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REVIEW

Effectiveness of rapid antigen testing for screening of asymptomatic individuals to limit the transmission of SARS-CoV-2: A rapid review

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Abstract

Rapid antigen detection tests (RADTs) offer advantages over gold-standard reverse transcription polymerase chain reaction (RT-PCR) tests in that they are cheaper and provide faster results, thus enabling prompt isolation of positive SARS-CoV-2 cases and quarantine of close contacts. The aim of this study was to collate and synthesise empirical evidence on the effectiveness of rapid antigen testing for the screening (including serial testing) and surveillance of asymptomatic individuals to limit the transmission of SARS-CoV-2. A rapid review was undertaken in MEDLINE (EBSCO), EMBASE (OVID), Cochrane Library, Europe PMC and Google Scholar up until 19 July 2021, supplemented by a grey literature search. Of the identified 1222 records, 19 reports referring to 16 studies were included. Eight included studies examined the effectiveness of RADTs for population-level screening, four for pre-event screening and four for serial testing (schools, a prison, a university sports programme and in care homes). Overall, there is uncertainty regarding the effectiveness of rapid antigen testing for the screening of asymptomatic individuals to limit the transmission of SARS-CoV-2. This uncertainty is due to the inconsistent results, the relatively low number of studies identified, the predominantly observational and/or uncontrolled nature of the study designs used, and concerns regarding methodological quality. Given this uncertainty, more real-world research evidence in relevant settings, which is of good quality and timely, as well as economic evaluation, is required to inform public policy on the widespread use of RADTs in asymptomatic individuals.

KEYWORDS
antigen, asymptomatic, Covid-19, rapid testing, SARS-CoV-2, screening

Abbreviations: CDC, Centers for Disease Control and Prevention; Covid-19, coronavirus disease 2019; CrI, credible interval; Ct, cycle threshold; ERP, Events Research Programme; ICU, intensive care unit; IPC, infection prevention and control; NIH, National Institutes of Health; PPV, positive predictive value; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QALY, quality-adjusted life year; RADT, rapid antigen detection test; RCT, randomised controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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1 | INTRODUCTION

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.[1] Many types of Covid-19 tests are now available for both clinical and public health use, some of which are laboratory based and others which can be performed in pharmacies, general practitioner clinics, schools, workplaces, airports and at home.[2] However, it is important that the right tests are undertaken in the right people at the right time for the right purpose,[3] as testing under the wrong circumstances may lead to test performance inaccuracies that cause harm to individuals and populations, and may not represent an efficient use of scarce healthcare resources.[4]

Four different testing scenarios for SARS-CoV-2 have been described—diagnostic, close contact (including outbreaks), screening and surveillance—each of which serves different purposes and require different approaches.[2] Box 1 describes these four testing scenarios.

Reverse transcription polymerase chain reaction (RT-PCR) tests are considered the gold standard for diagnosing SARS-CoV-2 infection,[6] and they work by detecting fragments of the RNA genome of SARS-CoV-2.[1] However, given the very high sensitivity of RT-PCR tests,[6] individuals may continue to test positive for SARS-CoV-2 RNA for a prolonged period,[7] even when they are no longer infectious.[8] Rapid antigen detection tests (RADTs) work by detecting viral proteins (called antigens) on the surface of the virus.[9] RADTs offer advantages over RT-PCR tests in that they are cheaper (particularly if self-administered)[2] and provide faster results, thus enabling prompt isolation of positive cases and quarantine of their close contacts.[10] It is possible that the cases identified through RADTs are potentially the most infectious cases based on viral load.[11–13] However, it has been demonstrated in systematic reviews,[14,15] including a Cochrane review,[6] that RADTs have significantly lower sensitivity overall than RT-PCR tests, particularly in asymptomatic populations (RADT sensitivity relative to RT-PCR: 72% [95% CI 63.7%–79.0%] in symptomatic individuals vs. 58.1% [95% CI 40.2%–74.1%] in asymptomatic individuals),[6] and have reduced positive predictive values (PPVs) in low prevalence settings. The Cochrane review on this topic estimated that for the devices assessed, at 0.5% infection prevalence, the use of RADTs in asymptomatic people would result in PPVs of 11%–28%, meaning that between 7 in 10 and 9 in 10 positive results would be false positives, and between 1 in 2 and 1 in 3 cases would be missed.[6] It has been argued that the 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

BOX 1: Four main testing scenarios for SARS-CoV-2

Diagnostic	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. Aim is to identify infected individuals, so that medical care can be initiated where appropriate, and infection prevention and control (IPC) and public health measures implemented. Example: testing of a symptomatic person.
Close contact (including outbreaks)	Close contact testing is 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. Close contact testing may be considered a subset of diagnostic testing. Aim is to identify infected individuals, so that medical care can be initiated where appropriate, and IPC and public health measures implemented. Example: testing of an asymptomatic household contact.
Screening	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. Aim is to identify unknown cases so that measures can be taken to prevent further transmission. Example: screening of asymptomatic employees in a workplace.
Surveillance	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. Aim is to monitor population-level burden of disease from a public health perspective. Example: wastewater surveillance.

