population fully vaccinated (%):
17 April 2021 = 15
15 May 2021 = 30

Local epidemiological situation: In considering the findings in this report, it is</td><td>For events a negative Lateral Flow Test (LFT) result was required prior to the event to gain entry to the venue of the event. The platform used was not reported.

Participants were also asked to take voluntary PCR tests via home test kits that were usually posted out to their home address or collected from an asymptomatic testing site (ATS) or from the event venue. The instruction was to take one test on the day of the event and one 5 days later, with the results of these tests used for research purposes and outbreak control and not as a condition for entry. Self-administered LFD testing at home was used for the final two events of the ERP (FA</td></tr>
</table>

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	Emirates FA Cup Final Venue: Wembley Stadium, London 15 May; 18,720; Outdoor seated; Social distancing rules apply within the venue and attendees seated one seat apart (0.9m+) regardless of if in the same household; Alcohol and food on the concourse; Indoor hospitality; Face coverings mandated at all times; Limited Home LFT testing. The Good Business Festival Presents 'Change Business for Good' Venue: ACC Exhibition Centre, Liverpool 28 April; 149; Indoor mixed open/seated; No social distancing; Alcohol and food available indoors; No face coverings; LFT at ATS. Circus Presents 'The First Dance' Venue: Circus Nightclub(warehouse club),Liverpool 30 April - 1 May; Night 1: 3,138 Night 2: 3,870; Indoor open; No social distancing; Alcohol and food available indoors; No face coverings; LFT at ATS.			important to note that the studies were undertaken while the prevalence of the virus was low. **Variants:** At the time of the first event (17 April), The Alpha variant accounted for 95% of all sequenced samples, while Delta accounted for 2% and Beta accounted for 1%. By the time of the final event (15 May) the prevalence of the Delta variant increased to 34%, while Alpha decreased to 64% of all sequenced cases. The Beta variant accounted for <1% of all sequenced samples.	Cup Final and the Mass Participation Run) ▪ ***Table B: Testing process at each event*** **World Snooker Championship** Attendees were required to provide proof of a negative LFT result within 36 hours of the session they aimed to attend. **FA Cup Semi- Final** Attendees were required to provide proof of a negative LFT result within 24 hours. **Carabao Cup Final** Attendees from both clubs were allowed to attend on the basis that they complete an LFT Within 24 hours of attending. **ACC Business Event** LFT tests taken at registered Asymptomatic Testing Sites in the Liverpool City region. Attendees were required to complete an LFT within 36 hours of attending.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	<table><tr><td>Sefton Park Pilot(Outdoor music event) Venue: Tented Stage in Sefton Park, Liverpool 2 May</td><td>6,101</td><td>Outdoor unstructured</td><td>No social distancing; Alcohol and food available outdoors; No face coverings; LFT at ATS.</td></tr><tr><td>BRIT Awards Venue: The O2,London 11 May</td><td>3,532</td><td>Indoor seated(mixed styles)</td><td>No social distancing; Alcohol and food available indoors; No face coverings inside the main arena, required elsewhere; LFT at ATS.</td></tr><tr><td>Reunion 5k Venue: Kempton Park, Surrey 15 May</td><td>1,981</td><td>Outdoor open</td><td>No social distancing; No face coverings; Home LFT testing allowed.</td></tr></table>*Two previously confirmed events did not proceed: a Hot Water Comedy Club, Liverpool and an Luna Outdoor Cinema, Liverpool. **All events required pre-event lateral flow test (LFT) testing as a mitigation. Pre and post-event PCR tests were also used for transmission research purposes only, and not as conditions of entry. **Timing:** 17 April - 15 May 2021 **Demographics:** NR **Resource use:** NR **Aim of antigen testing:** screening				<table><tr><td>**Circus Nightclub** A test to ticket system was utilised which was used to invalidate the tickets of attendees with a positive or voided LFT result. 96% of prospective attendees were matched with negative test results and therefore were able to proceed to the event.</td></tr><tr><td>**Sefton Park Pilot** A test to ticket system which was used to invalidate the tickets of attendees with a positive or voided LFT result. Around 96% of prospective attendees were successfully matched with negative LFT results (within36 hours).</td></tr><tr><td>**BRIT Awards** To gain entry, all attendees had to take a LFT at an Asymptomatic Test Site (ATS) within 36hrs of the event starting and show a negative test result along with their ticket and ID at the checkpoints.</td></tr></table>

