TECHNICAL REPORT

Options for the use of rapid antigen tests for COVID-19 in the EU/EEA and the UK

19 November 2020

Key messages

- Rapid antigen tests can contribute to overall COVID-19 testing capacity, offering advantages in terms of shorter turnaround times and reduced costs, especially in situations in which RT-PCR testing capacity is limited.
- Test sensitivity for rapid antigen tests is generally lower than for RT-PCR.
- Rapid antigen tests perform best in cases with high viral load, in pre-symptomatic and early symptomatic cases up to five days from symptom onset.
- ECDC agrees with the minimum performance requirements set by WHO at ≥80% sensitivity and ≥97% specificity.
- ECDC recommends that EU Member States perform independent and setting-specific validations of rapid antigen tests before their implementation.
- The use of rapid antigen tests is appropriate in high prevalence settings when a positive result is likely to indicate true infection, as well as in low prevalence settings to rapidly identify highly infectious cases.
- Rapid antigen tests can help reduce further transmission through early detection of highly infectious cases, enabling a rapid start of contact tracing.

Scope of this document

On 28 October 2020, a European Commission Recommendation on COVID-19 testing strategies, including the use of rapid antigen tests was published [1]. That recommendation calls for European Union/European Economic Area (EU/EEA) Member States and the United Kingdom (UK) to agree on criteria to be used for the selection of rapid antigen tests, and to share and discuss information regarding the results of validation studies. This ECDC document is intended to facilitate further discussions between Member States with the aim of reaching agreement on the criteria to be used for the selection of rapid antigen tests, as well as scenarios and settings during which it is appropriate to use rapid antigen tests. This document is also intended to support clinical validations of rapid antigen tests.

Summary

To date, testing for SARS-CoV-2 infection mostly relies on reverse transcription polymerase chain reaction (RT-PCR) performed on a nasopharyngeal specimen. This testing method remains the gold standard for detecting SARS-CoV-2 and is characterised by both high sensitivity and specificity in detecting viral ribonucleic acid (RNA).

The high volume of samples reaching the laboratories could, however, lead to a shortage of reagents and disposables and to a further increase in the turn-around time for RT-PCR tests.

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Rapid antigen tests are easy to use and offer rapid results at low cost, but show lower sensitivity.

Rapid antigen tests offer multiple benefits in comparison to RT-PCR tests for the 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 normally generated in 10 to 30 minutes after the start of the analysis, and at low cost. Most currently available rapid antigen tests 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 rapid antigen tests may be 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), which likely account for a significant proportion of transmissions.

WHO recommends rapid antigen tests that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity, while ECDC suggests aiming to use tests with a performance closer to RT-PCR, i.e. ≥90% sensitivity and ≥97% specificity.

Rapid antigen tests should be applied in a way that compensates for the lower performance compared to RT-PCR, i.e. by including repeat testing for screening purposes and confirming test results by RT-PCR.

Besides the performance of the test, other practical and strategic aspects play a significant role in deciding if a test can be used and with which indications. Examples of these considerations are the timeliness of test results, the scalability, the simplicity of use, instrumentation availability, human and material resources, and overall logistical arrangements for sampling and testing and costs. The epidemiological situation per setting, local area, region and nationwide also affect the testing strategy.

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

Due to the timeliness of results, rapid antigen tests can provide added value e.g. in the patient triage process in healthcare settings at admission. In the context of contact tracing, rapid antigen tests can allow for a faster identification of infectious contacts.

When considering whether to use rapid antigen tests, a careful analysis of the expected sample volumes, availability of resources, equipment and supplies and logistical arrangements, including the expected need for confirmatory testing and supplies for those, needs to be carried out.

Background

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 the EU with specific recommendations by level of virus circulation in the community, taking into account available public health resources and testing capacities [2].