Source: Adapted from the US Centers for Disease Control and Prevention (CDC).[5]

community transmission.[16] While findings from mathematical modelling studies support this hypothesis,[17–19] real-world evidence of effectiveness needs to be evaluated to determine if the expected benefits are realised in practice. Therefore, the aim of this rapid review was to collate and synthesise the empirical evidence on the effectiveness of rapid antigen testing for screening and surveillance of asymptomatic individuals at limiting the transmission of SARS-CoV-2.

2 | METHODS

We conducted a rapid review in accordance with a pre-defined protocol,[20] in keeping with Cochrane rapid review methodology guidance.[21] 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. 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', 'antigen testing' AND 'screening' on Google https://www.google.com/ on 19 July 2021. Government and public health agency websites as outlined in the protocol were searched on 16 July 2021.[20] Cited references and citations from relevant papers were screened using the Web of Science Core Collection database.

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 (Table 1).

TABLE 1 Inclusion and exclusion criteria

PICOS	Inclusion and exclusion criteria
Population	Asymptomatic (or pre-symptomatic) populations, in any setting
Intervention	SARS-CoV-2 rapid antigen testing for the purpose of screening (including serial testing) and surveillance.
Comparator(s) (if relevant)	No testing, or laboratory-based RT-PCR.
Outcome	Primary outcomes ▪ transmission outcomes (e.g., infection rates, onward transmission [as measured by whole genome sequencing or contact tracing]). Secondary outcomes ▪ biological outcomes (e.g., concordance with RT-PCR or viral culture positivity) ▪ mortality ▪ healthcare utilisation outcomes (e.g., hospitalisation, intensive care unit (ICU) rates) ▪ behavioural outcomes (e.g., adherence to self-isolation, uptake of testing, knowledge, attitudes and beliefs) ▪ costs, resources and cost-effectiveness outcomes (e.g., cost per quality-adjusted life year [QALY] gained) ▪ time in quarantine/isolation (e.g., as a result of being identified as a positive case or close contact) ▪ time present for in-person education (e.g., for second- and third-level students).
Study design	Include: ▪ primary research studies including interventional studies, observational studies, ecological studies, and epidemiological investigations, of SARS-CoV-2 rapid antigen testing, where the aim of testing was screening or surveillance. ▪ single or serial rapid antigen testing studies. Exclude: ▪ animal studies ▪ mathematical and statistical modelling studies ▪ diagnostic test accuracy studies (except where these have relevant transmission outcomes) ▪ studies without the primary outcome of interest ▪ studies where rapid antigen testing was used for diagnostic or close contact purposes (that is, in symptomatic individuals, in close contacts or in outbreak situations) ▪ studies relating to non-SARS-CoV-2 infectious diseases ▪ reviews ▪ media reports and press releases ▪ editorials and opinion pieces.

A second reviewer double screened all excluded full-text articles (Supplementary material A).

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 Quality Assessment Tool was used for the quality appraisal of included studies.[22]

Key epidemiological indicators relating to SARS-CoV-2 incidence, Covid-19 vaccination and variants of concern were extracted for the purpose of describing the national epidemiological situation at the time the included studies took place. These data were extracted from the Oxford Martin School, University of Oxford (Our World in Data)[23] and CoVariants.org[24] on 30 July 2021. This rapid review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement.[25]

3 | RESULTS

3.1 | Search findings

A total of 1222 records were identified (1210 via databases up until 19 July 2021 and 12 via other methods, Figure 1). Among the records identified via database searching (n = 1210), the titles and abstracts of 837 records were screened for relevance following removal of duplicates, with 72 full texts assessed for eligibility and 63 subsequently excluded. Of the 12 records identified via website and citation searching, 2 were excluded. At the end of this process, 19 reports in total were included in this review,[26–44] 9 of which were identified via databases[30–33,35,37,39–41] and 10 via other methods.[26–29,34,36,38,42–44] These 19 included reports refer to 16 unique studies (Figure 1).