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
					Reunion 5k All participants and spectators accessing the site had to undertake a LFT test, either at home or at an Asymptomatic Test Site, and present a negative test result to gain entry. Five people were turned away without a test result having declined onsite testing mitigation. Automated PCR tests were delivered for pre and post event testing. **FA Cup Final** Ticket holders from both clubs and the Brent area were allowed to attend on the basis that they completed an LFT test within 36 hours of the event and tested negative.
Barcelona					
Revollo 2021 **Spain** **https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00268-1/fulltext** **RCT**	**Sample size:** Total number randomly assigned = 1,047 With full follow-up data = 960: 465 in experimental arm, 495 in control arm Staff members = 58 **Demographics:** Eligible participants were adults aged 18 to 59 years	**Setting:** Indoor, live event, with an active crowd Salo Apolo, Barcelona, Spain. 12 December 2020. Duration of 5 hours. Night time. **Aim of testing:** Screening	**Public health measures in place:** <u>Pre-event</u> ▪ Exclusion of vulnerable groups. ▪ Installation of 2 Apps (contact tracing app and app for transferring results/	**National (Spain) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 219 **Total number of COVID-19 vaccine**	**Testing strategy:** ▪ Ag-RDT from 9 hours before the event alongside sampling for TMA and RT-PCR. ▪ Participants with negative Ag-RDT were randomly assigned to experimental arm or control arm.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
(peer reviewed)	with a negative result in an Ag-RDT performed on a nasopharyngeal swab collected immediately before entering the event. Participants with known COVID-19 diagnosis within the 14 days before the event, relevant comorbidities, or living with older people were excluded. Mean age, 33.6 years (SD 8.6); male, 783 (81.6%) **Timing of study:** 12 December 2020 **Resource use:** Before starting the music event, the health-care staff (45 nurses and one physician) collected nasopharyngeal swabs from all eligible participants in a screening structure set up outdoors in front of the concert venue, with 24 awnings. The mass screening started at 8:00 am and finished at 3:30 pm on the day the music event took place (Dec 12, 2020).		completing questionnaires). ▪ Limited numbers. <u>Day of the event</u> ▪ Health screening ▪ Antigen testing ▪ Face masks (N95) – mandatory ▪ Adequate ventilation ▪ Congestion control ▪ Specific area for drinking and smoking ▪ Hand sanitiser ▪ Temperature and CO2 control ▪ Adequate ventilation ▪ All staff tested <u>After the event</u> ▪ Health screening (10 days after event) ▪ Follow-up testing – day 8	**doses administered per 100 population:** 0 **Proportion of population fully vaccinated (%):** 0 **Variants:** At the time of the event (12 December 2020) the Alpha variant accounted for only 3 of all sequenced cases (<1%), however WGS was still relatively limited at the time.	▪ TMA result reported 24-48 hours after the event. ▪ All TMA positive samples were re-tested for RT-PCR, assessed for viral isolation on cell culture, and affected patients were contacted via phone for a structured interview. ▪ All study participants were visited 8 days after the event for follow up RT-PCR, Ag-RDT and TMA test ▪ Health-care staff (45 nurses and one physician) collected nasopharyngeal swabs from all eligible participants in a screening structure set up outdoors in front of the concert venue.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
Llibre 2021 **Spain** **Uncontrolled before-after study** **https://www.acpjournals.org/doi/10.7326/M21-2278** **(peer reviewed)**	**Sample size:** 5,000 **Demographics:** Details on the demographics of all other attendees were not provided. **Timing of study:** 27 March 2021 **Resource use:** On the day of the event (from 8:00 a.m. to 3:00 p. m.), a team of 74 nurses performed Ag-RDTs (Panbio COVID-19 Ag Rapid Test) for all attendees at 3 screening sites.	**Setting:** Concert held in Palau Sant Jordi stadium (Barcelona, Spain) **Aim of testing:** Screening	▪ Singing and dancing were allowed, and no physical distancing was required. ▪ The use of filtering face piece 2 masks (which are able to filter at least 94% of airborne particles) was mandatory during the entire event. ▪ All attendees were located on the central floor of the stadium, which was at full capacity, and grouped into 3 delimited areas; the stadium stands, with a capacity for 13, 000 people, were not occupied. ▪ Inner ventilation was optimized to provide 6 complete (100%) air changes per hour. ▪ During Ag-RDT screening, written consents were obtained for post event follow-up via electronic health	**National (Spain) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 153 **Total number of COVID-19 vaccine doses administered per 100 population:** 15 **Proportion of population fully vaccinated (%):** 5 **Local epidemiology:** By the time of the event, the age-standardized 14-day cumulative incidence rate in Barcelona was 259.5 cases per 100 000 inhabitants, and the country-level vaccination rate for COVID-19 (2 doses) was 6.3%, mainly administered to	On the day of the event (from 8:00 a.m. to 3:00 p.m.), a team of nurses performed Ag-RDTs (Panbio COVID-19 Ag Rapid Test) for all attendees at 3 screening sites.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
			records or phone calls, in collaboration with the Catalan Public Health Department. ▪ Travel in and out of the city area was constrained to essential activities at the time of the study.	nursing home residents, older adults, and healthcare workers. **Variants:** At the time of the event (27 March 2021), the Alpha variant accounted for 85% of all sequenced cases, while the Gamma and Beta variants accounted for 3% and 2% respectively.	
The Netherlands					
Fieldlab, 2021 **The Netherlands** **Uncontrolled, before-after study.** **https://fieldlabevenementen.nl/wp-content/uploads/2021/04/Fieldlab-Evenementen-Adviesaanvraag-Type-III-versie-1.0.pdf** **(technical report)**	**Sample size:** 5,108 **Demographics:** Excluded vulnerable groups excluded (people over 70 years and those with specific underlying conditions as determined by RIVM) **Timing of study:** 27 March 2021, Johan Crujiff Area, Amsterdam, the Netherlands	**Setting:** Outdoor setting, with an active audience. **Aim of testing:** Screening	**Public health measures in place:** Pre-event ▪ exclusion of vulnerable groups ▪ request installation CoronaMelder app for contact tracing ▪ limited numbers ▪ rapid antigen test same day as event. Day of event	**National (The Netherlands) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 566 **Total number of COVID-19 vaccine doses administered per 100 population:** 12.7	**Testing strategy:** ▪ Rapid antigen test same day, ▪ rapid antigen test (Panbio™ COVID-19 Ag Rapid Test from Abbott) in random sample during, and ▪ Rapid antigen 5 days after. ▪ All tests (nasal swab) were professionally administered.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
			▪ rapid test on match day ▪ triage questions ▪ temperature measurement ▪ group size limitation ▪ event logistics ▪ cohorting ▪ face mask ▪ hand sanitiser. <u>After the event</u> ▪ rapid antigen test on day 5 after the event visit ▪ refrain from visiting vulnerable groups up to 10 days after the event, or until receipt of a negative test result.	**Proportion of population fully vaccinated (%):** 3.3 **Variants:** At the time of the event (27 March 2021), the Alpha variant accounted for 92% of all sequenced cases, while Beta and Gamma variants accounted for 3% and 2% respectively.	
Serial testing- sports programme					
USA					
Moreno 2021 **USA** **Case series (epidemiological investigation)**	**Sample size** 188 in total: 44 athletes and staff across two outbreaks (plus 144 secondary cases)	**Setting:** University athletics program **Aim of antigen testing:** Screening	In addition to daily antigen testing, the athletic programs implemented a physical distancing policy requiring all students and staff to be	**National (USA) epidemiological situation:** No dates are provided other than 'Fall 2020' to protect the privacy of the affected individuals.	**Testing process:** Students and staff affiliated with the 2 athletics programs began daily antigen testing for SARS-CoV-2 in September 2020.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
https://academic.oup.com/cid/article/73/Supplement_1/S45/6274297 **(peer reviewed)**	Outbreak 1 included 133 total individuals, and Outbreak 2: included 55 total individuals **Demographics:** NR **Timing of study:** Fall 2020 semester. University names, specific sports, and relevant dates have been removed from the report to protect the privacy of the students and staff involved.		at least 6 feet apart during meetings, with mandatory mask use during team activities. A negative antigen result meant that an individual could engage in all sport-related activities, such as indoor meetings, practices, scrimmages, and intercollegiate competitions. Athletes and staff with positive antigen results were immediately excluded from team activities by department medical staff and subject to confirmatory testing with RT-PCR using the TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific).	In the US Fall runs from 1 Sept until 30 Nov. **14 day incidence of COVID-19 per 100,000 population:** 1 Sep 2020 = 177 30 Nov 2020 = 714 Peaked on 30 Nov 2020 = 714 **Total number of COVID-19 vaccine doses administered per 100 population:** 1 Sep 2020 = 0 30 Nov 2020 = 0 **Proportion of population fully vaccinated (%):** 1 Sep 2020 = 0 30 Nov 2020 = 0 **Vaccination status:** No students or staff received COVID-19 vaccines, as these were not yet widely available. **Variants:**	Before September 2020, all athletes were tested with real-time reverse-transcription polymerase chain reaction (RT-PCR) once or twice a week. Daily antigen testing was not required for persons with an RT-PCR–confirmed SARS-CoV-2 infection in the past 3 months or those experiencing symptoms consistent with coronavirus disease 2019 (COVID-19), as symptomatic persons received RT-PCR testing without initial antigen testing. For remaining asymptomatic students and staff, antigen testing was conducted using anterior nasal swab samples that were self-collected each morning under the direct supervision of a nurse. Athletes and staff in both programs were

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
				No dates are provided other than 'Fall 2020' to protect the privacy of the affected individuals. In the US Fall runs from 1 Sept until 30 Nov. During this period there was only a very limited number of Alpha variants sequenced (in total 15 Alpha variants). However WGS was still relatively limited at the time.	tested daily using Quidel's Sofia SARS AntigenFluorescent Immunoassay. Positive antigen results were immediately excluded from team activities by department medical staff and subject to confirmatory testing with RT-PCR using the TaqPath COVID-19 Combo Kit
Serial testing – health and social care setting					
England					
Tulloch 2021 **Liverpool, UK** **Prospective cohort study with qualitative evaluation** **https://academic.oup.com/ageing/advance-article/doi/10.1093/ageing/afab162/6322881**	**Sample size:** 1,638 LFD rapid tests were performed on 407 staff **Demographics:** NR **Timing of study:** Between 1st of December 2020 and the 10th of January 2021 **Resource use:**	**Setting:** All 86 care homes within the LCC region were approached to take part in the study. Of these 11 care homes agreed to participate. **Aim of antigen testing:** screening	In England, at the time of this study, the standard protocol had been to PCR test residents monthly, or between times if they became symptomatic; and to PCR test staff weekly, or if symptomatic. Visitors were not tested, and only outdoors visits were permitted, unless	**National (UK) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 1 Dec 2020 = 343 10 Jan 2021 = 1158 Peaked on 10 Jan 2021 = 1158	**Testing process (staff):** LFD tests were self-administered. A PCR test was performed simultaneously alongside the second test each week as part of the existing PCR testing regime in care homes. Innova SARS-CoV-2 antigen rapid LFD

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
(peer reviewed)	Upon enrolment, care home staff were trained by members of the armed forces, who had delivered LFD testing during the Liverpool community testing pilot. LFD test results were required to be registered using dedicated website portals (Government testing portals), for auditing purposes. Each test had to be recorded individually. The log-in procedure had many steps and was time consuming. As the portals were not directly linked with the care home records system, extra staff required to be allocated to administer this. This was exacerbated by variation in the numbers of staff being tested at the same time, due to shift times and availability, thus, slowing down the diagnostic process. Visitor testing required additional staff work. Managing visitors required supervision, to enable a smooth process and to safeguard residents. Visitors not familiar with the procedure and/or with digital technologies struggled to		it was an end-of-life situation, when indoor visits with appropriate personal protective equipment (PPE) were allowed.	**Total number of COVID-19 vaccine doses administered per 100 population:** 1 Dec 2020 = 0 10 Jan 2021 = 4 **Proportion of population fully vaccinated (%):** 1 Dec 2020 = 0 10 Jan 2021 = 1 **Local epidemiology** All were outbreak-free at the start of the study. **Variants:** At the start of the study (1 December 2020), The Alpha variant accounted for 12% of all sequenced samples. By the end of the study (10 January 2021) the prevalence of the Alpha variant increased to 75%. The Beta variant accounted for <1% of all sequenced samples.	were used (at the times these were in widespread use across UK care homes). **Testing process (visitors):** Visitor testing protocols stipulated that 2 negative LFD tests within a 24-hour period were provided prior to care home visits. The first test took place at a city centre site, where a trained nurse observed self-swabbing technique. Concurrent PCR testing was performed as quality assurance. If the LFD was negative, then a second LFD test (within 24 hours and undertaken by care home staff) was taken before visiting was allowed. If either LFD test result was positive, the visitor was asked to immediately self-isolate according to Government guidelines

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	navigate the interface and staff members were frequently asked to support them with this, placing additional pressures and distracting them from other tasks.				and request a confirmatory PCR test. It is noted in this paper that at the time of this study visitors were not tested as only outdoors visits were permitted, unless it was an end-of-life situation, when indoor visits with appropriate PPE were allowed. **Frequency of testing:** Staff were tested using LFDs twice weekly. **Additional information:** At the time of this study, the standard protocol had been to PCR test residents monthly, or between times if they became symptomatic; and to PCR test staff weekly, or if symptomatic. Visitors were not tested, and only outdoors visits were permitted.