To date, testing for SARS-CoV-2 infection mostly relies on reverse transcription polymerase chain reaction (RT-PCR) performed on a nasopharyngeal specimen. This testing method remains the gold standard for detecting SARS-CoV-2 and is characterised by both high sensitivity and specificity to detect viral ribonucleic acid (RNA). The current EU-level case definition of a confirmed COVID-19 case relies on detection of SARS-CoV-2 RNA in a clinical specimen by RT-PCR [3], however, there are intentions to update the case definition shortly.

Diagnostic laboratories routinely perform RT-PCR 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 RT-PCR 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. Limited internal laboratory capacity, including trained staff, and high sample volumes, may also contribute to the delayed processing of samples. As a result, the turnaround time can easily increase to several days. Early in the pandemic, most of the testing capacity was reserved to identifying 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. The current upsurge of COVID-19 cases in Europe, coupled with the usual rise of other respiratory infections during autumn, has led to a dramatic increase in the demand for SARS-CoV-2 tests. The high volume of samples reaching the laboratories could lead to a shortage of reagents and disposables as already reported by some countries, and to a further increase in the turnaround time for RT-PCR tests.

To complement RT-PCR testing, several countries have already started clinical validation of rapid antigen tests' performance and some have integrated rapid antigen tests use in their national testing strategies [4-10]. WHO [11], Health Canada [12] and the US Centers for Disease Control and Prevention (CDC) have recently issued guidelines for the use of rapid antigen tests [13].

Benefits and challenges of the use of rapid antigen tests

Rapid antigen tests offer multiple operational benefits in comparison to RT-PCR tests for detection of SARS-CoV-2. Rapid antigen tests 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. Some rapid antigen tests require a laboratory instrument for the analysis, but others do not as the analysis is performed on a handheld cartridge with visual readout (Annex 1). Rapid antigen tests generally offer low-cost testing and relatively simple handling. Due to the timeliness of results, rapid antigen tests can provide added value e.g. in the patient triage process in healthcare settings at admission. In the context of contact tracing, rapid antigen tests can allow for a more rapid identification of infectious contacts.

There are also some operational drawbacks associated with the use of rapid antigen tests. Sampling for detection of SARS-CoV-2 by rapid antigen test relies mostly on nasopharyngeal specimens, as indicated by the manufacturers. As of today, these specimens require professional sampling and the use of personal protective equipment during sampling and processing. Self-sampling is not currently clinically validated for rapid antigen tests. Unlike RT-PCR, rapid antigen tests lack controls for confirmation of appropriate sampling. As many of the rapid antigen tests 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 the rapid antigen tests is that the specimens are not necessarily shipped to public health laboratories for further characterisation, such as sequencing.

In contrast to RT-PCR, which amplifies the virus target sequences, rapid antigen tests detect the presence of a viral antigen in the patient's specimen without amplification. As a result, most currently available rapid antigen tests show a lower sensitivity compared to the standard RT-PCR test (Annex 1). However, their specificity is generally reported to be high (Annex 1) [14,15]. Furthermore, rapid antigen tests may be 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 (Annex 1). Several countries that started to use rapid antigen tests target early detection of COVID-19 cases, i.e. testing individuals with COVID-19-compatible symptoms early after disease onset.

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)[1]. The currently applicable legislative framework for these devices at EU level is Directive 98/79/EC[2]. 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[3] as well as in is most recent recommendation of 18 November [16], 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[4].

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

Current data on rapid antigen test performance and use

The WHO initiative FIND (Foundation for Innovative New Diagnostics) gives an overview of SARS-CoV-2 tests that are commercially available or in development for diagnosis of COVID-19, including an indication if they have CE-markings [17]. As of 11 November 2020, there are 56 antigen tests with a CE-marking listed on the FIND database.

Both WHO and the United States Food and Drug Administration (FDA) have provided emergency use listings or authorisations, respectively, for rapid antigen tests. WHO has listed two [18] and FDA seven rapid antigen tests [12,19].