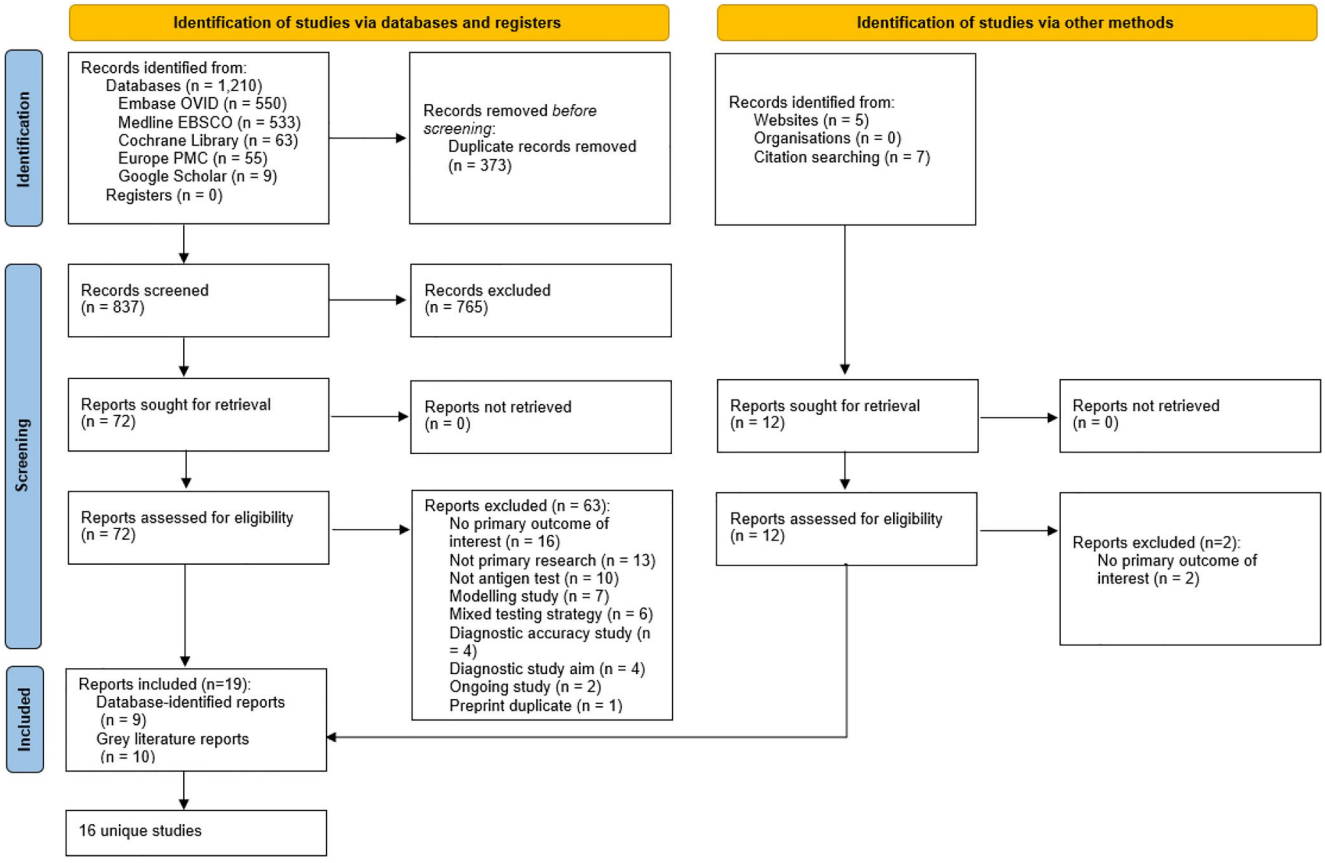

FIGURE 1 PRISMA 2020 flow diagram of included studies. *Record*—The title or abstract (or both) of a report indexed in a database or website (such as a title or abstract for an article indexed in Medline). Records that refer to the same report (such as the same journal article) are 'duplicates'; however, records that refer to reports that are merely similar (such as a similar abstract submitted to two different conferences) are considered unique. *Report*—A document (paper or electronic) supplying information about a particular study. It could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information. *Study*—An investigation, such as a clinical trial, that includes a defined group of participants and one or more interventions and outcomes. A 'study' might have multiple reports. For example, reports could include the protocol, statistical analysis plan, baseline characteristics, results for the primary outcome, results for harms, results for secondary outcomes and results for additional mediator and moderator analyses

3.2 | Characteristics of included studies

Of the 16 included studies, 8 examined the effectiveness of RADTs for population-level screening,[27,28,30–33,36–38,40,42] 4 for pre-event screening (e.g., concerts and football matches),[26,29,34,39] and 4 for serial testing (schools,[43] a prison,[44] a university sports programme for athletes and staff,[35] and in care homes; Table 2; Supplementary material B).[41] The eight population-level screening studies referred to programmes that occurred in England (Liverpool),[31,32,42] Wales (Merthyr Tydfil and Lower Cynon Valley),[27,38] Slovakia (whole-country)[30,33,37] and Italy (South Tyrol).[28,36,40]