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
Serial testing – school setting					
USA					
Lanier 2021 **Utah, USA** **Observational study** **https://www.cdc.gov/mmwr/volumes/70/wr/mm7021e2.htm** **(peer reviewed)**	**Sample size:** 148,262 tests conducted in 50,400 students 'Test to Play' was implemented at 127 (66%) of Utah's 193 public high schools **Demographics:** High school students **Timing of study:** 30 November 2020 – 20 March 2021 **Resource use: NR**	**Setting:** High school testing programme **Test to Play**, in which testing every 14 days was mandated for participation in extracurricular activities; Test to Play was implemented at 127 (66%) of Utah's 193 public high schools. **Aim of testing:** screening	On 9 Nov, statewide COVID-19 restrictions were ordered in Utah. The measures included: ▪ mask mandate (3 years and older) ▪ social gatherings ban (except in bars and restaurants) ▪ cessation of extracurricular activities (except high school football and intercollegiate or professional sports). At the time of the study, the authors note that masking, physical distancing, hand hygiene, and improved ventilation were commonly used in schools to reduce transmission of SARS-CoV-2.	**National (US) epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 30 Nov = 714 20 Mar = 231 Peaked on 15 Jan = 1,022 **Total number of COVID-19 vaccine doses administered per 100 population:** 30 Nov 2020 = 0 20 Mar 2021 = 36 **Proportion of population fully vaccinated (%):** 30 Nov 2020 = 0 20 Mar 2021 = 13 **Local epidemiology**	**Testing process:** The Utah Department of Health (UDOH) provided training and rapid antigen test kits to school staff members, who performed school-based rapid antigen testing (e.g., in school gymnasiums), supported by UDOH and local health departments. Parental permission was required for students to receive school based testing. Schools were required to report all test results to UDOH. In lieu of school-based testing, students could participate in these programs by receiving testing elsewhere (e.g., via community testing). **Platform:** Abbott BinaxNOW rapid antigen nasal swab test kits

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
			As of Aug 2020, schools were advised to transition to remote instruction for 14 days when the number of school-associated cases among students and staff members crossed a specified outbreak threshold. This threshold changed throughout the course of the school year. **Test to play programme:** Students who had a negative test result were allowed to continue to participate in in-person instruction and extracurricular activities; students who had a positive test result were required to isolate for 10 days from the date of the test, and close contacts were required to quarantine.	In September 2020, COVID-19 incidence in Utah among persons aged 14–17 years rose rapidly, followed by similar but smaller increases among persons aged 5–13 years. **Variants:** At the start of the study (30 November 2020), the Alpha variant accounted for <0.01% of all sequenced samples (n=6 samples). By the end of the study (20 March 2021) the prevalence of the Alpha variant increased to 36%.	**Frequency of testing:** **Test to Play,** testing every 14 days was mandated for participation in extracurricular activities

First author **Country** **Design** **URL**	**Sample size** **Demographics** **Timing of study** **Resource use**	**Setting** **Aim of antigen testing**	**Public health measures and restrictions in place**	**Epidemiological situation vaccination coverage**	**Testing process** **Platform** **Frequency of testing**
Mass testing programme – prison setting					
Italy					
Stufano 2021 **Italy** **Retrospective cohort study** **https://www.frontiersin.org/articles/10.3389/fpubh.2021.694795/full** **(peer reviewed)**	Two SARS-CoV-2 antigen testing campaigns were carried out for all the prisoners and correctional workers, including correctional officers (CO), administrative staff (AS), correctional health care workers (HCW), and operators working with people completing their sentence outside the prison (OOP). **Sample size**: **First campaign** ***Inmates,*** 426 inmates (64 new and 362 residential detainees, 23 of which were staying in the integrated health care service.) Across groups, 100% of inmates agreed to participate in the first campaign. ***Correctional workers,*** A total of 367 correctional workers was tested at the first campaign, consisting of 216	**Setting:** Bari (Apulia, Italy) correctional facility **Aim of testing:** screening **Public health measures in place:** Protected separate pathways were created, new inmates were obliged to disinfect their hands and wear a certified medical mask prior to entry, and a new filter area system was introduced, including three different filter areas: - *Yellow area:* dedicated to asymptomatic new inmates; in this area, they underwent the first antigen test. If negative, they were then allocated to single cells for 72 h, following which a second antigen test was performed. In cases when the first or second test was positive, the new inmates were immediately moved to the red area. - *Green area:* dedicated to quarantine for 7 days of the new inmates from the yellow area who had a negative second test. At the end of day 7 they underwent a new antigen test and, if negative, they were admitted to the prison community. - *Red area:* dedicated to the new inmates with suspected COVID-19. They were kept in this area and immediately tested by RT-PCR test that	**National epidemiological situation:** **14 day incidence of COVID-19 per 100,000 population:** 10 Nov = 712 27 Jan = 301 Peaked on 19 Nov = 800 **Total number of COVID-19 vaccine doses administered per 100 population:** 10 Nov = 0 27 Jan = 3 **Proportion of population fully vaccinated (%):** 10 Nov = 0 27 Jan = 1 **Local epidemiology**	**Testing process:** The samples were collected by trained health personnel in the sanitary area of the correctional facility. All the subjects with confirmed positivity to the antigen test underwent confirmation by rRT-PCR test on samples collected within 1 h after the positive antigen test. Only subjects with a confirmed rRT-PCR positive test were considered as confirmed cases. All subjects positive at the first campaign were excluded from the second campaign. **Platform:** Antigen testing was conducted on nasopharyngeal swab specimens, using a fluorescence

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	CO, 77 HCW, 66 AS, and 8 external personnel who usually entered the detection facility. The participation rate was 90.0% for CO, 96.3% for HCW, 89.2% for AS, 100% for external personnel. ***Second campaign*** ***Inmates,*** 480 inmates were tested, 112 new and 368 residential detainees, 21 of which were hospitalised in the integrated health care service. The participation rate was 100% for the new inmates and 99.5% for the residential inmates. A total of 353 detainees participated in both the campaigns, including 45 new inmates at the first campaign and 308 residential inmates. ***Correctional workers,*** 325 correctional workers, consisting of 202 CO, 47 HCW, 49 AS, 23 OOP, and 4 external personnel, were tested. The participation rate was 85.6% for CO, 59.5% for HCW,	was repeated after 10 days of isolation. If both the tests were negative, they were admitted to the prison community in the following 48 h, while in cases of a positive result on entry but negative after 10 days, they were kept in isolation and repeated the RT-PCR test on day 14. However, admission to the prison community for previously RT-PCR positive cases was permitted only after 2 negative RT-PCR tests, performed at least 24 h apart. The red area was also reserved to residential inmates with suspect symptoms and to confirmed COVID-19 cases. All the internal spaces dedicated to social interchange, including the church and the areas dedicated to training and schooling, were closed, while the walkways and the outdoor common spaces remained open, separately for each section, and could be used for at least 4 h per day. Meetings with relatives or lawyers took place in the dedicated areas equipped with separator screens and physical contact with external visitors was forbidden. If a contact occurred, the detainee was isolated for 72 h, after which an RT-PCR test was performed before readmitting him to his section. All staff, both CO and HCW, working in the yellow, green and red areas used full PPE, including a disposable protective gown, face shield and goggles, FFP2 respirators, disposable gloves, and shoe covers. Outside these areas, all		During the study period, a marked increase in the daily incidence of new COVID-19 cases was observed in Apulia, the region where the correctional facility is located, despite the implementation of more restrictive measures at National and Regional level. In Apulia, the total number of COVID-19 new confirmed cases in the study period was equal to 86,457, with a cumulative incidence rate of 2196.6 per 100,000 inhabitants and a daily incidence ranging between 5.6 and 47.9 per 100,000 inhabitants **Variants:** At the start of the study (10 Nov 2020), the Alpha variant accounted for 0.01% (n=2) of all sequenced	immunoassay for the qualitative detection of nucleocapsid SARS-CoV-2 antigen. **Frequency of testing:** **On entry:** Inmates were tested at entry to the correctional facility. Inmates were antigen tested after 72hrs of stay if asymptomatic, if they received a negative result they would receive another rapid antigenic test after 7 days of stay. **Mass testing campaign** Every subject underwent two antigen tests at least 30 days apart

