

# Options for the use of rapid antigen detection tests for COVID-19 in the EU/EEA – first update

26 October 2021

## Key messages

- Rapid antigen detection tests (RADTs) can contribute to overall COVID-19 testing capacity, offering advantages in terms of shorter turnaround times and reduced costs, especially in situations in which Nucleic Acid Amplification Testing (NAAT) capacity is limited.
- RADTs can help reduce further transmission through early detection of highly infectious cases, enabling a rapid start of isolation and contact tracing.
- RADTs are sensitive enough to detect cases with high viral load, early in the course of infection in pre-symptomatic and early symptomatic cases up to five days from symptom onset.
- The predictive value of RADTs is highest in settings where SARS-CoV-2 prevalence is high.
- RADTs are less sensitive than NAATs, especially in asymptomatic patients.
- RADTs can also be used in low prevalence settings to rapidly identify infectious cases with high viral load.
- Proper clinical validation studies should be done before introducing new tests in the different settings.

## New information in this document

- The EU Health Security Committee (HSC) established a technical working group on COVID-19 diagnostic tests which has agreed on a common, frequently updated list of COVID-19 RADTs that meet defined performance criteria.
- Despite the emergence of virus variants, no reduction in test sensitivity has been observed so far.
- Studies on the performance of RADTs in vaccinated individuals infected with SARS-CoV-2 have not yet been published.

## Changes in advice for the use of RADTs in this document:

- ECDC agrees with the World Health Organization (WHO) minimum performance criteria of  $\geq 80\%$  sensitivity and  $\geq 97\%$  specificity, but also advocates for the use of higher performance tests ( $\geq 90\%$  sensitivity and  $> 98\%$  specificity). In low prevalence settings and/or if RADTs are to be used to certify recovery, RADTs with a high specificity ( $> 98\%$ ) are preferable for first-line testing to reduce false positive results.
- Contact tracing testing algorithms have been revised to differentiate between vaccinated and unvaccinated contacts of COVID-19 cases.
- Laboratories should remain vigilant to identify reductions in RADT sensitivity or specificity due to the potential emergence and circulation of new SARS-CoV-2 variants.

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# 1. Scope of this document

On 28 October 2020, a European Commission Recommendation on COVID-19 testing strategies, including the use of rapid antigen detection tests (RADTs) was published [1]. That recommendation called for European Union/European Economic Area (EU/EEA) Member States to agree on criteria to be used for the selection of RADTs, and to share and discuss information regarding the results of validation studies.

In November 2020, ECDC published a technical report defining the 'Options for the use of rapid antigen detection tests (RADTs) for COVID-19 in the EU/EEA' [2], also summarised in Commission Recommendation 2020/1743 [3].

In February 2021, the EU Health Security Committee (HSC) established a list of mutually-recognised RADTs for public health measures, including those related to travel, together with a definition of clinical performance criteria [4]. Diagnostic tests to detect COVID-19 have been further developed during the pandemic and in this context, the HSC established a Technical working group (HSC TWG) on COVID-19 diagnostic tests in May 2021. As a result, the common list of mutually-recognised COVID-19 RADTs is frequently updated [4]. The work of this group is presented in this document.

This document is the first update of the technical report 'Options for the use of rapid antigen detection tests (RADTs) for COVID-19 in the EU/EEA' [2]. It is intended to facilitate further discussions between Member States on the settings and purpose for which it is appropriate to use RADTs and summarises key considerations for their implementation. Reaching an agreement on settings and performance criteria will be critical for the success of EU/EEA-wide surveillance purposes and for measures related to cross-border travel.

## 2. What is new in this document?

- Recommendations regarding the use of higher sensitivity and specificity tests in accordance with the HSC technical working group recommendations;
- Latest evidence on performance characteristics of available RADTs;
- Implications for RADTs performance of new circulating variants;
- Implications for RADTs performance of the increase in vaccination coverage;
- Considerations for the use of RADTs for the detection of SARS-CoV-2 and to certify recovery of an individual from COVID-19;
- Alignment with updated recommendations for contact tracing of vaccinated and unvaccinated contacts.

## 3. Summary

Throughout the pandemic, nucleic acid amplification tests (NAAT) have remained the gold standard for detecting SARS-CoV-2 infection, as they are characterised by both high sensitivity and specificity in detecting viral ribonucleic acid (RNA). However, RADTs that are easy to use and offer rapid results at low cost have been increasingly used in EU/EEA countries. Since December 2020, the EU case definition for COVID-19 includes the detection of antigens in the clinical specimens and therefore the use of RADTs as a diagnostic method [5].

RADTs offer multiple operational benefits in comparison to NAATs, such as reverse transcription polymerase chain reaction (RT-PCR) tests, for the detection of SARS-CoV-2. They can be used as near-patient (point-of-care) tests and results are normally generated in 10 to 30 minutes after the start of the analysis, and at low cost. Many currently available RADTs show a lower sensitivity compared to the standard RT-PCR test, while their specificity is generally reported to be high. It is important to note that RADTs are sensitive enough to detect cases with a high viral load, i.e. pre-symptomatic and early symptomatic cases (up to five days from symptom onset; or low RT-PCR cycle threshold (Ct) value <25). Such cases are likely to account for a significant proportion of transmissions. The predictive value of RADTs varies depending on the prevalence of the virus in the setting and the performance characteristics (i.e. sensitivity and specificity) of the specific test. A low positive predictive and high negative predictive value are expected in low prevalence settings and therefore it is recommended that positive results are confirmed by a second method (preferably NAAT or another RADT of different brand). It needs to be noted that a lower positive predictive value in such settings is similarly expected with any test type, including NAATs, and is variable depending on the expected specificity of each test. RADTs should be applied in a way that compensates for the lower sensitivity compared to NAAT, i.e. by including repeat testing for screening purposes and confirming test results by NAAT when appropriate.

Diagnostic testing for SARS-CoV-2 is a critical component to the overall prevention and control strategy for COVID-19. All SARS-CoV-2 testing should be linked to public health actions to ensure appropriate clinical care of patients and to carry out contact tracing to break chains of transmission. WHO recommends RADTs that meet the minimum performance requirements of  $\geq 80\%$  sensitivity and  $\geq 97\%$  specificity [6]. The HSC TWG

recommends RADTs that show clinical performance of  $\geq 80\%$  (for all samples) to  $\geq 90\%$  sensitivity (for samples with  $Ct < 25$ ) and  $> 98\%$  specificity to certify testing for COVID-19 [4]. ECDC agrees with the minimal criteria set by WHO and advocates for the use of tests with a performance closer to NAAT, i.e.  $\geq 90\%$  sensitivity (for samples with  $Ct < 25$ ) and  $> 98\%$  specificity, fully supporting the recommendations by the HSC TWG.

RADTs can be used for the early detection of cases when NAAT testing capacities are not available and when receiving timely results is critical, e.g. for isolation and contact tracing purposes. RADTs can offer a significant advantage over NAAT in terms of the timeliness of results.

Besides the performance and timeliness of the test, other practical and strategic aspects play a significant role in deciding if a test can be used and for which reason. Examples of such aspects that need to be considered are the scalability, the simplicity of use, instrumentation availability, human and material resources, and overall logistical arrangements for sampling, testing and costs. Even the expected need for confirmatory testing and supplies for those to be carried out needs to be considered. The epidemiological situation per setting, local area, region and nationwide also affects the testing strategy.