ECDC has performed a meta-analysis of the clinical performance of commercial SARS-CoV-2 tests, including four rapid antigen tests, up until 22 August 2020 [14]. Searching literature (pre-prints and peer-reviewed articles and including personal information from the European COVID-19 laboratory network partners) for rapid antigen tests with a CE-marking, we could retrieve additional results of clinical evaluation studies for nine rapid antigen tests from eight companies by 23 October 2020. Independent evaluations were performed in several countries, predominantly in symptomatic populations. The sensitivities and specificities were calculated against RT-PCR tests and ranged between 29% (95%CI 15.7-42.3) and 93.9% (95% CI 86.5-97.4) for test sensitivity and between 80.2% (95% CI 71.1-86.7) and 100% (95% CI 98.8-100) for test specificity. The substantial differences in performance noted between the tests and between the studies can be partially explained by different populations and time of testing (proportion of persons that were tested early versus late in the course of the disease), and may also be affected by different RT-PCR assays used as gold-standard comparators, extraction methods or type of samples.

Some studies confirmed that the sensitivity of tests was higher in specimens obtained within seven days following the onset of symptoms and for samples with lower Ct value at RT-PCR testing indicating higher viral load. The data collected from validations of tests with CE-marking presented in Annex 1 contains available information on time point of sampling and stratification by Ct values if those were reported.

Infectiousness is likely associated with high viral loads resulting in RT-PCR Ct values below 25-30 [20]. RT-PCR-positives cases with higher Ct values have been considered non-infectious in one study [13]. Since positive rapid

[1] See the complete definition of in vitro diagnostic medical device in Article 1 (2) (b) of Directive 98/79/EC.
[2] 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.
[3] 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.
[4] See Article 168 of the Treaty on Functioning of the European Union, OJ C 115, 9.5.2008, p. 122–124.
[5] 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.

antigen test results are generally found in samples with high viral load, identification of potentially infectious cases is a possible use for rapid antigen tests. False negative rapid antigen test results have been identified in samples with a low viral load, consistent with low number of viable virus and likely low infectiousness.

As a result, most rapid antigen tests available on the market are developed for testing in symptomatic persons and are not currently recommended for use in asymptomatic persons.

The use of rapid antigen tests in EU/EEA Member States and the UK

A survey, conducted by the European Commission Health Security Committee in September 2020, investigated the Member States' practices in using rapid antigen tests. Overall, of the 15 EU Member States that responded to the survey, five EU Member States are using rapid antigen tests for some aspect of the response to the COVID-19 pandemic. Nine of the 15 countries are currently carrying out clinical validation studies or pilots to assess the clinical/diagnostic performance and potential use of rapid antigen tests, and two Member States are not considering the use of rapid antigen tests [personal communication[6]]. According to this survey, some countries use the tests as part of their testing strategy for early identification of cases, conducting contact tracing, and/or implementing rapid isolation and quarantine of detected cases and their contacts. Other countries use rapid antigen tests specifically to ensure laboratory testing in remote areas where the gold standard RT-PCR is not available or timely enough. One country uses them for testing incoming travellers from other countries and in schools.

Options for the use of rapid antigen tests

Apart from the performance of the test, 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 rapid antigen test 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 for sampling and testing, and last but no least the associated cost. 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. In this section, we outline some situations that countries may encounter and provide corresponding options for the use of rapid antigen test.

Minimum performance requirements

WHO recommends that rapid antigen tests that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity can be used to diagnose SARS-CoV-2 infections in a range of settings where RT-PCR is unavailable or where an excessive turnaround time would preclude clinical and public health utility of results [20]. ECDC agrees with the WHO minimal criteria and acknowledges that the tests need to be validated for the intended setting and situation. It is important to note that rapid antigen tests perform best in the symptomatic population and soon after onset of symptoms.

Rapid antigen tests should be applied in a manner that compensates for their lower performance as compared to RT-PCR, i.e. by including confirmatory or repeat testing in certain situations (see Figure 1). As the positive (PPV) and negative (NPV) predictive values of all tests are dependent on the epidemiological situation in combination with test performance, ECDC would suggest, especially in situations of low COVID-19 prevalence, to aim for use of tests with performance closer to RT-PCR, i.e. ≥90% sensitivity and ≥97% specificity [21].