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	74.2% for AS, 100% for OOP and external workers. **Demographics:** **<u>First Campaign</u>** ***Inmates,*** Median age was 36.7 years for the new inmates and 42.2 years for the residential inmates, and the majority of participants was Caucasian (96.9% of the new and 95.3% of the resident inmates). ***Correctional workers,*** Median age for these participants was lower for the correctional HCW (38.8 years) than for the other groups, in which median age was over 50 years. All the correctional workers were Caucasian, with a prevalence of male for CO (85.6%) and AS (74.3%), but not HCW (31.2%). **<u>Second Campaign</u>** ***Inmates,*** Median age of the new inmates was 36.8 years, and 99.1% were Caucasian, while residential inmates showed similar general characteristics to those	the correctional workers wear FFP2 respirators, disposable gloves and shoe covers, and all the detainees have to wear mandatory medical certified masks during matriculation procedures, meetings with visitors, video hearings medical examinations. A health check filter and temperature measurement were implemented for everyone who entered the prison. In addition, all the correctional workers were asked to conduct self-health monitoring.		samples. By the end of the study (27 Jan 2021) the prevalence of the Alpha variant increased to 59%.	

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	observed in participants in the first campaign. ***Correctional workers,*** OOP were prevalently male (43.5%), with a median age of 53.8 years, while for the other groups the general characteristics were similar to those observed in the first campaign. A total of 182 CO, 44 HCW, 47 AS, and 2 external workers participated in both the campaigns. **Additional information:** Correctional workers at the investigated facility include: correctional officers (CO), administrative staff (AS), operators working with people completing their sentence outside the prison (OOP), correctional health care workers (HCW), employed exclusively in the facility, or spending a part of their working time inside the prison.				

First author Country Design URL	Sample size Demographics Timing of study Resource use	Setting Aim of antigen testing	Public health measures and restrictions in place	Epidemiological situation vaccination coverage	Testing process Platform Frequency of testing
	Timing of study: First campaign, 10 Nov – 09 Dec 2020 Second campaign - 10 Dec 2020 – 27 Jan 2021 **Resource use: NR**				

Key: AS – administration staff; Ag-RDT – antigen rapid detection test; ATS – asymptomatic testing site; CO – correctional officer; HCW – health care worker; LCC – Liverpool City Council; LFD – lateral flow device; LFT – lateral flow test; NR – not reported; OOP – operators working with people completing their sentence outside the prison; PCR – polymerase chain reaction; RCT – randomised controlled trial; RIVM- National Institute for Public Health and the Environment (Netherlands); RT-PCR – reverse transcription-polymerase chain reaction; TMA – transcription mediated amplification; UDOH – Utah department of health; WGS – whole genome sequencing

Appendix 3 Outcomes of included studies

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
Mass testing studies		
England		
University of Liverpool **England** **Prospective cohort study (Ecological study)** **https://www.liverpool.ac.uk/coronavirus/research-and-analysis/covid-smart-pilot/** **(Technical report)** **[Linked peer-reviewed papers https://www.bmj.com/content/374/bmj.n1637 and https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00084-3/fulltext]**	*Compared with a synthetic control using log linear Poisson regression model* **Transmission:** ▪ 18% (7% to 29%) increase in case detection vs control areas. ▪ This is equivalent to an additional 4,766 cases (95% CI 1,878 - 7940) of SARS-CoV-2 being identified between 6 Nov 2020 and 30 Apr 2021 than would not have been identified without community testing. ▪ This compares to an estimated 5,429 true positive cases, identified via LFT over this period. Hence the estimated the proportion of these cases that that would have been picked up in the absence of community testing, would be 12% (deadweight loss). ▪ 21% (95% CI, 12-27%) reduction in cases up to mid-Dec. ▪ No statistically significant difference in case rates (compared with the synthetic control group) is found after this time when the Alpha variant surged through England and a national lockdown was implemented. ▪ Pessimistic model suggests 850 (95% CI, 500-1,350) infections were prevented. ▪ Optimistic model suggests 6,600 (95% CI 4,840-9,070) infections were prevented. **Healthcare utilisation:** ▪ There was an estimated small, but non-significant reduction in hospital admissions. ▪ The estimated overall effect over that period is a 16% reduction in admissions, although the credible intervals of this estimate are large and cross zero (95% CI 53% reduction to 15% increase). **Behavioural:** *Overall testing:*	A low-cost, rapid, no-lab test of infectiousness saves time and extends the reach of health protection measures. SARS-CoV-2 antigen rapid lateral flow testing meets this need when coordinated by an effective local public health service**.**

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	▪ Test uptake was lower and infection rates were higher in deprived areas, in areas with fewer digital resources or lower digital literacy, and among non-White ethnic groups. Fear of income loss from self-isolation was a key barrier to testing. ▪ There was strong public awareness of, and a largely positive attitude toward community testing, motivated by shared identity, civic pride and a wish to protect others. ▪ Misunderstanding, particularly over test performance was a substantial problem needing intensive local communications to address. ▪ There was only sparse evidence of a negative test result licensing Covid-unsafe behaviours. The ONS survey showed that only 4% of respondents intended to carry out social activities following a negative test, even though Liverpool was in Tier 2 for Christmas and social activities were permitted. ▪ There was some hesitancy driven by concerns over inconvenience or perceived risk of infection at testing site. ▪ Confirmatory PCR uptake (between the period of 6-22 Nov and 23 Nov-12 Dec) improved from 19% to 79% after moving from self-testing at home to a dedicated testing site, although a reduction was observed from the end of January. *Survey response:* ▪ Response to a positive LFT: 55% (N=724) outlined actions in line with government guidelines (e.g. self-isolate, stay at home, work from home). *Response to a negative test:* ▪ The highest number of respondents highlighted the need to consider following guidance (442, 39%) and resume restrictions at work (99, 9%). *Test-to-protect in nursing homes* ▪ Introducing enhanced staff testing in care homes saw poor adherence due to high workload, low morale and lack of resources to support the additional workload of testing; so, unsurprisingly the pilot scheme did not reduce the number and size of outbreak. *Test-to-enable in schools:* ▪ The need for testing in schools was well understood. The Liverpool schools' pilot was welcomed. All staff felt testing was less disruptive than anticipated, but was still administratively burdensome.	

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	▪ It was agreed by all focus group participants that the biggest barrier to testing is the financial one – the loss of income (and mobility) associated with positive test result. This is particularly problematic for single parent families. ▪ Using schools as local testing sites open to parents was mentioned as a potential way to get more people involved in testing. It was felt that fuller engagement of non-consenting parents/ staff would be critical to efficacy. ▪ Misinformation may have affected public confidence and uptake in the first phase of the pilot. Specifically, miscommunication from one of the schools to parents regarding the nature of testing, fuelled negative discussion about the testing programme on social media, which damaged uptake at the school. Rates of consent varied considerably by school. An average of 52.6% of pupils at participating secondary schools (31 out of 33) were tested. A total of 32,411 tests (84% pupils; 16% staff) were done at schools in the period to 2 Dec 2020. **Biological:** *Quality assurance study of Innova LFD vs RT-PCR.* ▪ n=5,869 paired samples. Excluding void results: Sensitivity = 40.0% (95% CI, 28.5-52.8%), Specificity = 99.9% (95% CI, 99.8-99.99%), PPV = 90.3% (95% CI, 74.2-98.0%) and NPV = 99.2% (95% CI, 99.0-99.4%). excluding void results. ▪ Assuming void results were negative, Sensitivity = 37.8% (95% CI, 26.8 - 49.9%), Specificity of 99.6% (95% CI, 99.4% - 99.8%), PPV= 84.8% (95% CI, 68.1 - 94.9%), and NPV = 93.4% (95% CI, 92.7 - 94.0%). ▪ The sensitivity in participants with an RT-qPCR cycle threshold (Ct) of <18.3 = 90.9% (95% CI, 58.7 - 99.8%), a Ct of <24.4 = 69.4% (95% CI, 51.9% - 83.7%), and a Ct of >24.4 = 9.7% (95%CI, 1.9% - 23.7%). ▪ LFT was found to likely to detect at least 3/5 and at most 998 in every 1,000 people with a positive RT-qPCR test result with high viral load. *Test positivity* ▪ A total of 739,553 LFTs were conducted, of which 6,300 were positive (0.9%). ▪ Test uptake decreased over time, with spikes before Christmas and the third lockdown. ▪ In total there were 6,109 individuals who tested positive via LFT between 6 Nov 2020 and 30 Apr 2021, and 3,547 of these received a PCR test within 5 days (58%). Of these 3,547 confirmatory PCR tests, 3,216 were PCR positive (90.7%), 295 were PCR negative (8.3%) and 36 were void (1.0%)	