The choice of RADT should be based on the HSC common and updated list of COVID-19 RADTs and on independent evaluations of the tests.

The emergence of virus variants triggered general concern about whether the analytical performance of RADTs could be affected. So far, the available data provide reassuring results for the use of RADTs to detect emerging virus variants with only a limited number of reports suggesting lower sensitivity against variants with certain uncommon mutations at the nucleoprotein gene. Although it is likely that performance of RADTs against currently circulating variants will continue to be unaffected, laboratories should remain vigilant to identify reductions in RADTs sensitivity and proper validation studies should be done before introducing new tests in different settings.

In the light of increasing vaccine coverage, questions have been raised about the performance of RADTs in vaccinated individuals infected with SARS-CoV-2, irrespective of virus variants. Studies on this topic have, however, not yet been published.

## 4. General considerations on the use of RADTs for the detection of COVID-19

Timely and accurate COVID-19 testing is an essential part of surveillance, contact tracing, infection prevention and control, and clinical management of COVID-19. ECDC has proposed an objective-driven testing strategy for EU/EEA countries with specific recommendations by level of virus circulation in the community, taking into account available public health resources and testing capacities [7].

Throughout the pandemic, testing for SARS-CoV-2 infection with NAAT has remained the gold standard for detecting SARS-CoV-2 and is characterised by both high sensitivity and specificity in detecting viral ribonucleic acid (RNA).

Diagnostic laboratories routinely perform NAAT tests, which require extraction of viral RNA as well as stationary instrumentation for nucleic acid amplification and detection. Theoretically, the time required to perform the NAAT test is a few hours, but in practice specimens often need to be transported from the place of sampling to the laboratory, and additional time then elapses until the specimen is processed.

Early in the pandemic, most of the testing capacity was reserved to identify cases in hospitals and high risk-settings. Since then, laboratory capacity has increased, and testing has been extended to comprehensively identify symptomatic cases and contacts of cases, and to perform screening programmes.

To complement NAAT testing, countries are increasingly using RADTs and, consequently, have integrated RADTs in their national testing strategies [8-13]. As mentioned above, since December 2020, the EU case definition for COVID-19 includes the detection of antigens in the clinical specimens and therefore the use of RADTs as a diagnostic method [5].

### Benefits and challenges in the use of RADTs

RADTs offer multiple operational benefits in comparison to NAAT tests for detection of SARS-CoV-2. They have been developed as both laboratory-based tests and for near-patient use (point-of-care), and results are usually generated in 10 to 30 minutes after the start of the analysis. The cost of initially isolating some false positives or missing some negative cases may be considered to be offset by the fact that RADTs offer the fastest alternative to identify and isolate infectious individuals. RADTs generally offer low-cost testing and relatively simple handling.

There are also some operational drawbacks associated with the use of RADTs. Sampling for detection of SARS-CoV-2 by RADTs relies mostly on nasopharyngeal specimens, as indicated by the manufacturers. Self-sampling is not currently clinically validated for RADTs. Unlike NAAT, RADTs lack controls for confirmation of appropriate

sampling. As many of the RADTs are processed individually, analysis of large volumes of specimens simultaneously is difficult and multiplex analysis of other respiratory pathogens is, as of today, not possible. An additional drawback with RADTs is that specimens are not usually shipped to public health laboratories, or may not be even suitable, for further virus characterisation, such as sequencing or antigenic characterisation that requires virus isolation.

In contrast to NAAT, which amplifies the virus target sequences, RADTs detect the presence of a viral antigen in the patient's specimen without amplification. As a result, most currently available RADTs show a lower sensitivity compared to the standard NAATs, while their specificity is generally reported to be high and often similar to NAATs [14,15]. RADTs also have a lower risk of contamination of the sample that may be the cause of false positive results when techniques like RT-PCR with very high sensitivity are used [16]. It is important to note, that RADTs are sensitive enough to detect cases with high viral load, i.e. pre-symptomatic and early symptomatic cases (up to five days from symptom onset; or low RT-PCR cycle threshold (Ct) value <25), which likely account for a significant proportion of transmission [17-19].

## EU health preparedness: a common list of COVID-19 RADTs

The HSC agreed on 17 September 2020 on 'Recommendations for a common EU testing approach for COVID-19' [20] setting out various actions for consideration by countries when updating or adapting their testing strategies. The Recommendations included Member States' first experiences with RADTs and their deliberations concerning the settings and situations in which these tests should be used. Since then, the Committee has been discussing the use and application of RADTs in great depth and has brought together a wealth of (technical) information on the types of tests used in European countries and the conditions applied.

On 21 January 2021, Member States unanimously agreed on a Council Recommendation setting a common framework for the use of RADTs and the mutual recognition of COVID-19 test results across the EU [21]. The Council Recommendation called on Member States to agree on three concrete deliverables:

1. A common list of COVID-19 rapid antigen tests that are considered appropriate for use in the context of the situations described in the Council Recommendation, that are in line with countries' testing strategies.
2. A selection of rapid antigen tests of which Member States will mutually recognise the test results for public health measures.
3. A common standardised set of data to be included in COVID-19 test result certificates, further facilitating the mutual recognition of COVID-19 test results.

Based on the information collected by the HSC, and taking into consideration the current epidemiological situation and the testing strategies and approaches that have been put in place across the EU, the document sets out the deliverables as agreed to by Member States [4]. In the context of the COVID-19 pandemic, the HSC established a technical working group (TWG) on COVID-19 diagnostic tests in May 2021, bringing together experts from the 27 EU countries and Norway, as well as representatives from the Directorate-General for Health and Food Safety, the Joint Research Centre (JRC) and ECDC.

The aim of the technical working group is, in particular, to review the proposals put forward by EU countries as well as manufacturers for COVID-19 RADTs to be included in the EU common list of RADTs. The HSC TWG assesses these proposals against the criteria established by Council Recommendation EU 2021/C 24/01 as well as additional criteria that were agreed by the experts on 21 September 2021.

The common list of RADTs tests is reviewed by Member States, and, if necessary, can be updated in line with new results from independent validation studies becoming available and new tests entering the market [4]. These updates, the most recent one published on 20 October 2021, also consider how mutations of the SARS-CoV-2 virus may affect the efficacy of any particular RADT, allowing for the removal of tests if they are no longer deemed effective.

Moreover, the HSC TWG agreed on 6 July 2021 that, for now, the common list only includes RADTs for which their clinical performance was measured based on samples collected from nasal, oropharyngeal or nasopharyngeal specimens and not on alternative sample types like saliva. The common list does not include rapid antigen self-tests. As of July 2021, proposals can be submitted and are assessed for laboratory-based antigenic assays (e.g. ELISA) to be included in a separate list and assessed against the same criteria with RADTs.

A negative test result produced by any of the RADTs included in the EU common list can be used for the issuance of the EU Digital COVID-19 Testing Certificate.

## Current data on performance requirements and test validations

WHO recommends that RADTs that meet the minimum performance requirements of  $\geq 80\%$  sensitivity and  $\geq 97\%$  specificity can be used to diagnose SARS-CoV-2 infections in a range of settings where NAAT is unavailable or where an excessive turnaround time would preclude clinical and public health utility of results [6].

ECDC agrees with the WHO criteria as minimal standards, and in addition, advocates using tests with a performance closer to NAAT, i.e.  $\geq 90\%$  sensitivity and  $>98\%$  specificity, according to the HSC TWG recommendations. ECDC also acknowledges that the tests need to be validated for the intended setting and situation.