The four pre-event screening studies, as well as the Italian population-based screening programme, used once-off rapid antigen testing[26,28,29,34,36,39,40]; the prison testing programme conducted two whole-of-prison testing campaigns 30 days apart[44]; the schools testing programme was undertaken every 14 days[43]; for the Slovakian population-level screening programme, four rounds of testing were undertaken with a gap of 1–2 weeks between each round[30,33,37]; for the care home testing programme, staff were tested twice a week[41]; while the intercollegiate sports programme involved daily rapid antigen testing of students and staff.[35] The English and the Welsh population-based screening programmes allowed individuals to avail of repeated antigen testing over the course of the study.[27,31,32,38,42] The interval between testing and event admission varied between same day for the Barcelona and Fieldlab events[29,34,39] to 24–36 h depending on the pilot (of which there were nine) for the UK Events Research Programme (ERP).[26]

The sample size varied substantially between the included studies, with the largest involving over 5.2 million RADTs conducted in Slovakia,[30,33,37] and the smallest involving 188 cases across two specific outbreaks that occurred with daily antigen testing in the United States.[35] All 16 included studies used RADTs for the purpose of screening in asymptomatic populations; none used them for surveillance in accordance with the definitions outlined in Box 1. Four of the included reports provided some additional information on the economics of asymptomatic screening or surveillance using RADTs.[27,30,36,38]

3.3 | Context: Public health measures and restrictions

All four population-based screening programmes, reported in eight studies[27,28,30–33,36–38,40,42] were initiated in the context of high SARS-CoV-2 incidence and relatively stringent background public health restrictions. All of the four countries undertaking population-based screening programmes had re-imposed a lockdown within several weeks of commencing antigen testing in light of the rapidly deteriorating epidemiological situation and the emergence of variants of concern across Europe.[45]

The number and intensity of public health measures implemented varied across studies, and no study relied solely on RADT for mitigation. Besides antigen testing, the most commonly implemented public health measures were health screening (e.g., temperature or symptoms)[26,29,34,35,39,41] contact tracing,[26,29,34,35,39,41] and wearing of face masks.[26,29,34,35,39,41]

3.4 | Study findings

3.4.1 | Population-level screening

Liverpool

The Liverpool Covid-SMART community testing pilot was a public health intervention, open to everyone aged over 5 years old without symptoms in the city of Liverpool.[42] Between 6 November 2020 and 30 April 2021, 283,338 Liverpool residents, comprising 57% of the eligible population, took an RADT; testing was voluntary. This pilot used only supervised self-sampling. A total of 739,553 RADTs were conducted, of which 6300 (0.9%) were positive.

The authors modelled the relative change in case detection rates before and after the introduction of community testing in Liverpool, compared to the change in case detection rates in similar local authorities over the same time periods, as a log linear Poisson regression model. Compared with a synthetic control the authors estimated that the community testing pilot was associated with an 18% (95% confidence interval [CI], 7%–29%) increase in case detection, equivalent to an additional 4766 cases (95% CI, 1878–7940) 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. The authors' pessimistic model estimated that 850 (95% CI, 500–1350) infections were prevented, whereas their optimistic model suggested that 6600 (95% CI, 4840–9070) 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. 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.

The researchers' estimated impacts of the pilot 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 (ranging from 19% initially to a peak of 79% after implementation of a dedicated testing site). 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.

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.[30,33,37] Coinciding with the introduction of a national lockdown, a pilot took place between 23 and 25 October in the four most

TABLE 2 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[a]	Total vaccine doses administered per 100 people nationally[a]	Share of the national population fully vaccinated (%)[a]	Overall quality rating[b]
Population-level screening										
University of Liverpool (2021)	England	6 Nov 2020–30 Apr 2021	Before-after 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	Before-after 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[c] (2021)	Slovakia	23 Oct – 7 Nov 2020	Before-after 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[c] (2021)	Slovakia	23 Oct – 7 Nov 2020	Before-after 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[c] (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
Pagani[d] (2021)	Italy	20-22 Nov 2020	Before-after study	General population of South Tyrol	Screening (voluntary)	361,781 RADTs	20 Nov = 799	20 Nov = 0	20 Nov = 0	Poor
Ferrari[d] (2021)	Italy	20-22 Nov 2020	Before-after study	General population of South Tyrol	Screening (voluntary)	361,781 RADTs	20 Nov = 799	20 Nov = 0	20 Nov = 0	Fair
Ricco[d] (2021)	Italy	20-22 Nov 2020	Before-after 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	Before-after study	9 mass gathering events	Screening (mandatory)	58,103 participants across 9 events	17 April = 44 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)	1047 participants	12 Dec = 219	12 Dec = 0	12 Dec = 0	Fair
Llibre (2021)	Spain	27 Mar 2021	Before-after study	1 concert	Screening (mandatory)	5000 participants	27 Mar = 153	27 Mar = 15	27 Mar = 5	Fair
Fieldlab (2021)	The Netherlands	27 Mar 2021	Before-after study	1 football match	Screening (mandatory)	5108 participants	27 Mar = 566	27 Mar = 12.7	27 Mar = 3.3	Fair
Serial testing- sports programme										
Moreno (2021)	US	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 2020–10 Jan 2021	Descriptive epidemiological analysis alongside a qualitative exploratory study	11 care homes	Screening: care home staff (mandatory, but poor adherence)	1638 RADTs on 407 staff	1 Dec = 343 10 Jan = 1158	1 Dec = 0 10 Jan = 4	1 Dec = 0 10 Jan = 1	Fair