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	Schools testing: ▪ There were 26,880 LFTs conducted on 5–11-year olds, identifying 162 positive tests. Of these, 91 had a confirmatory PCR within 5 days, yielding 86 positives (94.5%) and 5 negatives (5.5%). ▪ There were 129,657 LFTs conducted on 12–18-year-olds, detecting 454 positives tests. 262 of these had a confirmatory PCR within 5 days (57.7%), yielding 228 positive PCRs (87.0%) and 33 negatives (13.0%).	
Wales		
Public Health Wales **Wales** **Prospective cohort study (Ecological study)** **https://cwmtafmorgannwg.wales/Docs/Publications/FINAL_V2_Whole%20Area%20Testing%20Evaluation%20Full%20Report%20020210325.pdf** **(Technical report)** **[Linked economic evaluation report https://www.medrxiv.org/content/10.1101/2021.05.10.21256816v1 (pre-print)]**	*Analysis based on n=33,822 LFTs from Merthyr Tydfil and n=14,304 LTFs from Lower Cynon Valley)* **Transmission, mortality, healthcare utility** R_t was estimated to be 0.8 on 20 Nov and rose to 1.9 by 9 Dec before falling to a low of 0.6 by 25 Dec and rising again into Jan (truncated data). An estimated 353 cases (95% CI 306-409) (both asymptomatic and symptomatic), 24 (95% CI, 16-36) hospitalisations, 5 (95% CI, 3-6) ICU admissions and 14 (95% CI, 11-19) deaths, that would have otherwise occurred without the implementation of the pilot, were prevented. This represents a reduction in mean daily incidence rate of 13.6 (95% CI, 11.8 - 15.8) cases per 100,000 per day. 12.2% (95% CI, 10.6-14.1%) of cases that would have occurred on a 6 week period were prevented, translating into a predicted 6-12% reduction in burden on the healthcare system. **Behavioural** There was lower uptake in males, younger people (11-29 years) and those living in the most deprived quintiles of the population. Low uptake in those groups with high positivity. Of the 1,135 positive LFTs, 622 (55%) availed of confirmatory PCR.	The Whole Area Testing pilot in Merthyr Tydfil and the lower Cynon Valley has demonstrated that mass testing using LFD tests is acceptable to the community, effective in preventing cases, hospitalisations and deaths and cost effective as an intervention. The use of mass testing for asymptomatic members of the community should be considered an important and effective part of any COVID-19 Control Plan.

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	Return rate of home LFTs was 39%. **Biological:** LFD positivity rates: Merthyr Tydfil, 2.3%. Lower Cynon Valley, 2.6%. Of the 49,799 LFTs undertaken outside of school 1,114 were positive (2.2%). Of the 4,064 LFTs undertaken in schools, there were 15 positive test results (0.37%). There were only 21 individuals who had positive LFD results, and subsequently went on to have negative PCR results. **Cost-effectiveness:** The average cost of community testing per test was £20, school testing was £21 and home testing £38. Cost per positive LFT (non-schools) = £895 Cost per positive LFT (schools) = £5,753 Merthyr Tydfil: Highly cost-effective with an ICER = £2,292 per QALY (£2,143 stated in linked paper). Net monetary benefit for the intervention, which is cost savings, plus the value of QALYs gained was £5.8 million (£6.2 million in accompanying study).	
Slovakia		
Pavelka **Slovakia** **Retrospective cohort study (Ecological study)**	**Transmission outcomes:** *Based on changes in test positivity between rounds of testing.* Observed prevalence decreased by 58% (95% CI: 57 to 58%) within 1 week in the 45 counties that were subject to (at least) 2 rounds of mass testing, an estimate that remained robust when adjusting for attendance rates, reproduction number, and prevalence in previous rounds.	The combination of nationwide restrictions and mass testing with quarantining of household contacts of test positives rapidly reduced the prevalence of infectious residents in Slovakia. Although it was impossible to disentangle the precise contribution of control measures and mass testing, the latter is likely to have had a

First author **Country** **Design** **URL**	**Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)***	**Author conclusions**
https://science.sciencemag.org/content/372/6542/635 **(Peer-reviewed)**	In the 4 counties that underwent 3 rounds of testing, observed infection prevalence decreased by 82% (95% CI, 81-83%) between the pilot and 2nd round. *Micro simulation model:* Adjusting for epidemic growth of 4.4% (1.1 to 6.9%) per day preceding the mass testing campaign, the estimated decrease in prevalence compared with a scenario of unmitigated growth was 70% (67 to 73%). Modelling indicated that this decrease could not be explained solely by infection control measures but required the addition of the isolation and quarantine of household members of those testing positive. Among the multiple intervention scenarios tested, only the scenario that assumed a substantial impact of both the additional contact reducing measures and the mass testing campaigns was able to generate reductions in test positivity rates between testing rounds that were similar to those observed. **Biological outcomes:** 50,466 participants tested positive of 5,276,832 completed tests (0.96%). The positivity rate was 3.91% in the pilot, 1.01% in round 1 and 0.62% in round 2.	substantial effect in curbing the pandemic in Slovakia and may provide a valuable tool in future containment of SARS-CoV-2 elsewhere.
Kahanec **Slovakia** **Retrospective cohort study (Ecological study)** **https://link.springer.com/article/10.1007/s00148-021-00856-z** **(peer-reviewed)**	*Authors used a difference-in-differences model to compare changes in incidence (passive surveillance) and reproductive number between states who underwent 1 round of testing and those who underwent 2 rounds.* *Study excluded 4 pilot counties* Authors reported that differences in the average number of cases (between the treatment (twice tested) and control (once tested) groups) decreased between the first and second mass testing event. With regards to R_0, there was a clear increase in this parameter in the control group (tested only once) versus the treatment group (tested twice). Indicating the relatively short lived benefits of mass testing. The second wave of mass antigen testing was associated with a reduction of the 7-day average in infections measured 14 days after Round 2 by approximately 2.3 daily cases per 100.000 inhabitants (36% reduction), and decreased R_0, by 0.28 (31% reduction), more than control groups.	Our results suggest that mass testing coupled with the quarantining of positive cases and their contacts could be an effective tool in mitigating pandemics. For lasting effects, re-testing at regular intervals would likely be necessary.

First author **Country** **Design** **URL**	**Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)***	**Author conclusions**
	After reaching the maximum reduction in cases 15 days after Round 2, the effect diminished toward the zero effect. About 3 weeks after the second mass testing, the estimated impact of repeated mass testing on R0 is statistically indistinct from zero. The results presented imply that mass testing conducted only irregularly and after long time intervals is unlikely to be sustainably suppressing the pandemic.	
Frnda **Slovakia** **Mathematical modelling study based on Ecological study** **https://www.mdpi.com/2036-7449/13/1/7** **(peer-reviewed)**	*Mathematical models developed to estimate the impact of self-isolation for antigen test-positive cases who may not have otherwise been tested by RT–PCR due to their asymptomatic status:* The authors estimated that based on a prevalence of 5% in the 4 worst affected counties, the pilot round of testing identified between 36% and 68% of all infected individuals in the population. The authors estimated that PCR could only trace about 11% of these infected individuals at this time (due to capacity issues). Authors estimate this prevented 70-149 hospitalisations and 5-11 ICU admissions (within 2-3 weeks after the pilot testing). During the nationwide testing, the authors estimated that antigen testing identified between 40% and 76% of all infected cases at the time (assuming prevalence of 1.5%), compared with 12% by PCR. Authors estimate this prevented 557-1,111 hospitalisations and 42-85 ICU admissions (within 2-3 weeks after the mass testing). However, significant concerns regarding the underpinning assumptions (i.e. sensitivity of test not considered) and the data (antigen positivity).	Antigen testing in hotspots can flatten the curve of daily newly reported cases significantly, but in regions with low-risk of COVID-19, the benefit of such testing is questionable.
Italy		
Pagani **Italy** **Prospective cohort study (Ecological study)**	**Transmission outcomes:** R_0 decreased from a peak of ~1.8 on 3 Nov to a trough of 0.6 on 24 Nov, before increasing to ~0.8 by 1 Dec, and plateauing at ~0.7 by 6 Dec. Information past the 6 Dec is not provided.	**NR**