While test sensitivities are variable, it is important to note that RADTs' validity is best in symptomatic individuals and in the first five days after symptom onset [14,15]. This is because RADTs have comparable sensitivity to laboratory-based NAATs when viral load in the specimen is high and the person is likely to be most contagious [22,23].

The specificity of RADTs is generally as high as most NAATs, which means that false positive test results are unlikely when an antigen test is used according to the manufacturer's instructions. Indeed, a recent meta-analysis on RADT performance confirmed that average specificities were high even in asymptomatic participants (overall summary specificity 99.6%, 95% CI 99.0% to 99.8%) [15]. Despite the high specificity of RADTs, false positive results will occur, especially when used in settings where the prevalence of infection is low. However, this is a circumstance that is true for all in vitro diagnostic tests that have specificity below 100%, including the NAATs (e.g. RT-PCR).

As the predictive values of all tests are dependent on the epidemiological situation in combination with test performance (i.e. sensitivity and specificity), ECDC suggests, especially in situations of lower COVID-19 prevalence, to use tests with diagnostic performance closer to NAAT, i.e.  $\geq 90\%$  sensitivity and  $>98\%$  specificity, according to the HSC TWG criteria [24]. If tests are intended to be used for verifying an individual's recovery, tests with higher specificity will ensure greater validity of test results.

Generally, RADTs are a suitable tool for detection of infectious persons regardless of the presence of COVID-19 specific symptoms, if the sample is of good quality and enough antigen is present. However, they should be applied in a manner that takes into account their potentially lower performance as compared to NAAT, i.e. by including confirmatory or repeat testing in certain situations (see Figure 1). A risk analysis should be performed that includes the probability of incorrect results, and the potential impact of these on the individuals tested and on the intended public health goals.

## Independent validation studies

Manufacturer-independent evaluations are important to provide an objective assessment of a test's accuracy. Therefore, Foundation for Innovative New Diagnostics (FIND), the global alliance for diagnostics, is conducting prospective diagnostic evaluation studies in collaboration with multiple, independent sites to determine the accuracy of COVID-19 RADTs [25]. Additionally, such reports are listed on the Diagnostics Global Health site [26].

Building on the interim definitions and criteria that were agreed by the experts on 29 June 2021, the TWG agreed, on 21 September 2021, on further definitions, scope, considerations and criteria to be applied to independent validation studies assessing the clinical performance of RADTs for COVID-19 diagnosis. These further definitions, scope, considerations and criteria are used by the TWG when assessing the proposals for new RADTs to be included in the EU common list, in addition to the ones presented in Council Recommendation 2021/24/01 [4].

Agreed definition and considerations of an independent validation study:

- A study that may involve collaborations with or that may involve funding by private entities, however, there is always a public body involved and the study is performed objectively and in the public interest.
- Such a study should be performed by an independent and accredited laboratory, which is a laboratory not owned nor operated by the manufacturer or sponsor of the test, and which is not related to the operator by ownership, familial relationships, nor contractual or other relationships that result in the laboratory being controlled by or being under the common control of the operator.
- Such a study should preferably be based on a prospective clinical field study design, testing unselected symptomatic and asymptomatic participants for SARS-CoV-2 infection.
- 'Unselected' means no prior knowledge of SARS-CoV-2 diagnosis (e.g. determined by PCR); inclusion is allowed based on general possible COVID-like symptoms (or close contact with COVID-19 cases); and exclusion of children is allowed (e.g. under 16 years) or for medical ethical permission reasons.

Agreed clinical performance criteria for independent validation studies:

1. Prospective clinical field studies:
  - A sensitivity of over 80% when testing unselected symptomatic participants within the first seven days after symptom onset or asymptomatic participants, where the diagnosis is confirmed by RT-PCR in independent field studies, will be accepted.

OR

In independent evaluations of unselected participants, assays should have a sensitivity of 90% or greater for subjects with a Ct < 25.

- The study population shall be clearly defined, stating the inclusion criteria of participants (symptomatic individuals, close contacts or asymptomatic individuals without known exposure). Ideally, the sensitivity for each group should be discernible from the report. The RT-PCR protocol and the distribution of Ct values should be described. Samples should represent naturally occurring viral loads.
  - Target population considered in the context of an independent validation study should be based on at least 100 RT-PCR positive samples and at least 300 RT-PCR negative samples. Each specimen type should be evaluated separately.
  - In case of multiple smaller prospective clinical field studies that do not meet the minimum number of positive and/or negative samples separately but that do meet all the other criteria as agreed by the TWG, the number of samples may be combined, provided that the different studies applied the same or similar methodologies and that sufficient details are provided on their study design.
  - Assays should have a specificity over 98%.
  - In line with the [MDCG Guidance on performance evaluation of SARS-CoV-2 in vitro diagnostic medical devices](#), preference is given to samples being compared against RT-PCR results on nasopharyngeal swabs. However, in independent validation studies, samples can also be compared against RT-PCR results on oropharyngeal or nasal swabs if reasoning is provided (e.g. when assessing the clinical performance of rapid antigen tests among children).
2. Retrospective in vitro studies:
- A sensitivity over 80% when testing all specimen in the reference panel will be accepted;
- OR
- Assays should have a sensitivity of 90% or greater for subjects with a Ct < 25.
- The composition of the reference panel should be as follows:
    - A panel of at least 50 pooled clinical specimens that cover naturally occurring viral loads with SARS-CoV-2 concentration ranging from approximately  $1.1 \times 10^9$  to  $4.2 \times 10^2$  genome copies per mL of specimen [https://ec.europa.eu/health/sites/default/files/md\\_sector/docs/mdcg\\_2021-21\\_en.pdf](https://ec.europa.eu/health/sites/default/files/md_sector/docs/mdcg_2021-21_en.pdf) 7 and Ct values between 17 and 36.
    - The whole evaluation panel should be subdivided into three subgroups: panel members, which are characterised by:
      - Very high viral load (Ct value 17-25; about 40% of the total number of pooled clinical specimens);
      - High viral load (Ct value 25-30; about 40% of the total number of pooled clinical specimens);
      - Moderate viral load (Ct value 30-36; about 20% of the total number of pooled clinical specimens).
    - For each pool, up to ten clinical respiratory specimens (nasopharyngeal/oropharyngeal) obtained for routine diagnostics with different virus loads may be used. The sample volume per panel member should be sufficient to allow comparative evaluation with different tests included in the evaluation.
    - RT-PCR needs to be applied to determine the RNA load per pool.
    - Ethical approval by an institutional review board is mandatory.
    - For each rapid antigen test and panel member, a pre-defined aliquot needs to be completely absorbed using the specimen collection device, e.g. swab, provided with the respective test.
    - Further steps need to be strictly performed following the respective instructions for use (IFU).
    - The stability of the panel (antigen) must be considered throughout the preparation of the panel and the workflow up to the test.
  - Assays should have a specificity of over 98%, as measured through the retrospective in vitro evaluation study or as specified by the manufacturer in the IFU.
  - In line with the MDCG Guidance on performance evaluation of SARS-CoV-2 in vitro diagnostic medical devices<sup>11</sup>, preference is given to samples compared against RT-PCR results on nasopharyngeal swabs. However, in independent validation studies, samples can also be compared against RT-PCR results on oropharyngeal or nasal swabs if reasoning is provided (e.g. when assessing the clinical performance of rapid antigen tests among children).