However, rapid antigen tests that only meet the minimum performance criteria can be successfully used in certain testing scenarios. 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. Sub-optimal performance of tests can be mitigated by confirmatory testing by RT-PCR (see below for examples of settings and needs for confirmatory testing and figure 1), or by using a scheme of repeated rapid antigen test testing that maximises the chances to test individuals when viral loads are within the sensitivity range of the tests.

Considerations for test validations

The clinical performance of a test should be evaluated for the intended use and conditions, including the target population (symptomatic or asymptomatic), type of specimen, sampling method, RNA extraction and RT-PCR method, as well as pre-analytical factors. A test intended for early detection of cases needs to be validated using samples from cases in this phase of infection, i.e. within the first seven days after onset of symptoms. A validation

[6] Health Security Committee Secretariat (email communication, October 2020)

exercise using a sample collection covering the full spectrum of infected individuals in different stages of infection would lead to an underestimation of the performance of the test. In addition, the manufacturer's instructions should be carefully followed for validation and the practical use of the test [22,23]. Preferably, such validation studies would be complemented with virus cultivation data from patient samples.

ECDC concurs with the validation model for rapid antigen tests presented by FIND [23]. In the validation study, the performance of the new test should be compared to the current gold standard RT-PCR. Prospective clinical comparison using fresh respiratory swabs is the preferred study model, however, a retrospective approach using frozen respiratory specimens from confirmed cases in the adapted medium might be used. Clinical performance established on frozen specimens may be different compared to fresh clinical specimens. Manufacturer's instructions for specimen handling need to be followed.

In the prospective study design, two respiratory swabs are collected per participant at the same time point: one for RT-PCR testing and diagnosis, and one for rapid antigen testing. If the same buffer/transport medium proves to be suitable for both RT-PCR and rapid antigen testing, one swab can be used for both tests. For clinical validation, data collection should continue until a minimum of 100 COVID-19 RT-PCR positives and 100 COVID-19 RT-PCR negatives are included in the study. Preferably, a total of 300 negative samples should be included.

For retrospective study design, remnant swab specimens, which have been collected from individuals suspected to have COVID-19 are used, following the manufacturer's instructions on sample handling and storage procedures. A sample set should include samples representing the target population and setting for the intended use. Different validation studies could include specimens from different time points after onset of symptom and preferably span specimens from pre- or asymptomatic individuals to severe infections. A minimum of 100 COVID-19 RT-PCR positive and 100 PCR negative samples should be included in the study. Preferably, a total of 300 negative samples should be included. For a full description of study design, please see FIND's webpage [23].

Depending on the target population or situation the test is validated for, the laboratories need to ensure the correct stratification of specimens and that they correspond to the intended use. Examples of stratification can be by days post-onset of symptoms or viral load characterised by Ct values or viral copy number.

Target population and epidemiological situation

PPV and NPV of a test depend on disease prevalence in the target population and the test performance and both should be considered when choosing to use a rapid antigen test with suboptimal sensitivity and specificity.

Table 1 shows examples of the expected prevalence of COVID-19 in different target populations in different situations. Table 2 shows the corresponding NPV and PPV when applying hypothetical rapid antigen test and RT-PCR tests with a sensitivity/specificity of 80/98% and 98/99.9% respectively, to these populations.

Table 1. Estimated prevalence ranges in different target populations in different settings

Target population	Example prevalence range
Community with high prevalence, outbreak setting, symptomatic healthcare workers	High to very high (10-≥30%)
Asymptomatic healthcare workers with significant exposure, community with high prevalence	High (10%)
Contacts of confirmed cases	Low to very high (2-30%)
Symptomatic persons in community when transmission is low	Low to high (2-10%)
Asymptomatic general population	Very low to low (≤2%)

Modified from FIND [17]

Use of rapid antigen tests by public health objectives

The public health objectives, based on the ECDC COVID-19 testing strategy [2], for which the use of rapid antigen tests may be beneficial, are the following:

- 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.