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
https://www.quotidianosanita.it/allegati/allegato9528306.pdf **(online presentation)**	The 7-day moving average of positive cases decreased from a peak of ~600 from the 5-10 Nov, to a low of ~250 on 6 Dec. Information past the 6 Dec is not provided. *Based on modelling (unclear methods):* By 6 Dec: ▪ Observed R_0 = 0.7 ▪ Without mass testing R_0 = 0.8 ▪ With 50% participation R_0 = 0.8 ▪ With 70% participation, R_0 = 0.5 **Biological:** 3,619 positive antigen tests (1%). **Healthcare utilisation:** Between 24 Nov and 11 Dec 2021, the number of COVID-19 cases fell: ▪ in general hospital beds from 323 to 239 (26% reduction) ▪ in ICU beds from 38 to 31 (18% reduction) ▪ in other hospital areas from 148 to 138 (7% reduction). The authors estimated that 612 deaths were avoided during this time period. After 14 days follow-up 55 Ag-negative individuals were hospitalised in a COVID-19/ICU ward. Additionally, 3,072 Ag-negative individuals had become symptomatic. **Performance:** Within a proportion of 1,469 with both Ag and PCR samples: Sensitivity = 73.1% Specificity = 97.6% PPV = 95.8% NPV = 82.3% (PCR and Ag tests not performed on same day, or from same sample. Selection of subjects not random either).	
Ferrari	**Transmission:**	The authors conclude that mass testing campaigns are useful instruments

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Italy **Mathematical modelling study based on an Ecological study** **https://arxiv.org/abs/2104.14813** **(pre-print)**	*Estimated by embedding a semi-parametric growth model into a synthetic control framework.* The mass test campaign decreased the growth rate of Covid-19 by 39% (95% CI, 29-49%) which corresponds to a reduction in the total additional cases of 14%, 18%, 30% and 56% within 7, 10, 20 and 40 days from the intervention date, respectively (assuming that the post-intervention transmission growth rate remained constant).	for mitigating the pandemic.
Ricco **Italy** **Retrospective cohort study (Ecological study)** **https://www.journalofinfection.com/article/S0163-4453(21)00034-7/fulltext** **(peer-reviewed)**	*Based on comparison between two neighbouring provinces (Trentino and Tyrol):* After mass testing in South Tyrol, the 7-day average of daily notification rates dropped from 110.9 (20/11/2020) to 31.5 cases/100,000 inhabitants (23/12/2020), being afterwards comparable to those of Trentino (on average: 34.5/100,000, 95%CI 32.0–36.9 for South Tyrol, vs. 35.0 95% CI 33.1–37.0, for Trentino), but still higher than those of Tyrol (10.5/100,000 inhabitants, 95%CI 9.7–11.2). However, after daily rates were percent normalised to their respective maximum values in order to cope with the different diagnostic strategies, epidemic curves of the 3 regions substantially overlapped until the end of Dec 2020, as sharing a common trend. Normalised rates were similar in the 14 days following the mass screening test in South Tyrol (i.e. 78.9%, 95%CI 73.2–84.7 for South Tyrol; 81.5%, 95%CI 77.7–85.2 for Trentino; 76.6%, 95%CI 71.2–82.0 for Tyrol, ANOVA p value = 0.285), and they remained well correlated across all the assessed timeframe (i.e. $r = 0.818$, $p < 0.001$ for South-Tyrol vs. Trentino, and 0.973, $p < 0.001$ for South Tyrol vs. Tyrol).	In summary, available estimates cannot confirm the unambiguous effect of the large-scale screening intervention on the circulation of SARS-CoV-2 in South Tyrol. The authors urge a more cautious implementation of RAD tests for SARS-CoV-2 in mass scale testing.
Pre-event screening		
England		
UK Government 2021 **UK**	**Key scientific observations:**	The cases recorded are likely an underestimate of the true number given (a) some attendees managed to enter events without proof of

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Uncontrolled, before-after study.
 	
https://www.gov.uk/government/publications/events-research-programme-phase-i-findings/events-research-programme-phase-i-findings
 	
(technical report)
	The ERP pilots demonstrated how risk mitigation measures could be put in place to reduce and manage the risks identified for events, building on previous SAGE-EMG's conclusions.
	
	Pre-event lateral flow testing, questionnaire-based screening and consent to link event booking and test result data, as conditions of admittance to events, were accepted by audiences for most types of events and helped public health teams to respond to any potential outbreaks.
	
	Timely access to linked testing and ticketing data was effective in enabling rapid contact tracing around Liverpool events. Areas for further risk-mitigation that were identified included: moving the time of testing closer to events; and automatically cancelling tickets when positive test results appear.
	
	It is challenging to generate robust, generalisable evidence of the transmission risk associated with particular events. Phase I pilots were necessarily limited in scale, and took place during a period of low prevalence of the virus. Further, they were insufficient in scale, scope and study designs to generate any direct evidence based on transmission data. Therefore, evidence on case numbers should be treated with caution.
	
	Cases associated with events
	A total of 28 positive cases have been identified to date potentially related to the pilots undertaken, of which 11 were identified as potentially infectious at an event and a further 17 were identified as potentially infected at or around the time of an event.
	Number of cases associated with each event:
	▪ The Good Business Festival, Venue: ACC Exhibition Centre (0)
	▪ Circus Presents 'The First Dance' (Circus Nightclub),
	  ○ Night 1 (5)
	  ○ Night 2 (5)
	▪ Sefton Park Pilot, Venue: Sefton Park, Tented stage (2)
	▪ Snooker Competition, Venue: Crucible Theatre (6)
	▪ Emirates FA Cup Semi-Final, Venue Wembley stadium (0)
	▪ Carabao Cup Final, Venue: Wembley stadium (2)
	▪ BRIT Awards, Venue: The O2 (0)
		LFT negative results, and (b) post-event PCR return rates were lower than expected. In addition, the studies did not include comparison groups, thus making it difficult to attribute infection to attending events. Higher levels of audience participation in testing and thorough data linkage with public health surveillance systems are needed to better understand the transmission risks around events.

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	▪ Emirates FA Cup Final, Venue: Wembley stadium (6) ▪ Reunion 5k, Venue: Kempton Park (2) **Survey findings:** COVID-19 mitigations at events could significantly increase or decrease the likelihood of an individual attending an event. *Evidence from ONS' Opinions and Lifestyle Survey:* (survey of 3,810 adults in Great Britain, 28 April to 3 May 2021) suggests the following mitigations will have an effect on attendance: ▪ COVID-19 pre-event testing: 15% more likely to attend an event ▪ social Distancing (1m+): 2% less likely to attend an event ▪ face coverings required (2hrs): 28% less likely to attend an event ▪ no food/drink allowed at the event: 43% less likely to attend ▪ 2-hour delay to enter and exit: 62% less likely to attend an event. **PCR test results:** It is hard to know if positive post-event tests are as a result of transmission at events or other activity carried out by the individual over a similar period. Return rates for PCR tests were low at pilot events significantly limiting the ability to estimate rates of infection after attending events. The average return rate across all events for both 'pre' and 'post' testing was 15%. The proportion of participants returning PCR tests, varied between 8% and 74% for the 'pre-event' (days -1 to 3) test and between 13% and 66% for the 'post-event' (days 4-7) test. Extremely low PCR test returns were seen in the early days of the World Snooker Championship, when participants had to order tests online. For later events, such as the Emirates FA Cup Final, the BRIT awards show and the Reunion 5k organised run, PCR tests were automatically posted to attendees (rather than needing to order them), leading to higher return rates. The organised run had a particularly high return rate at 61% for both tests. Events offering incentives, such as a chance to win future festival tickets, saw higher return rates than those that did not offer an incentive. This low and varied level rate of PCR test return significantly limits the direct evidence of transmission from the events, and further reduces the possibility of	

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	comparing data pooling across events to give an indication of transmission risks between events. It does, however, provide important behavioural insights, showing that attendees are not sufficiently motivated to get tested after attending an event.	
Barcelona		
Revollo 2021 **Spain** **https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00268-1/fulltext** **RCT** **(peer reviewed)**	**Biological/epidemiological:** Pre-event ▪ Of 960 randomised participants, 0 had a positive Ag RDT at baseline screen, but 28 (2.9%) had a positive TMA result (13 in experimental and 15 in control arms), of them 2 had a positive RT-PCR (1 in experimental and 1 in control arms). Ct value of both was 37. ▪ All 28 TMA positive participants had previously been diagnosed with COVID-19 within a median of 50 days prior to the event. 0/28 samples showed a cytopathic effect on cell culture. ▪ All staff tested negative for Ag-RDT and RT-PCR at baseline. After the event: ▪ 0/465 people in the experimental arm became infected with SARS-CoV-2 (observed incidence 0%; Bayesian estimated incidence 0.14%; 95%CI: 0% to 0.61%) versus 2 out of 495 controls (0.31%; 95%CI: 0.04% to 0.73%). ▪ No significant difference in incidence between the two arms. ▪ The Bayesian estimate for the incidence between the experimental and control groups was –0.15% (95% CI –0.72 to 0.44). ▪ All staff tested negative for RT-PCR at follow up. **Environmental:** ▪ The air concentration of CO_2 did not exceed the recommended threshold of 800 ppm at any measurement during the event. ▪ The number of complete air exchanges per hour in the 2 rooms ranged from 11 to 13. **Behavioural:** Participants spent an average of 2 hours 40 mins in the concert.	▪ This study provides evidence on the safety of indoor mass gathering events conducted during a COVID-19 outbreak under a comprehensive preventive intervention based on same-day screening with Ag-RDT, compulsory facial mask-wearing, and adequate ventilation. ▪ The results regarding virological assessment suggest that a baseline screening might allow easing some of the additional preventive measures, particularly in indoor events with pre-assigned seats (i.e., theatres), associated with lower transmission risk.