As a wide range of different methodologies and protocols are being applied in different countries, discussions on testing approaches will continue, with the overall goal of the TWG to develop and agree on an EU-harmonised approach for validation studies assessing the clinical performance of COVID-19 rapid antigen tests. This work will consider the ongoing work by the In Vitro Diagnostics Working Group of the Medical Device Coordination Group regarding guidance on the performance of COVID-19 tests in the context of CE-marking and common specifications under Article 9 of Regulation (EU) 2017/746. Independent validation of tests which are not included in the common list of COVID-19 RADTs should be performed for the intended settings and situations before using them. It is always recommended that clinical validation is performed before a new test is introduced in different settings.

## 5. Use of RADTs in different populations and settings

Besides test performance, other practical and strategic aspects play a significant role in deciding whether a test can be used, and with which indications. Practical aspects that can influence the choice of RADTs are the intended timeliness of test results, the scalability in case of increased demand, the simplicity of use, the availability of instrumentation and of human and material resources, the possibility to set-up all logistical arrangements considering the cost for sampling and testing, including the expected need for confirmatory testing. Furthermore, the epidemiological situation in specific settings or in an area/region/country will influence the choice of the most appropriate testing strategy and test selection.

### Use of RADTs by public health objective

The public health objectives, for which the use of RADTs may be beneficial, are the following:

- quick identification of SARS-CoV-2 infection in people with influenza-like symptoms or acute respiratory infections;
- prompt clinical management of cases with COVID-19-compatible symptoms at admission;
- control transmission: early detection of cases, contact tracing, population-wide testing;
- mitigate the impact of COVID-19 in healthcare and social-care settings: triage at admission, early detection and isolation;
- identify clusters or outbreaks in specific settings: early detection and isolation;
- providing EU DCC to support opening of societies, including occupational and educational settings as well as travel options [27-29].

In the situations described above, RADTs can offer a significant advantage over NAAT in terms of bringing testing closer to persons to test and timeliness of results, as well as the timely initiation of adequate public health actions and clinical treatment.

### Considerations for the use of RADTs in settings of low and high virus prevalence and the need for confirmatory testing

The predictive values of RADTs vary depending on the prevalence of the virus in the respective setting and the performance characteristics (specificity and sensitivity) of the test.

In a **high prevalence setting** (e.g. of  $\geq 10\%$ ), RADTs will have a high PPV (Table 1). In such a situation (e.g. an outbreak in a closed setting), a positive result from a RADT (even with a lower specificity and thus a higher probability of false positivity) is likely to indicate a true infection and may not require confirmation. The first positive cases of an outbreak (e.g. in a long-term care facility, LTCF) should be confirmed preferably with a second method, NAAT or, if not available, with another RADT of a different brand. If a RADT of different brand is also unavailable, the same RADT brand can be used for confirmation, but it will not exclude the possibility of a false positive result due to an inherent technical issue of the test (especially if it is of the same batch) or cross-reaction with another seasonal coronavirus. On the other hand, after clinical assessment considering the epidemiological situation, clinical history, vaccination status, presentation and available testing resources, negative test results may also need confirmation by NAAT or, in case of unavailability of NAAT, with another RADT. This is especially important in closed settings (e.g. LTCFs) and in symptomatic cases with high clinical suspicion. In vulnerable populations with symptoms, a multiplex RT-PCR test would be best suited for confirmation to exclude symptoms caused by other respiratory pathogens.

In a **low prevalence setting** (e.g. of <5%), RADTs will generally have a high NPV but a low PPV, with variable levels depending on the inherent performance characteristics of the tests (specificity and sensitivity) (Table 1). It needs to be noted that a lower PPV in such settings is also expected for other test types such as NAATs and will depend on the actual specificity of the used test. At prevalence <10%, the PPV of a test with 98% specificity would be over 82%. ECDC recommends the use of NAAT or RADTs with high specificity for testing to increase the PPV; even in a lower prevalence setting of <5%, as if the specificity of the test is 99% the PPV will be over 80%.

If used correctly (i.e. within five days from symptom onset or seven days from exposure) and repeated if necessary, RADTs should be able to rule out a highly infectious case in such a setting (Figure 1). A negative test result may not require confirmation by NAAT, whereas a positive test will need confirmation preferably by a second method, NAAT or, if not available, with another RADT of a different brand. The first positive cases in an outbreak should be confirmed. Recurring testing by RADT every two to three days with the aim of identifying infectious cases in a population can partly mitigate the lower sensitivity of the test and can be used in certain settings such as with staff in healthcare settings.

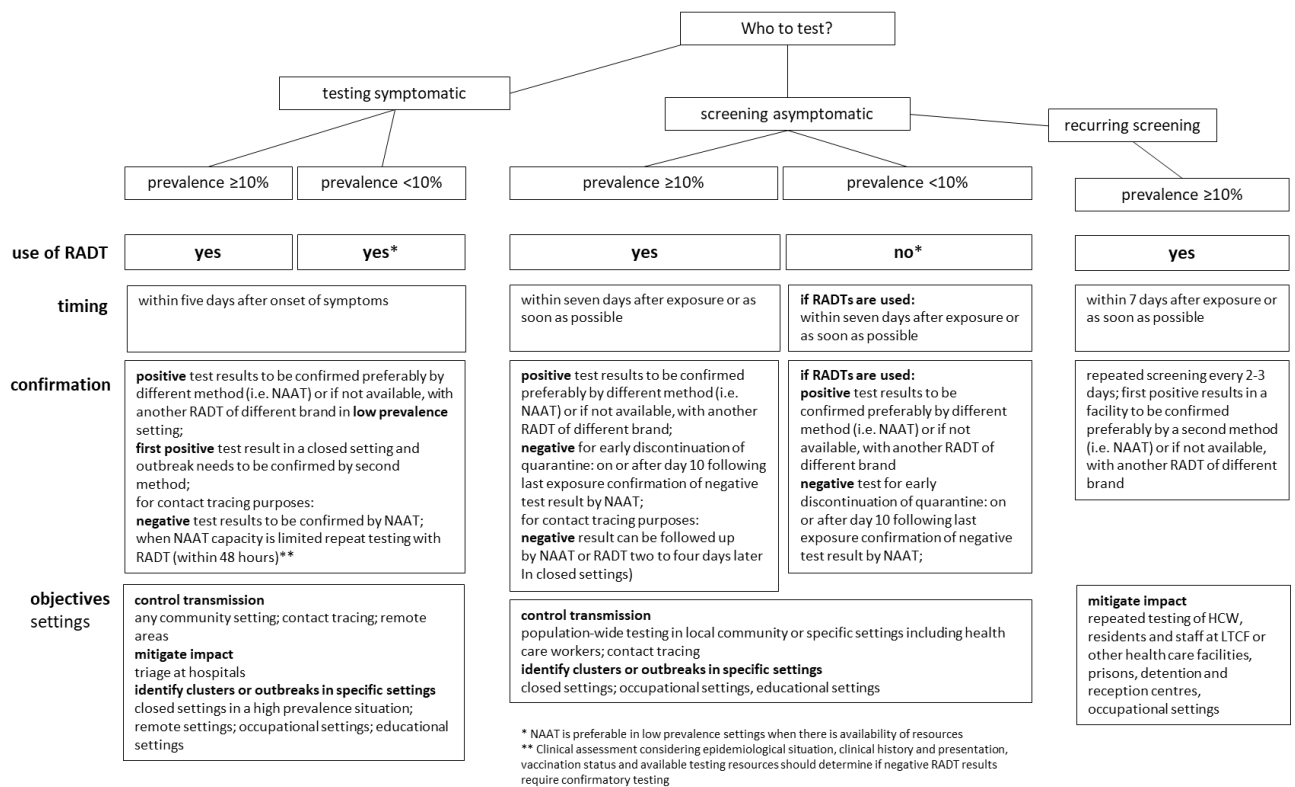
In low prevalence settings, sufficient NAAT and logistics capacity will probably be in place to ensure a rapid turnaround of results. However, there could still be an added value to the use of RADTs because of the low cost and rapid turnaround time of analysis. Here, a careful cost-benefit calculation must be made in order not to exhaust the overall testing capacity in settings which have low impact on the course of the epidemic, and the resources should rather be reserved for settings where highly infectious persons need to be detected.