TABLE 2 (Continued)

First author (year)	Country	Dates	Study design	Setting	Aim of testing	Sample size	National 14-day incidence rate per 100,000 population[a]	Total vaccine doses administered per 100 people nationally[a]	Share of the national population fully vaccinated (%)[a]	Overall quality rating[b]
Serial testing - schools										
Lanier (2021)	US	30 Nov 2020–20 Mar 2021	Before–after 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	Repeated cross sectional 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

Abbreviations: RADT, rapid antigen detection test; RCT, randomised controlled trial.

[a]Source: Oxford Martin School, University of Oxford (Our World in Data; extracted on 30 July 2021).

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

[c]All three studies evaluating the Slovakian population-level screening programme conducted unique analyses of the same dataset.

[d]All three studies evaluating the Italian population-level screening programme conducted unique analyses of the same dataset.

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. Samples were taken by trained medical personnel. Additionally, those who tested positive by RADT along with their household members and self-traced recent contacts 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.[46] The results from the third round of mass testing were not discussed in any of the included studies.

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. Overall, an estimated €30 million was spent on military staffing, €52 million was spent on rapid antigen test kits,[30] and the programme involved over 60,000 personnel.[37]

Pavelka et al. conducted a before–after study and estimated changes in prevalence based on changes in RADT positivity between rounds of testing.[37] 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, 57–58%) within 1 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, 81–83%) between the pilot and round 2. Assuming an epidemic growth of 4.4% (95% CI, 1.1%–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%–73%).

There have been a number of criticisms of this study, the most fundamental of which is the use of RADT positivity to measure changes in SARS-CoV-2 prevalence between rounds.[47] 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. Additionally, 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.

Kahanec et al. conducted a before–after study of the mass testing programme.[33] 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 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. 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 3 weeks after the second round of mass testing, the estimated impact of repeated mass testing on R_0 was statistically indistinct from zero. 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.[33]

A mathematical modelling study based on data from the mass testing programme in Slovakia was conducted by Frnda et al.[30] 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 concluded that mass antigen testing in areas of high prevalence can reduce the incidence significantly, but in low prevalence regions, the benefit of such testing is questionable. However, there are significant concerns regarding the underpinning assumptions for the associated models (e.g., assuming 100% sensitivity of RADTs for detecting infectious cases).

South Wales

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. The pilot was voluntary and was open to anyone without symptoms. The tests were conducted in test centres, however it is unclear if swabs were professionally sampled or self-sampled under supervision. In total, 55,765 RADTs were performed, with uptake rates of 49% and 56% observed in Merthyr Tydfil and lower Cynon Valley, respectively. 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).[38]

In order to model the impact of the testing pilot, the authors used the reproduction number (Rt) in Merthyr Tydfil at the time of the study and a series of assumptions regarding the natural history of the infection and performance of the test to estimate the number of outcomes prevented. These were applied to a time-lagged regression model, resulting in the authors estimating that 353 cases (95% CI, 306–409; both asymptomatic and symptomatic), 24 hospitalisations (95% CI, 16–36), five ICU admissions (95% CI, 3–6) and 14 deaths (95% CI, 11–19), were prevented by the implementation of the pilot. The estimated 353 cases prevented represents 12.2% (95% CI, 10.6–14.1%) of cases that would have occurred in a 6-week period; on the assumption of these cases being avoided, the authors in turn estimated a 6%–12% reduction in burden on the healthcare system.[38]

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 this pilot, 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 £2143 to £2292 per quality-adjusted life year (QALY) gained. Net monetary benefit for the intervention, which represents cost savings plus the value of QALYs gained (valued at £60,000 per QALY), was estimated to be £5.8 million to £6.2 million.[27,38] However, 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 in the study. Additionally, no comparator was included in the economic evaluation and hence the ICER is based on the potential cost savings and QALY gains arising from mass testing versus no testing at all, which may be an oversimplification of policy approaches. Based on the assumptions and models used in this study, the authors concluded that mass testing using RADTs is effective in preventing cases, hospitalisations and deaths and is a cost-effective intervention. In addition to the concerns noted above regarding the validity of the economic model structure and model inputs, it is important to note that this was a relatively small study conducted over a short period of time, and, as such, the data which emerged from the study and informed the authors' estimates should be treated with caution.