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	In the post-event questionnaire, participants expressed their willingness to attend another activity with the same safety protocol (median score 9.29 out of 10, IQR 9–10). **Healthcare utilisation:** NR	
Llibre 2021 **Spain** **Uncontrolled before-after study** **https://www.acpjournals.org/doi/10.7326/M21-2278** **(peer reviewed)**	Of the 5000 Ag-RDT–screened individuals, 6 (prevalence, 120 cases per 100,000 persons) tested positive and were not allowed to enter the concert, as well as 2 of their close contacts despite testing negative. The final analysis included 4,584 attendees. 6 attendees (1 man and 5 women; median age, 36 years [range, 27 to 46 years]), none of whom were vaccinated, were diagnosed with COVID-19 within the 2 weeks after the concert (median, 8.5 days [range, 4 to 12 days]); all of these persons had mild symptoms (14-day cumulative incidence, 130.9 cases per 100,000 persons). 3 of them had been located in the front-right area of the stadium and 3 in the front left. Of these 6 persons, 3 were identified in contact tracing studies of known index cases who had not attended the concert; therefore, their contagion was unlikely to occur during the event. One woman who participated in the event was oligosymptomatic, though she tested negative in the pre-event Ag-RDT screening and again 48 hours after the event; 4 days after the concert, COVID-19 diagnosis was confirmed by PCR testing. Therefore, she presumably attended the event during the incubation period. The transmission source of the 2 remaining cases could not be identified.	Our results build on our previously reported clinical trial data (and suggest that the implementation of same-day Ag-RDT screening, use of facemasks, and improved ventilation can prevent high rates of SARS-CoV-2 transmission in indoor mass-gathering live concerts without physical distancing. These findings must be read in the context of a case study conducted in a community with low vaccination rates and a moderate infection rate. Nevertheless, they are a key step for creating safe environments in not only live music events but also other mass-gathering indoor events.
Netherlands		
Fieldlab, 2021 **The Netherlands** **Uncontrolled, before-after study.**	**Biological/epidemiological:** Pre-event tests Match (rapid test) (n=5,108 tested): + 18 (0.35%) - 5,090 ? 0	The authors conclude that: ▪ the risk per hour at events of these type (with measures and pre-testing) is equal to the risk in social situations at home or with a visit to home (without testing). ▪ social distance measures within the venue can be relaxed by using pre-event or

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
https://fieldlabevenementen.nl/wp-content/uploads/2021/04/Fieldlab-Evenementen-Adviesaanvraag-Type-III-versie-1.0.pdf **(technical report)**	Post-event tests Match (rapid test) (n=3,718 tested, 73% of pre-tests) + 3 (0.08%) - 3,718 ? 0 (Authors notified of 3 other positive cases via national contact tracing service. Not known where cases became infected). **Behavioural:** Survey Perception of measures by attendees (out of 10, higher scores = more positive) ▪ Rapid test, 8.0 ▪ PCR test, 8.8.	access testing and other recommended measures. The authors also concluded that these types of events can, with the right set of measures, take place safely, even at high prevalence of SARS-CoV-2. These measures include: ▪ Rapid test at a decentralized location, close to home ▪ Rapid test at max 24 hours from the end of the event ▪ Using an app or otherwise access control for a negative test result ▪ Occupation of the location with 50-75% of the capacity and thus the abandonment of the 1.5m measure from the regular RIVM framework within the event location
Serial testing – sports programme		
USA		
Moreno 2021 **USA** **https://academic.oup.com/cid/article/73/Supplement_1/S45/6274297** **Case series (epidemiological investigation)** **(peer reviewed)**	Both sports involved in the outbreaks were considered "high risk" by the National Collegiate Athletics Association owing to frequent contact and collision between athletes during play. **Outbreak 1 outcomes:** Overall, during outbreak 1, a total of 32 individuals (22 students and 10 staff) from the program had laboratory-confirmed SARS-CoV-2 infections. Of persons with confirmed cases, 4 (13%) were tested by RT-PCR because they were symptomatic, 7 (22%) were antigen positive and received RT-PCR confirmation, and 21 (66%) were positive during mass RT-PCR testing. Mass RT-PCR testing identified 21 new SARS-CoV-2 infections among students and staff. Of these, 18 (86%) were negative on contemporaneous rapid antigen tests.	These findings suggest that antigen testing alone, even when mandated and directly observed, may not be sufficient as an intervention to prevent SARS-CoV-2 outbreaks in congregate settings, and they highlight the importance of vaccination to prevent SARS-CoV-2 outbreak in congregate settings.

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	Among 11 positive antigen results obtained during mass testing, 4 (36%) were confirmed with RT-PCR and 7 (64%) received negative RT-PCR results. **Outbreak 2 outcomes:** Both teams underwent daily antigen testing and received all negative antigen results in the week preceding the competitions, including both competition days (days 0 and 1). No testing was conducted on day 2. On day 3, an athlete from team 2 received a positive antigen test result, which was confirmed by RT-PCR. No athletes or staff on either team were quarantined from contact with the index athlete that occurred during competition on days 0 and 1. During days 5–10, multiple athletes on both teams began experiencing symptoms and received positive antigen and RT-PCR results. On day 6, all athletes on team 1 were tested with RT-PCR only, with 2 individuals testing positive, and in-person team activities were suspended. Overall, 12 athletes (7 from team 1 and 5 from team 2) had confirmed SARS-CoV-2 infections during this outbreak. **Total number of cases associated with each outbreak:** Outbreak 1 included 133 total individuals, and outbreak 2 included 55 total individuals (32 on team 1 and 23 on team 2). **Study findings in relation to public health measures:** Contact tracing during outbreak 1 identified interactions among individuals that may have contributed to at least 21 (66%) of the 32 confirmed cases. In particular, the team continued to have physically distanced (6-feet-apart) in-person meetings with cloth masks until all in-person team activities were suspended to prevent further spread. Per public health and university guidelines, unvaccinated attendees in these meetings were not quarantined, a step that might have prevented onward transmission during this outbreak. Roommates and household contacts of student-athletes could represent additional sources of infection in outbreak 1, as they were not required to quarantine owing to the large size of the house and the university's assessment that physical distancing was achievable in this area. Continuing indoor in-person meetings and not quarantining potential contacts represent possible breaches in university's	

First author Country Design URL	Outcomes (*transmission, behavioural, mortality, healthcare utilisation, biological, cost-effectiveness, costs)*	Author conclusions
	SARS-CoV-2 mitigation plan that, combined with the limitation of antigen testing, permitted viral spread throughout the team in outbreak 1. In outbreak 2, genomic sequencing was used to demonstrate that SARS-CoV-2 transmission likely occurred between 2 teams during athletic competition even though both teams received negative antigen results immediately before competition.	
Serial testing- Health and social care setting		
England		
Tulloch 2021 **Liverpool, UK** **Prospective cohort study with qualitative evaluation** **https://academic.oup.com/ageing/advance-article/doi/10.1093/ageing/afab162/6322881** **(pre-print)**	All were outbreak-free at the start of the study. By the end of the study period, 7 out of the 11 homes had identified COVID-19 positive individuals amongst one or more residents or staff. Cases were identified through the pilot scheme, through pre-existing standard resident testing, and through testing of staff not following the test protocol (i.e. they had a PCR test but did not perform any LFD tests). In only 1 out of the 6 outbreak homes was a positive LFD result identified before the outbreak. The remaining homes' index cases were identified solely through PCR. There was no statistical difference in the proportion of outbreaks observed during the study period (odds ratio 2.1; 95% CI 0.5- 9.4%; p=0.32) between pilot care homes (54.5%; 95% CI 23.4-83.3%, 6/11) and other care homes (36.6%; 95% CI 25.5-48.9%, 26/71). There was no statistical difference in the size of outbreak amongst residents and staff (p=0.42) between pilot homes (median 0%, range 0-38.8%, n=6) and other homes (median 0%, range: 0-64.8%, n=26). There was no statistical difference (Mann-Whitney U Test, p=0.58) between the size (total residents and staff) of pilot (median 82, range: 44-136) and other (median 79, range: 9-364) care homes. **LFD performance:** During the study, 1638 LFD tests were performed, of which 828 had matched PCR tests. The resultant prevalence was 0.31 (95% CI 0.10-0.71) positive tests per 100 LFD tests performed (n=5), and 1.23 (95% CI 0.40-2.84) positive staff members per 100 staff tested via LFD. All positive LFDs results were confirmed by PCR tests. No false positive or false negative LFD test results were identified. There were no void or unreadable LFD results recorded. 11 PCR results were void. Of the 5 LFD and PCR positive cases, 3 performed only 1 LFD test during the	This study highlights the importance of implementation over test performance for staff testing, and the need for more than one negative LFD for visitor testing. Due to the highly vulnerable nature of care home residents, consideration needs to be given to whether a single LFD strategy should be used to facilitate close physical interactions with the highly vulnerable care home resident population. Without addressing the contextual and human factors that lead to poor adherence of testing protocols, these testing regimes will not have the opportunity to perform at the required level to prevent outbreaks in care homes.