**Table 1. NPV and PPV of a test at different prevalence levels of infection in a given setting using two different tests with different sensitivities and specificities (conceptual example)**

Example prevalence	Sensitivity	Specificity	NPV	PPV	True positive	False positive	True negative	False negative	Nr with disease	Nr of positive tests in total
50/100 000	0.8	0.98	1.000	0.020	40	1 999	97 951	10	50	2 039
50/100 000	0.98	0.999	1.000	0.329	49	100	99 850	1	50	149
100/100 000	0.8	0.98	1.000	0.038	80	1 998	97 902	20	100	2 078
100/100 000	0.98	0.999	1.000	0.495	98	100	99 800	2	100	198
500/100 000	0.8	0.98	0.999	0.167	400	1 990	97 510	100	500	2 390
500/100 000	0.98	0.999	1.000	0.831	490	100	99 401	10	500	590
1 000/100 000	0.8	0.98	0.998	0.288	800	1 980	97 020	200	1 000	2 780
1 000/100 000	0.98	0.999	1.000	0.908	980	99	98 901	20	1 000	1 079
5 000/100 000	0.8	0.98	0.989	0.678	4 000	1 900	93 100	1 000	5 000	5 900
5 000/100 000	0.98	0.999	0.999	0.981	4 900	95	94 905	100	5 000	4 995
10 000/100 000	0.8	0.98	0.978	0.816	8 000	1 800	88 200	2 000	10 000	9 800
10 000/100 000	0.98	0.999	0.998	0.991	9 800	90	89 910	200	10 000	9 890
20 000/100 000	0.8	0.98	0.951	0.909	16 000	1 600	78 400	4 000	20 000	17 600
20 000/100 000	0.98	0.999	0.995	0.996	19 600	80	79 920	400	20 000	19 680
50 000/100 000	0.8	0.98	0.831	0.976	40 000	1 000	49 000	10 000	50 000	41 000
50 000/100 000	0.98	0.999	0.980	0.999	49 000	50	49 950	1 000	50 000	49 050



**Figure 1. Flowchart describing objectives and settings on when to use RADTs**



## Using RADTs to test people with symptoms

The use of RADTs can be considered for individuals with COVID-19-compatible symptoms. In settings with prevalence of <10%, positive samples should be confirmed preferably by a second method (e.g. RT-PCR) or, if not available, with another RADT of a different brand; however, even if the confirmatory NAAT or RADT method generates a negative result, the symptomatic patient should stay at home until symptoms resolve. Further investigation is warranted when there are several occasions of RADT positive results that turn out negative with NAAT; this can be a signal of an emerged new variant that may cause primer mismatch and false negative NAAT results.

RADTs may be used in the situations and settings listed below, but only if sampling can be performed within five days of symptom onset. Clinical assessment considering epidemiological situation, clinical history, vaccination status, presentation and available testing resources should determine if negative RADT results require confirmatory testing. If there is no NAAT capacity, the RADT tests should be repeated within 48 hours.

Below is a list of situations in which RADTs may be used to test people with symptoms:

- In high prevalence situations, RADTs can be applied for testing possible and probable COVID-19 cases presenting to healthcare.
- In NAAT-confirmed outbreaks and in closed settings (e.g. LTCFs), RADTs can be used for testing symptomatic contacts to facilitate early detection of further cases as part of contact tracing and outbreak investigation.
- To mitigate the impact of COVID-19 in healthcare and social-care settings, RADTs can be used for the triage of symptomatic patients or residents at admission and to test symptomatic patients or staff for early detection of cases. Results of testing can guide timely isolation and type of personal protective equipment required.
- For contact tracing purposes, all contacts (irrespective of the vaccination status) who have symptoms or develop symptoms during follow-up should be tested as soon as possible to allow for case isolation and further contact tracing [30]. Both NAAT and RADTs can be considered, but RADTs will offer the advantage of timeliness. If RADTs are used, symptomatic contacts should be tested as soon as possible but within five days of symptom onset. Accounting for the high degree of clinical suspicion, negative RADT results should be confirmed with RT-PCR or repeated within 48 hours.

- For sentinel surveillance, NAAT should be the preferred option. Sentinel samples need to be tested for influenza and other respiratory viruses in parallel, and representative samples should be selected for further genetic and antigenic characterisation which is not possible when sampling only for RADTs is used [31]. If RADTs are used, representativity of the samples that are channelled to the sentinel systems and public health laboratories should be ensured.

Before using RADTs, a risk assessment is needed to evaluate the probability and impact of incorrect results. Capacity for confirmatory testing by NAAT and/or a second RADT should be in place.

## Using RADTs to test people without symptoms

The use of RADTs can be recommended for testing individuals regardless of symptoms in settings in which the prevalence of infection is expected to be  $\geq 10\%$ , e.g. during an outbreak in a closed setting. In high prevalence situations, RADT NPV and PPV are expected to be high. In situations in which the time of exposure to a confirmed COVID-19 case is known, testing using RADTs should be performed as soon as possible after the contacts have been identified. If more than seven days have passed since known exposure, it is recommended that negative RADTs are confirmed by NAAT.

Viral load in asymptomatic or pre-symptomatic cases can be similar to symptomatic cases [32,33]. However, some studies have shown a reduced viral load in asymptomatic individuals with a primary infection compared to symptomatic individuals [34,35], while the exact infectious period cannot be determined due to the absence of symptoms. Therefore, the performance of RADTs may be lower in asymptomatic primary cases. In primary infections after vaccination or in a secondary infection, the viral load in asymptomatic persons might be lower than in cases of primary infection [36]. A recent meta-analysis has confirmed that RADT sensitivity is lower in asymptomatic compared with symptomatic patients [15]. In another meta-analysis, the average RADT specificities were high in asymptomatic participants, with overall summary specificity 99.6% (95% CI 99.0% to 99.8%) for most brands [14].

Asymptomatic individuals in a high prevalence setting should potentially be considered a low prevalence pool, although exposure will be variable depending on the virus prevalence in their settings. A study among asymptomatic athletes showed, that despite the low PPV of the RADTs used in the low-prevalence community, the absolute number of individuals that required confirmatory testing with NAAT was about 1% of the tests performed. That means, employing a two-tiered testing strategy, i.e. confirming a positive RADT result by NAAT, might be a fast and cost-effective solution for screening of asymptomatic individuals in a low-prevalence setting [23,37]. To control transmission, RADTs can be used for testing asymptomatic high-risk exposure contacts as part of contact tracing [30]. The cost of initially isolating some false positive cases is compensated by the fact that RADTs offer the fastest alternative to identify and isolate infectious individuals. Negative test results should be confirmed by NAAT if more than seven days since exposure have passed.