In the situations described above, rapid antigen tests can offer a significant advantage over RT-PCR in terms of bringing testing closer to persons to test and timeliness of results.

Use of rapid antigen tests by settings

Considerations for the use of rapid antigen tests in settings of low and high infection prevalence and the need for confirmatory testing

In a **high prevalence setting**, rapid antigen tests will have a high PPV (Table 2). In such a situation, a positive result from a rapid antigen test (even with a lower specificity than in RT-PCR tests and thus a higher probability of false positivity) is likely to indicate a true infection and may not require confirmation by RT-PCR. On the other hand, any negative test result should be confirmed by RT-PCR immediately or, in case of unavailability of RT-PCR, with another rapid antigen test a few days later (to allow the viral load to increase in previously false negative result). This is particularly true for asymptomatic cases with a known history of exposure. In any high-risk settings with vulnerable populations only RT-PCR should be used, unless RT-PCR capacity is limited. In vulnerable populations with symptoms, multiplex RT-PCR would be best suited for confirmation to exclude symptoms caused by other respiratory pathogens.

In a **low prevalence setting**, rapid antigen tests will have a high NPV but a low PPV (Table 2). Therefore, if used correctly, rapid antigen tests should be able to rule out a highly infectious case in such a setting. A negative test result may not require confirmation by RT-PCR, whereas a positive test will need immediate sampling for a confirmation by RT-PCR. Recurring testing by rapid antigen test every 2-3 days with the aim to identify infectious cases in a population can partly mitigate the lower sensitivity of the test and can be used in certain settings such as in staff of health care settings.

In low prevalence settings, sufficient RT-PCR 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 rapid antigen tests because of the low cost and rapid turnaround time of analysis. Here, a careful cost-benefit calculation has to 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.

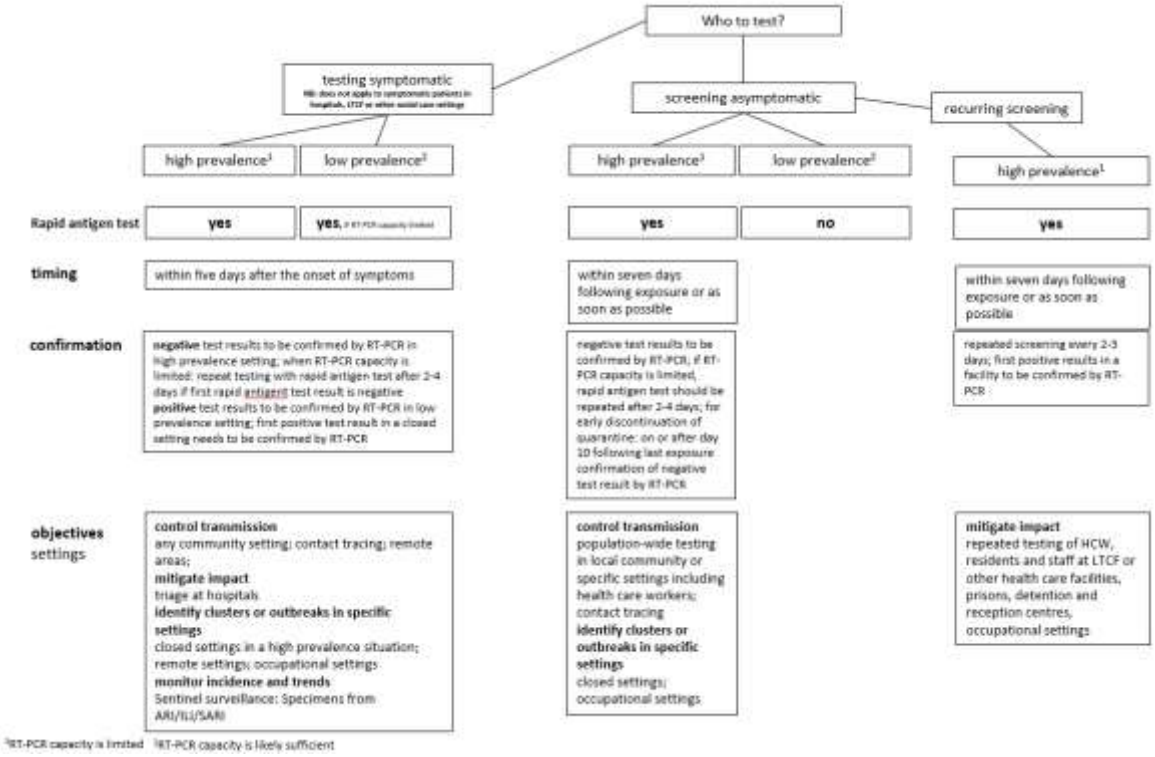
Table 2. NPV and PPV at 0.5, 1.0, 10 and 20% Covid-19 prevalence using a test with two different sensitivities and specificities, for comparison of typical performance of rapid antigen and RT-PCR tests (conceptual example)