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	study period. The two of other cases adhered with the number of LFD tests expected. **Adherence to testing:** The majority of staff participated in the study (81.7%, 407/498), though this was highly variable between homes. The overall testing ratio was 1.98 LFD tests to 1 PCR test, yet only 64 individuals (15.7%) achieved the expected testing ratio of 2:1. 8.6% of staff members performed more than 9 tests (≥75% protocol adherence), 25.3% performed 6 or more (≥50% adherence), and the majority (62.9%) performed 4 tests or less (≤25% adherence). The proportion of staff achieving test adherence varied considerably between homes. There was no apparent trend between testing protocol adherence and outbreak status, and the sample size was too small to effectively stratify the results to perform robust modelling of the data. **Visitor testing outcomes:** Only outdoors visits were permitted, unless it was an end-of-life situation. 8 out of 11 study care homes participated in visitor testing. 113 care home visitors attended the central testing site. LFD testing identified 9 COVID-19 positive individuals, who were then requested to self-isolate according to Government guidelines. Subsequently, PCR testing identified 2 of these individuals as false positives. 104 individuals tested negative and could proceed to visit a pilot care home. One individual was identified as LFD negative and PCR positive and was informed before arriving at a care home and did not enter it. Of the eligible visitors, 101 arrived at their respective care homes and all tested negative on arrival. **Qualitative findings:** Two themes were identified: 'service integration' and 'social factors'. ***The 'Service Integration' theme*** describes pragmatic aspects of test integration and procedural factors. The perceived experience with the test and attitudes of staff members are also categorised under this theme, which consists of 4 sub themes 1) administrative tasks	

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	2) training 3) testing pathways and procedures 4) changes in workload. **1) Administration tasks:** LFD test results were required to be registered using dedicated website portals (Government testing portals), for auditing purposes. Each test had to be recorded individually. The log-in procedure had many steps and was time consuming. As the portals were not directly linked with the care home records system, extra staff required to be allocated to administer this. This was exacerbated by variation in the numbers of staff being tested at the same time, due to shift times and availability, thus, slowing down the diagnostic process. Visitor testing required additional staff work. Managing visitors required supervision, to enable a smooth process and to safeguard residents. Visitors not familiar with the procedure and/or with digital technologies struggled to navigate the interface and staff members were frequently asked to support them with this, placing additional pressures and distracting them from other tasks. Most participating homes limited the number of visitors allowed at any one time to enable staff to continue with routine tasks without testing "taking over". **2) Training:** Training was provided by army personnel and consisted of a 2-hour live demonstration conducted at the Exhibition Centre in Liverpool. Staff attendees then trained their colleagues (cascade training). The main criticalities associated with the training process were: 1) inconsistencies with training from the army and the test-as-conducted, especially the expected waiting time to read results and correct process of use; 2) unsupervised cascade training. This could create discrepancies in the process. 3) trained staff members did not have the chance to directly trial the device during training and no instruction material was left for reference. As a result, not all staff members were confident in conducting the test after completion of training. **3) Testing pathway and procedures:** A critical issue affecting testing was the lack of a standardized process, in part due to inadequate testing areas (e.g. limited space). Care homes had a diverse range	

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	of facilities and rooms allocated for testing and equipment. This variability hindered the standardization and potentially affected adherence to the recommended protocol. Staff members were asked to regularly return to the care home for testing. This was often outside their rostered shifts and they were reluctant to comply. **4) Changes in the workload for staff members**: Conducting the test for staff members and visitors in accordance with IPC measures and social distancing required significant planning. The combination of LFDs and PCR tests on a regular basis increased pressure on staff, adding to an already saturated workflow, exacerbated by COVID restrictions. The **'Social Factors'** theme showed that rapid testing had the potential to enable connections, to reopen care homes to visitors, and to gradually lift restrictions. In addition to the impact on family visits, restrictions have also limited visits from GPs and healthcare professionals. The restoration of these visits, with increased healthcare support for residents, and healthcare advice for care home staff, was seen as a potential positive outcome. Despite the lack of clarity about testing procedures and their reliability, staff members indicated that they had joined the pilot with a sense of positivity because of the potential to improve care for residents and family members.	
Serial testing – school setting		
USA		
Lanier 2021 **USA** **Retrospective cohort study** **https://www.cdc.gov/mmwr/volumes/70/wr/mm7021e2.htm** **(peer reviewed)**	Among 50,400 students receiving testing at least once, representing an estimated two thirds (67%) of all high school students participating in extracurricular activities, 1,771 (3.5%) had a positive result. During 3 Jan – 20 Mar, 2021, the percentage of positive tests declined, consistent with decreasing state-wide incidence among school-aged children during this period. Test to Play allowed extracurricular activities to occur in the context of mandated testing; during 30 Nov 2020– 20 Feb 2021, approximately 95% of the 11,379 scheduled competition events for high school extracurricular winter athletics were	School-based COVID-19 testing should be considered as part of a comprehensive prevention strategy to help identify SARS-CoV-2 infections in schools and sustain extracurricular activities.

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	completed. An estimated 75,510 high school students participated in extracurricular activities during late November 2020–early March 2021 according to the Utah High School Activities Association. Antigen test positivity peaked at about 6% on 20 Dec (during period of low testing of 2,000 tests per week). Positivity rate remained below 2% from January onwards, and below 1% from February, with at least 8,000 tests done weekly	
Mass testing programme – prison setting		
Italy		
Stufano 2021 **Italy** **Retrospective cohort study** **https://www.frontiersin.org/articles/10.3389/fpubh.2021.694795/full** **(peer reviewed)**	**Cases detected among inmates:** Only 2 new inmates had positive results at the first campaign and there were no positive cases at the second campaign. Both positive cases were asymptomatic and negative at the antigen test performed at entry to the correctional facility, and then positive at the test performed 72 h after entry. Both the positive cases remained asymptomatic until recovery. During the study period, no further positive cases were observed among the inmates outside of the testing campaigns. No spread was observed among inmates. **Cases detected among correctional workers:** In the first testing campaign 4 CO and 2 HCW had positive results, while no new positive cases were observed in the second campaign. The frequency of positive cases was not significantly different among the groups, including inmates (p = 0.06). All the positive cases were asymptomatic at the testing, then 1 HCW referred the onset of fever, coughing, and muscle pain during the isolation period at home. During the study period, 1 CO, and 1 HCW were also recorded as positive outside the testing campaign for the onset of symptoms while at home. All the high and low risk contacts were further tested and resulted negative. Regarding the activities performed by the positive workers during the study period, 3 of the CO acted as escort guards, and 2 of the HCW performed part of their working activity outside the correction facility. None of the positive cases referred high or low risk contact with any of the other positive cases.	The implementation of a full risk management plan in a correctional facility, including both a strict protocol for the application of preventive measures and a serial testing approach, seems to be able to prevent COVID-19 outbreaks in both inmates and correctional workers.

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Key: Ag-RDT – antigen rapid detection test; CI – confidence interval; CO – correctional officer; Ct – cycle threshold; HCW – health care worker; ICU – intensive care unit; IPC – infection prevention and control; LFD – Lateral flow device; LFT – Lateral flow test; NPV – negative predictive value; PCR – Polymerase chain reaction; PPV – positive predictive value; QALY- quality-adjusted life year; RADT – rapid antigen detection test; RCT – randomised controlled trial; R_0/ R_T – reproductive number.

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