Below is a list of situations in which RADTs may be used to test people without symptoms:

- For unvaccinated contacts, both high-risk exposure contacts and low-risk exposure contacts should be tested given the increased transmissibility of the Delta variant. If it is not feasible to test all low-risk unvaccinated contacts, at least those in settings with vulnerable populations, or in settings where transmission is likely, should be prioritised, such as health and social care settings, prisons, certain occupational settings and social events such as choirs or weddings.
- Vaccinated high risk exposure contacts need to be tested for contact tracing purposes either with a NAAT or with a RADT. If the test is negative, they don't need to quarantine. Due to emerging data on lower effectiveness of vaccines against the Delta variant against infection together with evidence of waning immunity, it is also recommended that vaccinated high-risk exposure contacts receive a second NAAT or RADT after two to four days to increase the likelihood of identifying and isolating those infected.
- For early discontinuation of quarantine of exposed contacts of a case, a test can be done on or after day 10 following last exposure, but if a RADT is used it is recommended that the negative test is confirmed by NAAT.
- In closed settings (like LTCFs), asymptomatic contacts can be tested using a RADT. A negative result can be followed up by NAAT or by another RADT two to four days later if NAAT capacities are limited. This is to ensure effective further contact tracing. Early release from quarantine based on a negative RADT or NAAT needs to be assessed on a case-by-case basis for contacts working with vulnerable populations or contacts in high-risk settings such as long-term care facilities or prisons.
- In a high prevalence situation, in the context of circuit breaker strategies to detect individuals with high transmission potential in the community and to lower the pressure on healthcare settings and laboratories, the use of RADTs can be considered for a targeted population-wide testing approach, e.g. in a local community. In such a situation, the risk of not detecting all cases or the risk of false negative results is balanced out by the timeliness of results and the possibility of serial testing of individuals [38].

- RADTs can be used for screening and serial testing (every two to three days) of residents and staff in healthcare, home care, long-term care facilities, closed settings (e.g. prisons, migrant detention and reception centres) and occupational settings in areas in which there is ongoing community transmission [38]. A modelling study showed that outbreak control depends largely on the frequency of testing, the speed of reporting, and the application of interventions, and is only marginally improved by the sensitivity of the test [39]. Additional evidence showed that serial antigen testing every three days, or twice per week, will almost always identify SARS-CoV-2 during early stages of infection, and thus significantly reduce disease transmission [40]. Thus, if resources allow, serial antigen testing is a potentially important public health practice along with other prevention strategies. When a first case is confirmed in a resident or staff member of a closed setting, for example a LTCF, or in the event of widespread community transmission in the area (high prevalence situation), a comprehensive testing strategy of all residents and staff can be considered.

Symptomatic individuals should refrain from travelling, according to ECDC guidelines. As such, travellers can be assumed to belong mostly to a non-symptomatic subpopulation, with variable but lower probability of COVID-19 compared to the general population, and an estimated prevalence of COVID-19 at <1%. RADT tests performed before travelling can be used for the screening of outgoing/incoming travellers. However, due to their lower sensitivity, RADTs should not be the test type of choice for screening incoming travellers to prevent virus (re-) introduction in regions/countries that have achieved zero or very low levels of transmission. In these situations, NAAT should be used to reduce the risk of false negative results. For asymptomatic individuals with a positive RADT result, testing should be confirmed preferably by a second method (e.g. RT-PCR) or, if not available, with another RADT of a different brand. When considering the adoption of RADTs for screening travellers, several considerations require attention. Please refer to the guidance developed jointly by ECDC and EASA on travel-related measures for air travel [29].

## Considerations on the use of RADTs to certify recovery

The Council recommendation on a common framework for the use and validation of RADTs and the mutual recognition of COVID-19 test results in the EU (2021/C 24/01) calls for a common and updated list of COVID-19 RADTs that are considered appropriate for use for public health measures, including those related to travelling, and are in line with national testing strategies. Self-test RADTs should not be used for the purpose of issuing a formal certificate such as testing, or recovery certificates. For recovery certificates, NAATs are currently accepted.

ECDC considers that appropriately validated RADTs that carry CE marking and meet high specificity criteria of >98% could be used to certify that a person has recovered from a past COVID-19 infection. It is recommended that for certifying recovery, tests of higher specificity, preferably >98%, are used. The higher the specificity, the higher the test validity to be used for certifying a recovered individual. It needs to be noted that in order to increase validity of the test result, for asymptomatic individuals with a positive RADT result, testing should be confirmed preferably by a second method (e.g. RT-PCR) or, if not available, with another RADT of a different brand.

RADTs detect individuals with an ongoing infection, i.e. while they are most infectious. They generally have a lower sensitivity in comparison to NAAT but a high specificity, which is the important performance criterium for the purpose of verifying a recovered individual [14,24,25,40]. The list of mutually recognised RADTs is updated and made available by the HSC TWG group on COVID-19 diagnostic tests. While the minimum performance criterium for specificity of the listed tests list is >98%, the specificity of most of these tests is higher ( $\geq 99\%$ ) [4,41]. Two meta-analyses on test performance have recently been published. In one meta-analysis, the average RADT specificities were high in symptomatic and asymptomatic participants, for most brands, with overall summary specificity 99.6%, with 95% CI of 99.0% to 99.8% [14]. In the other meta-analysis, across all meta-analysed samples, results consistently showed a RADT specificity of 99.7% (95% CI 99.3 to 99.9) [13]. Notably, independent clinical evaluations of RADTs and NAATs have shown variable clinical specificities of available RADTs, but also NAATs, on the market [24,40]. Similar results have been observed in the first external quality assessment (EQA) of molecular detection of SARS-CoV-2 for European expert laboratories; specificity of RT-PCR tests used varied in the different laboratories [41]. Therefore, careful selection of tests with high sensitivity and specificity should be done to ensure the highest predictive values. ECDC recommends Member States to use RADTs that are listed on the common list of COVID-19 RADTs as agreed by the HSC. However, it is important to note that the work of the HSC TWG has focused so far on assessing sensitivity of the tests for the issuance of testing certificates. For the issuance of recovery certificates, further assessment will be required focusing on specificity and how this is assessed in evaluation studies. Here, a list of mutually recognised RADTs which meet agreed specificity criteria should be agreed upon by the HSC.

The lower the prevalence in the population to be tested, the higher the proportion of false positive will be when specificity of the used test is suboptimal. This means, there would be a proportion of people certified to have recovered, whereas they are still susceptible (i.e. people with a false positive RADT or NAAT result for COVID-19). All COVID-19 tests, including NAATs, have the risk of producing false-positive test results. If RADTs of lower specificity are used, this should be taken into consideration, especially in low prevalence settings when these tests are used for screening of asymptomatic individuals and where the positive predictive value of tests would thus be low.

## 6. Potential implications for RADT performance amidst the emergence and co-circulation of SARS-CoV-2 variants and seasonal coronaviruses

Overall, the impact of genetic variants on test performance is influenced by the type of change to the protein(s), the design of the test, and the prevalence of the variant in the population subject to testing. Antigen tests are designed to detect specific viral proteins. Theoretically, if changes in the viral genome alter the structure of a viral protein targeted by an antigen test, the test may not detect the virus, even if the virus is present, leading to false negative results. A cross-reaction with antigens from other circulating seasonal coronaviruses may cause a false positive result.