North-Eastern Italy

Three studies by three different research teams evaluated the impact of a population-based screening programme in South Tyrol in North-Eastern Italy between 20 and 22 November 2020.[28,36,40] All residents were invited to participate in the mass antigen testing programme, which was voluntary. Samples were taken by trained medical personnel. The mass testing programme involved almost 2000 staff and cost an estimated €4.5 million.[36]

In total, 361,781 RADTs were conducted; this equated to a 72.3% uptake rate among the eligible population ($n = 500,607$). There was an RADT positivity rate of 1% ($n = 3619$ positive tests).

Pagani et al. conducted a before–after study and estimated that the R_0 decreased from a peak of approximately 1.8 on 3 November to a low of 0.6 by 24 November and plateaued at around 0.7 until 6 December.[36] Between 24 November and 11 December 2020, the observed number of SARS-CoV-2 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 were truncated and no additional information was provided beyond 6 December, despite a rise in case numbers over the Christmas period, in line with the surge in the Alpha variant.

Ferrari et al. conducted a before–after study based on data from the mass testing programme in South Tyrol.[28] 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%–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 the interpretation of the findings.

Ricco et al. conducted an analysis comparing cases in South Tyrol with neighbouring provinces Trentino (in Italy) and Tyrol (in Austria), where population-level screening was not conducted.[40] During November 2020, South Tyrol experienced a surge of SARS-CoV-2 cases, which was double the rate of the bordering Italian region of Trentino, and the Austrian State of Tyrol. The authors found that after population-level screening 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 32.0–36.9 for South Tyrol, vs. 35.0 per 100,000, 95% CI 33.1–37.0, for Trentino), but still higher than that for Tyrol (10.5 per 100,000 inhabitants, 95% CI 9.7–11.2). 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.

3.4.2 | Pre-event screening

UK Events Research Programme (ERP)

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 UK ERP.[26] All nine events required a negative RADT for entry, taken 24–36 h prior to admission. Participants were also asked to take voluntary RT-PCR tests, before the event (on the same day) and 5 days after the event, for research purposes; however, these were not a requirement for entry. While professionally administered RADTs conducted at asymptomatic testing sites 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 (unsupervised).

Across all nine pilot events, a total of 28 RT-PCR positive cases were identified, all of whom would have required negative RADT for entry. Of these, 11 were identified as potentially infectious at an event (through same-day testing) and a further 17 were identified as potentially infected at or around the time of an event (through day 5 testing). No substantial outbreaks were identified by public health 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.

Caution is urged with regard to the interpretation of this study given that SARS-CoV-2 was not circulating widely in the community in England at the time, the very low uptake (15%) of pre- and post-event RT-PCR tests, along with the limited scale, scope and design of these Phase 1 pilots.

Barcelona concerts

Two studies by the same research group were conducted in Barcelona, Spain, to evaluate the effectiveness of pre-event RADT screening, plus respirator mask usage and adequate ventilation, without social distancing, at preventing SARS-CoV-2 transmission at live indoor music concerts.[34,39]

A randomised controlled trial (RCT) was conducted on 12 December 2020.[39] All study participants with a negative antigen test (tested by trained nurses within 9 h 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). A total of 1047 participants with a negative pre-event antigen test were randomised. 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%–0.61%) versus 2 out of 495 controls (0.31%; 95% CrI: 0.04%–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 1000 per arm.

A follow-on study was conducted on 27 March 2021 with a larger sample size (n = 5000), using a before-–after study design without a control group.[34] Same-day pre-event RADT screening was performed by trained nurses for all 5000 attendees. Of the 5000 people screened by RADT, 6 were found to be positive and 2 were close contacts of these positive cases, and so a total of 8 people were not allowed to enter the music event. The authors found that six attendees, none of whom were vaccinated, were diagnosed with SARS-CoV-2 infection within 2 weeks after the concert.

Fieldlab events

A comprehensive national event pilot programme called 'Fieldlab events' was conducted in the Netherlands.[48] 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. The included Fieldlab study examined the use of RADT in conjunction with other public health measures (e.g., temperature screening, reduced capacity and face mask use) at a football match that took place on 27 March 2021, which involved 5108 participants.[29] Same-day antigen testing (sample taken by a professional) was required for entry. Of the 5108 participants tested, 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 5 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. While RADT screening may have reduced the transmission rate at the football match, it is difficult to be certain because other factors, including mask wearing and reduced mixing in hospitality venues before and after the event, may also have played a part.

3.4.3 | Serial testing

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 self-sampled, directly observed daily antigen testing.[35]

In the first outbreak, 32 confirmed cases occurred within a university athletics programme after the pre-symptomatic 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. 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 congregated settings.