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	1800	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	1600	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	1000	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

Use of rapid antigen tests for symptomatic and asymptomatic cases

Figure 1 gives a simple overview to guide the use of rapid antigen tests for symptomatic and asymptomatic persons in a high or low prevalence situation.

Figure 1. Flowchart describing objectives and settings when to use rapid antigen tests



Using rapid antigen tests to test people with symptoms

When the availability of RT-PCR tests is temporarily limited, the use of rapid antigen tests can be considered for individuals with COVID-19-compatible symptoms in settings and situations where the proportion of test positivity is high or very high, e.g. ≥10%. In most settings with low prevalence ECDC still recommends the use of RT-PCR for testing to increase the PPV. In the situations and settings listed below, rapid antigen tests should only be considered when sampling can be performed within five days of symptom onset. Negative rapid antigen test results should be confirmed with RT-PCR, or in the absence of RT-PCR with another rapid antigen test 2-4 days later.

- In high prevalence situations, rapid antigen tests can be applied for testing possible and probable COVID-19 cases presenting to healthcare.
- In RT-PCR-confirmed outbreaks, rapid antigen tests can be used for testing symptomatic contacts to facilitate early detection of further cases as part of contact tracing and outbreak investigation.
- In closed settings, e.g. prisons, migrant detention and reception centres, rapid antigen tests can be used to test symptomatic persons when a case has already been confirmed by RT-PCR in the setting.
- To mitigate the impact of COVID-19 in healthcare and social-care settings, rapid antigen tests 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.
- ILI/ARI/SARI samples for sentinel surveillance can be tested with rapid antigen tests, although RT-PCR should be the preferred option. Sentinel samples need to be tested for influenza and other respiratory viruses in parallel [24].

Rapid antigen tests can also be considered in specific situations in which prevalence is not high but where there is no availability of RT-PCR at all, for example migrant detention centres or occupational settings located in remote areas.

Before using rapid antigen tests, a risk assessment is needed to evaluate the probability and impact of incorrect results. Capacity for confirmatory testing by RT-PCR should be in place, see section below on considerations for use of rapid antigen tests in settings of low and high infection prevalence and the need for confirmatory testing.

Using rapid antigen tests to test people without symptoms

The use of rapid antigen tests can be recommended for testing individuals regardless of symptoms in settings in which the proportion of test positivity is expected to be ≥10%. In situations in which the time of exposure to a confirmed COVID-19 is known, testing using rapid antigen tests should be performed as soon as possible after the contacts have been identified. If more than seven days have passed since the exposure, it is recommended that negative rapid antigen tests are confirmed by RT-PCR.