Mutations that are often observed in the currently circulating variants of concern (VOCs) like N501Y (B.1.1.7/B.1.351) and the H69/V70 deletion (B.1.1.7), can result in alterations of the spike protein (S-protein), which is currently less frequently used by RADTs [42]. The vast majority of SARS-CoV-2 RADTs currently available are based on detection of the nucleocapsid protein (N-protein). The HSC TWG is collecting information on the target protein of the different tests that is included in the common list as of 20 October 2021 [4].

Despite the higher stability of the N-protein compared to the S-protein, there are also some mutations present, which in some instances may alter its dynamic stability and immunogenic properties, resulting in false-negative RADT results [43,44]. There are few reports of mutations of the N gene that resulted in false-negative RADT results despite high viral loads confirmed by NAAT. These strains were found to have D3L and S235F or T205I and D399N mutations [45] or A376T and M241I mutations (position 229-374) in the N-gene [46]. Such N-protein mutations, which are already present or may emerge during the pandemic, could influence the performance of N-specific RADTs and generate false negative results. However, the currently available RADTs are targeting the C-terminus of the nucleocapsid protein, while the vast majority of the detected mutations are located in the N-terminus [47].

There are currently limited data from RADT clinical validation studies considering the emerging variants, but few studies have confirmed that no reduction in sensitivity has been observed [48-50]. It is likely that performance of RADTs with the currently circulating variants will continue to be unaffected, but we need to remain vigilant to detect reductions in sensitivity of RADTs due to variants with specific mutation profiles and further studies are needed to verify the reduction in sensitivity conferred by those. Proper validation studies should be done before introducing new tests in different settings.

Monitoring the impact of genetic variants on the performance of RADTs is not as straightforward as for nucleic acid detection tests. To assess the impact of novel variants on the analytical performance of RADTs, collection of clinical specimens obtained from individuals with novel viral variants is necessary, which can also be supported by using *in silico* and/or *in vitro* models to characterise the impact of certain mutations on the proteins responsible for eliciting an antibody response.

On the other hand, it is also possible that mutations may affect the performance of the NAATs that may be used for confirmation of positive RADT results. That would mean that a positive RADT test may then turn out to be falsely negative in NAAT if primer mismatch has occurred. Laboratories should remain vigilant to detect such signals and monitor the impact of new genetic variants on test performance.

Finally, it cannot be excluded that RADTs using the N-protein as a target mistakenly react against the N-protein of another seasonal coronavirus that may be co-circulating; that would mean that a false positive result is generated if a person is infected by a seasonal coronavirus. Clinical validations conducted at specific time-points and areas cannot exclude this possibility, because the circulation of respiratory viruses may have been different at the time-point and/or geographic location of the validation study. The aforementioned situation is, however, unlikely assuming that proper design, quality assurance and validation of tests has been conducted by the manufacturer.

## 7. Implications on the use of RADTs amidst increasing vaccination coverage in the EU/EEA

An individual vaccinated against SARS-CoV-2 will not test positive with a NAAT or a RADT because of the vaccination, i.e. the vaccine agent will not be detected by the diagnostic tests. The currently available mRNA-based vaccines consist of non-replicating mRNA which will be degraded after the cell has produced the viral protein and hence, vaccination with an mRNA vaccine will not lead to a positive NAAT nor RADT.

An important question is, however, to what extent prior vaccination against SARS-CoV-2 will impact viral loads in an infected individual. The sensitivity of RADTs primarily depends on viral loads in the specimen, as they perform best in highly-infectious individuals at RT-PCR cycle thresholds of <25, i.e. in pre-symptomatic and early symptomatic cases [2].

Before the emergence of the Delta variant, vaccination against COVID-19 was shown to reduce viral transmission in studies of individuals with vaccine breakthrough infections. Household studies, focusing on the previously dominating Alpha virus variant showed a reduction of onward transmission from individuals who were infected despite prior vaccination [51-54]. This reduction of onward transmission was potentially due to reduced viral load in vaccinated, yet infected individuals [36,55].

The chance (pre-test probability) that a vaccinated individual has COVID-19 is lower than in an unvaccinated individual. Similar to what is expected in a lower prevalence setting, the PPV of the test is reduced and, consequently, the number of false positive results may increase. Implementing serial testing schedules can reduce the risk of missing cases with an initial negative result who later convert to a positive result, i.e. it reduces the possibility of failure to detect infected individuals due to early sampling. Individuals with a positive RADT result should be confirmed preferably by a second method (e.g. RT-PCR) or, if not available, with another RADT of a different brand in a two-tier approach which can address the challenge posed by the lower PPV expected in vaccinated individuals.

With the emergence of the Delta variant, studies have shown that viral loads in previously vaccinated individuals with a breakthrough infection are similar to viral loads detected in unvaccinated individuals [56,57].

While a reduction of viral loads would theoretically decrease the performance of RADTs in vaccinated individuals, e.g. infected with the Alpha virus variant, the higher viral loads associated with an infection with the Delta variant, that is now predominating in EU/EEA and globally, appear not to be associated with such a significant risk of reduction in viral load that would impact on RADT performance [58,59].

Still, data describing the performance of RADTs in vaccinated individuals infected with SARS-CoV-2, irrespective of virus variants, have not yet been published.

Increasing vaccination coverage may also have a positive impact on the decrease of prevalence of COVID-19 in the respective population and in different settings. This may then impact the performance characteristics of RADTs and specifically the PPV. Even more so, if vaccination coverage will further increase, the approaches for repeated testing and confirmation may need to be revisited.

## 8. Operational considerations for the use of RADTs

### Sampling and user considerations

Sample collection is one of the most critical factors affecting the performance of any diagnostic test. Sampling for detection of SARS-CoV-2 by RADTs relies mostly on nasopharyngeal, and oropharyngeal or nasal swab specimens, as indicated by the manufacturers. Self-sampling using saliva is not currently clinically validated for RADTs. Unlike NAAT, RADTs lack controls for confirmation of appropriate sampling; they also lack an amplification step which limits their sensitivity [2]. Theoretically, saliva can serve as sample material for RADTs based on a lateral flow principle, as has been shown by a few academic groups [60,61]. The nature and heterogeneity of the saliva-containing sample types, however, can cause difficulties in the processing of the tests, and sensitivity of the RADT compared to NAAT is expected to be further reduced [62]. Therefore, the experts on the HSC technical working group decided in July 2021 to exclude RADTs that are based on saliva, blood, sputum and/or faeces [4].

For RADTs intended for use in point-of-care settings, trained healthcare or laboratory staff, or trained operators, are needed to carry out sampling, testing, test analysis and reporting of test results to clinical staff and public health authorities at local, regional, national and international level. Professional sampling is particularly important in the context of testing with RADTs as the test lacks a control showing successful sampling. Member States need to ensure sufficient capacities and resources for sampling, testing and reporting. To ensure these capacities, it is likely that additional healthcare personnel will need to be trained [63].

Self-sampling and/or self-tests using RADTs can offer advantages when used to complement professionally administered RADTs or NAAT tests as they can improve the accessibility to testing [27]. They allow individuals to obtain the result quickly, which could support the early detection and subsequent isolation of infectious cases and hence reduce further community transmission. However, shifting the responsibility of reporting test results from health professionals and laboratories to individuals could lead to underreporting, and make response measures such as contact tracing and quarantine of contacts and monitoring of disease trends over time even more challenging. While self-sampling under supervision and subsequent RADT performed at the laboratory can be an acceptable solution for a certified test, RADTs performed by untrained individuals should not be used for issuing of any formal certificate.