Liverpool care homes

This study by Tulloch et al. was conducted as part of the Liverpool Covid-SMART community testing pilot.[41] This descriptive epidemiological analysis, alongside a qualitative exploratory study, was conducted in 11 care homes in Liverpool from 1 December 2020 until 10 January 2021.

According to the testing protocol, care home staff were to be tested twice a week using self-administered RADTs. An RT-PCR test was performed simultaneously alongside the second test each week as part of the existing testing regime. During the study, 1638 RADTs were performed on 407 staff, of whom 5 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, 6 of these 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.

Utah high schools

Lanier et al. described the implementation of a RADT screening programme in high schools in Utah, United States, between November 2020 and March 2021.[43] 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 every 14 days, performed by trained school staff and supported by local public health departments. Students who received a positive test result were required to isolate for 10 days, and their close contacts were required to quarantine for 10–14 days.

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 67% of all high school students participating in extracurricular activities. Of the 50,400 students, 1771 (3.5%) had a positive result. 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 for this study, the effectiveness of this testing programme, compared with similar schools who did not participate, remains unclear.

Italian prison

Stufano et al. conducted a repeated cross-sectional study of a comprehensive mitigation plan in a prison in Bari, Italy.[44] 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 h and again after 7 days), health screening, face masks, hand sanitiser, physical distancing, congestion control, cohorting and contact tracing. Two voluntary rapid antigen testing campaigns were carried out among prisoners and staff. Samples were taken by trained medical personnel. A total of 426 and 480 prisoners partook in rounds 1 and 2 of testing, respectively. Two prisoners tested positive in round 1 and none tested 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. 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 comparators prevents ascertainment of the added benefit of the testing campaign to the existing measures.

3.5 | Quality appraisal

Overall, 10 of the 16 studies were rated as 'fair' quality[26,28,29,31–35,39,41,42,44] and 6 were rated as 'poor' quality.[27,30,36–38,40,43] No study was rated as 'good' quality (the highest quality rating; Supplementary material C).

4 | DISCUSSION

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 inconsistent results, 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. No studies were identified regarding the use of rapid antigen testing for surveillance of asymptomatic individuals.

While screening at a population-level using RADTs was reported by study authors in seven of the eight studies,[27,28,30–33,36–38,42] to be effective at reducing SARS-CoV-2 transmission, 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 restrictions. The reported estimated effect on transmission varied from minimal change in one study[40] to an 82% reduction in prevalence after three rounds of testing in another study,[37] highlighting the significant uncertainty regarding the effectiveness of this intervention. Notably, the comparator groups in these studies were largely modelled and hypothetical, sometimes based on questionable assumptions.[27,28,30,37,38,42] 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.[33] Moreover, it was evident that these population-based screening programmes were resource intensive,[27,30,36,38] with uncertainty regarding their cost-effectiveness.[27] Additionally, despite the population-level screening programmes' stated objective of only testing asymptomatic individuals, it is possible that some people with symptoms may have attended as a means of rapidly availing of a test. This may have influenced the pick-up rate of the programmes given that there is a higher PPV for RADTs in symptomatic individuals[6]; however, it may have also provided these individuals with a false sense of security given that the sensitivity of RADTs is lower than that of RT-PCR,[6] hence potentially facilitating riskier behaviours.[49] Better quality studies are needed to determine the effectiveness of RADT-based screening 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, and the conduct of an economic evaluation.[4]

While there was some evidence that repeated mass testing using RADTs may have had a short-term effect on limiting SARS-CoV-2 transmission,[33] the Liverpool Covid-SMART community testing pilot was unable to mitigate the surge of cases that occurred during December 2020–January 2021.[42] This finding suggests that any potential transmission-limiting effect of this population-level screening programme may have been insufficient to counter the increased transmissibility associated with the Alpha variant, which became the dominant strain during this period. This may suggest that in order to have had an impact, this programme would have required greater intensity, frequency and duration of testing, with consequent questions about feasibility and cost-effectiveness.[50] These studies and contextual factors support that RADTs should supplement, rather than replace, other public health measures and restrictions as a part of a potential mitigation strategy.

In relation to the use of RADTs for pre-event screening or serial testing, the additional benefit of RADTs over and above that of other public health measures is still unclear, especially if the prevalence of SARS-CoV-2 is low. A recent review found that implementing a package of public health measures, which could include RADTs, may reduce the risk of SARS-CoV-2 transmission at mass gatherings; however, it was not possible to determine the impact of any single measure.[51] The requirement for trained professionals to obtain or supervise samples and administer RADTs at events, presents additional logistical and cost implications, but is arguably necessary to ensure that testing is rigorous, of high quality, and prevents gaming of the system (e.g., by using someone else's test result or conducting minimal inadequate swabbing). For example, the study by Revollo et al. required 45 nurses and 1 physician to collect nasopharyngeal swabs from all 1047 eligible participants before the event.[39] Of note, this study did not detect any positive cases using RADTs pre-event. However, knowledge of planned pre-event testing may have acted as a deterrent for prospective attendees who were aware that they had symptoms or that they had been recently exposed to SARS-CoV-2. Awareness of the planned pre-event testing could also have altered prospective attendees' behaviours to engage better in mitigation measures in the days leading up to the event.

A recently published study found that the intensive Danish mass testing strategy (using both RT-PCR and RADTs) did not significantly reduce the prevalence of SARS-CoV-2 and had no impact on the number of hospitalisations.[52] The authors suggested that the mass testing may have increased risk behaviours of those tested, or that

antigen testing may have occurred too late in the course of the infection to prevent onward transmission, hence contributing to the spread of infection in the community. It is important to note that while RADTs can reliably detect some of those most likely to be infectious at the time of testing, transmission can still occur in those with high cycle threshold (C_t) values (indicative of low viral load) with no accepted cut-off of C_t values at which the risk of transmission is eliminated.[53] This point is illustrated in the study by Moreno et al., where screening missed some infectious cases despite the implementation of mandatory directly observed daily antigen testing.[35]

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.[26,27,29,30,34,36,38,39,41,42] For example, the largest of the included screening programmes that took place in Slovakia involving over 5 million RADTs, cost over €82 million,[30] and involved over 60,000 personnel.[37] 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, despite the high risk setting.[41] In the population-level screening 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.[32,38,42] Given uncertainty surrounding the clinical- and cost-effectiveness of RADT-based screening 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 as this could exacerbate health inequalities.[32,54]

4.1 | Strengths and limitations

A strength of this rapid review 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 policy-makers (such as infection and hospitalisation rates), rather than technical performance issues (such as sensitivity and specificity).[55]

A number of limitations need to be considered when interpreting the findings of this rapid review. Only one included study was an RCT,[39] and hence for the majority of included studies, there may have been inherent differences between populations in the intervention and comparison groups. It is unclear to what extent the implementation of RADT screening might influence population behaviour in relation to adherence to other mitigation measures. That is, knowing that individuals are due to be screened may increase awareness and adherence, or equally it could plausibly give rise to risk compensation. Therefore engaging in screening may change behaviour in a manner that alters the effect of the intervention relative to the counterfactual of no screening. This creates challenges for evaluating an intervention in the absence of a randomised control group.

Importantly, all included studies were published on or before 19 July 2021 and were, therefore, conducted before the emergence of the Delta or Omicron variants of concern. The Covid-19 epidemiological situation can change rapidly due to variants, and this may have implications for the diagnostic test accuracy of RADTs, both in terms of causing increased prevalence and hence higher PPVs,[56] or the development of mutations that can affect the ability of the test to detect the target antigens on the surface of the virus.[57,58] Hence the findings of the included studies may have limited transferability to settings where the dominant variant is associated with significantly different patterns of transmission.

All studies had noted methodological issues with none being assessed to be of 'good' quality, which lowers the overall certainty of the evidence. Additionally, 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.[59]

5 | CONCLUSIONS

Overall, there is uncertainty regarding the effectiveness of RADTs for screening in asymptomatic individuals, with no evidence found regarding their use for surveillance purposes at the time of writing. It is important to note that the studies included within this review were conducted before the emergence of the Delta and Omicron variants. As such, it is possible that the findings may be specific to scenarios of transmission that pre-dated these variants. Given uncertainty surrounding the clinical- and cost-effectiveness of RADT-based screening programmes in asymptomatic individuals to limit the transmission of SARS-CoV-2, more real-world research evidence in relevant settings, which is of good quality and timely, as well as economic evaluation, is required to inform public policy on the widespread use of RADTs in asymptomatic individuals. In light of these uncertain results from empirical evidence, data on the effectiveness of RADT screening based solely on modelling should be interpreted with caution. Where RADTs are being considered for screening asymptomatic populations, these should be considered as an additional public health measure, rather than a replacement for known mitigation measures (such as face masks, vaccination and physical distancing).

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CONFLICT OF INTEREST

No conflict of interest declared.

AUTHOR CONTRIBUTIONS

Kieran A. Walsh, Christopher G. Fawsitt, Susan Ahern, Katie M. O'Brien and Natasha Broderick scoped the question; Marie Carrigan constructed the systematic search; Kieran A. Walsh and Natasha Broderick screened titles/abstracts and full texts and completed the data extraction and quality appraisal. All authors were involved in the interpretation of the data. Kieran A. Walsh drafted the manuscript. All authors reviewed and contributed to the manuscript. All authors agreed the final version of the manuscript to be published.

ETHICS STATEMENT

Ethics approval was not required for this study as it involved a review of the published literature.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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