## Time of sampling

Based on the available evidence, replicating virus can be isolated from the nasopharyngeal specimens of individuals with mild to moderate symptoms from six days before to nine days after symptom onset [64]. The highest viral load has been observed in respiratory samples collected three days before to three days after the symptom onset [65].

As mentioned above, RADTs have been shown to be more efficient in detecting cases in the days around the onset of symptoms, when the viral load is highest. A RADT should therefore be used as soon as possible but within five days after the onset of symptoms. Clinical assessment considering epidemiological situation, clinical history, vaccination status and presentation and available testing resources should determine if negative RADT results require confirmatory testing. If there is no NAAT capacity, the RADT tests should be repeated within 48 hours.

For asymptomatic contacts of cases, tests should be performed as soon as possible after the contact has been traced. If more than seven days have passed since a known exposure, there may be an increased risk of a false negative due to a reduction of the viral load, depending on the actual incubation period of the virus. In these cases, a negative test result needs to be confirmed by NAAT. In case NAAT is unavailable, a second RADT can be done after two to four days. Although the recommendation is to test as soon as possible after contacts have been traced, performing a test too early (i.e. immediately or within the first two days after a known exposure) increases the possibility of a false negative result. However, SARS-CoV-2 virus variants might show specific viral dynamics. Therefore, the timing of sampling should be adjusted to the epidemiological situation in the setting.

## Biosafety considerations

Manufacturer instructions for sample collection, safe handling, proper waste management and use need to be followed precisely, including specimen type. Appropriate biosafety measures should always be in place, and a risk assessment performed when sampling, handling and processing specimens and tests. Such additional protective measures may include primary containment devices, or the use of a biological safety cabinet combined with appropriate personal protective equipment.

It is highly recommended that laboratory personnel and operators who handle specimens should be vaccinated.

## Interpretation of test results and implications for surveillance

If a RADT is used for SARS-CoV-2 detection during the influenza season, parallel testing for influenza viruses as well as subtyping and lineage determination, and testing for other respiratory viruses, should be performed.

For surveillance purposes, and for specimens originating from sentinel systems, NAAT remains the preferred method. Nonetheless, the EU case definition for COVID-19 accepts the detection of antigens in the clinical specimens and therefore the inclusion of RADTs results in reporting of cases for surveillance [5]. The countries applying RADTs would need to ensure that at minimum, a representative sample of specimens are shipped to national reference laboratories to ensure characterisation of circulating viruses for surveillance purposes.

## The EU regulatory framework for diagnostic tests

Reagents, control materials, testing kits, and instruments intended for medical use are referred to as *in vitro* diagnostic medical devices (IVDs)<sup>1</sup>. The currently applicable legislative framework for these devices at EU level is Directive 98/79/EC<sup>2</sup>. To place a device on the EU market, the manufacturer must demonstrate compliance with the applicable legal requirements in the Directive. This includes carrying out a performance evaluation of the device. For any devices intended for lay users, the manufacturer must also apply to a third-party body (called a notified body), which will examine the design aspects of the device and issue a corresponding certificate. For COVID-19 devices intended by the manufacturer for professional use, there is no requirement to apply to a notified body. Once the manufacturer has declared conformity of the device with the legal requirements, they may affix the CE-marking to the device and place it on the market.

Thus, the CE-marking is mostly based on a self-assessment and a self-declaration by the test manufacturer, including the claims on test performance, for which the manufacturer needs to have appropriate technical documentation and studies to back up the claims. Independent information on the clinical performance of these tests in terms of sensitivity and specificity is often limited, and yet this is critical for proper interpretation of results. This is especially challenging in the context of the evolving pandemic. In its Communication of 15 April 2020<sup>3</sup> as well as in its most recent recommendation of 18 November 2020 [66], the Commission recommended that Member States carry out validation studies before introducing devices into clinical practice.

The choice of tests to be used in national health systems is up to the individual Member States, as part of their national competences for organising and delivering health services and medical care<sup>4</sup>. The chosen test should ideally be part of the common list of COVID-19 RADTs, established by the HSC [4].

From 26 May 2022, the Directive will be replaced by Regulation (EU) 2017/746<sup>5</sup>. The Regulation will strengthen the requirements for the evidence on performance of the device and introduce a thorough assessment of COVID-19 tests, including RADTs, by notified bodies.

## 9. Conclusions

RADTs can contribute to the overall COVID-19 testing capacity offering an advantage in terms of shorter turnaround time and reduced cost, especially in situations where NAAT testing capacity is reduced. Together, these benefits of RADTs can contribute to more efficient interruption of transmission through more timely identification of cases and faster contact tracing.

There are currently many RADTs on the EU/EEA market, which vary in their performance characteristics. Independent evaluations have shown that RADTs have variable and lower sensitivity compared to NAAT tests but have a high specificity, often comparable to NAATs. The currently available data show that RADTs sensitivity is high (and can be equivalent to NAAT) in situations when the time of sampling is up to five days after symptom onset, i.e. during the infectious period. ECDC agrees with the minimum performance criteria set by WHO (sensitivity  $\geq 80\%$  and specificity  $\geq 97\%$ ) and recommends use of tests that have a higher sensitivity of  $\geq 90\%$  and minimum specificity of  $>98\%$ , in line with the HSC TWG list. Some of the available tests on the market are included in the HSC list of mutually recognised tests in the EU/EEA and meet the agreed clinical performance criteria. If tests are to be used to certify recovery from infection, higher specificity tests ( $>98\%$ ) are preferred.

ECDC recommends Member States use tests that are listed on the common list of COVID-19 RADTs as agreed by the HSC. It is highly recommended that independent setting-specific validations for the use of RADTs against NAAT tests should be performed before deciding to introduce new RADTs.

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<sup>1</sup> See the complete definition of in vitro diagnostic medical device in Article 1 (2) (b) of Directive 98/79/EC.

<sup>2</sup> Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices, OJ L 331, 7.12.1998, p. 1–37.

<sup>3</sup> Communication from the Commission Guidelines on COVID-19 in vitro diagnostic tests and their performance 2020/C 122 I/01, C/2020/2391, OJ C 122I, 15.4.2020, p. 1–7.

<sup>4</sup> See Article 168 of the Treaty on Functioning of the European Union, OJ C 115, 9.5.2008, p. 122–124.

<sup>5</sup> Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Text with EEA relevance.) OJ L 117, 5.5.2017, p. 176–332.

When testing by RADT is considered, test performance and prevalence in the target population need to be taken into consideration, as there continues to be a considerable risk of false negative and positive results with RADTs, depending on the prevalence. This risk needs to be taken into account when considering the use of RADTs in specific settings. The use of RADTs also changes the logistical arrangements for testing, including resources and procedures needed for confirmatory testing, thus posing a possible challenge for Member States.

Despite the emergence of virus variants, no reduction in test sensitivity against the currently circulating variants has been observed so far. As it still remains a possibility, further studies are needed to identify mutation profiles that could alter the N-protein in a way that may affect the RADT performance. Laboratories should always be vigilant to identify reductions in RADTs sensitivity or specificity. Studies on the performance of RADTs in vaccinated individuals infected with SARS-CoV-2 have not yet been published.

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## Disclaimer

All data published in this document are correct to the best of our knowledge at the time of publication.



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