- To control transmission, rapid antigen tests can be used for testing asymptomatic high-risk exposure contacts as part of contact tracing. Negative test results need to be followed up with a secondary RT-PCR test.
- In closed settings (like long term care facilities, LTCFs), asymptomatic low risk exposure contacts can be tested using a rapid antigen test. A negative result can be followed up by RT-PCR or another rapid antigen test two to four days later if RT-PCR capacities are limited. This is to ensure effective further contact tracing. Early release from quarantine based on a negative rapid antigen test or RT-PCR needs to be assessed on a case-by-case basis, especially 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 health-care settings and laboratories, rapid antigen tests' use can be considered for a targeted population-wide testing approach, e.g. in a local community. In such situation, the risk of not detecting all cases or risk of false negative results is balanced out by the timeliness of results and the possibility of serial testing of individuals.
- Rapid antigen tests 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 [25]. When a first case is confirmed in a resident or staff member of a closed setting, for example a long-term care facility, or in the event of widespread community transmission in the area (high prevalence situation), a comprehensive testing strategy of all residents and staff should be considered.

Rapid antigen tests are not suited 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, i.e. in a low prevalence population, only RT-PCR should be used to reduce the risk of false negative results. Air travellers belong mostly to a non-symptomatic subpopulation, with variable but lower probability of COVID-19 compared to the general population (estimated prevalence of COVID-19 at <1%). When considering the adoption of rapid antigen tests 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.

Further settings in which RT-PCR should be the preferred test option are diagnostic testing of patients with COVID-19-compatible symptoms in hospitals, long-term care facilities or other social care settings to avoid the consequences of false negative results. If rapid antigen tests are used in these settings, negative tests need to be confirmed with RT-PCR.

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 [26]. The highest viral load has been observed in respiratory samples collected three days before to three days after the symptom onset [27].

As mentioned above, rapid antigen tests 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 rapid antigen test should therefore be used within five days after the onset of symptoms. 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 at the viral load, depending on the actual incubation period of the virus. In these cases, the test needs to be repeated by RT-PCR. 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. For those contacts (especially high-risk exposure contacts), it is advised that the test is repeated two to four days later.

Testing capacities and availability of resources

The processing time for a sample analysed with a rapid antigen test is less than half an hour, making it considerably shorter than that of RT-PCR. However, rapid antigen tests are run individually, and some require an instrument for the read-out of the result. For some handheld rapid antigen test devices with visual readout, a small number of specimens (up to 10) can be analysed in parallel. As a result, completing a large number of tests might

be prohibitively time-consuming. In contrast, diagnostic laboratories are able to conduct RT-PCR testing on multiple samples simultaneously, and the turnaround time, when managing a very large number of samples, might be shorter.

When considering the use of rapid antigen tests, a careful analysis of the expected sample volumes, availability of resources, equipment and supplies, logistical arrangements including the expected need for confirmatory testing and supplies for those, needs to be carried out.

Biosafety considerations

At the time of writing, there is not enough evidence that buffers in the rapid antigen test testing systems are reliably inactivating SARS-CoV-2 within the short processing time. Appropriate biosafety measures must therefore 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.

Manufacturer instructions for sample collection, safe handling, proper waste management and use need to be followed precisely, including specimen type.

User considerations

For rapid antigen tests 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 rapid antigen tests 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 [28].

External quality assessment

As noted in the ECDC strategy for the external quality assessment (EQA) of public health microbiology laboratories [29], EQAs improve and maintain high quality and comparability of key laboratory surveillance data reported at the European level. One of the aims with EQAs is also to foster capabilities to detect emerging and epidemic diseases across the EU/EEA Member States and the UK. To establish high quality and comparability of rapid antigen test results for SARS-CoV-2, EQAs suitable for rapid antigen tests should be used in the diagnostic laboratories in regular intervals.

Interpretation of test results and implications for surveillance

The interpretation of rapid antigen test results and the need for confirmatory testing of results need to be agreed upon for clinical decision-making, surveillance and acceptance between regions and countries. At the moment, the EU/EEA COVID-19 case definition only includes cases with RT-PCR confirmation. The EU/EEA case definition will be updated in the near future [30].

ECDC proposes that a positive antigen test in a symptomatic person and/or a person with a clear exposure history and/or X-ray characteristic for COVID-19 should be considered as a laboratory-confirmed case. Rapid antigen test should then also be included when computing testing rates and test positivity rates. Positive confirmatory PCR or recurring rapid antigen test investigations in the same individual should not be included in these counts. If confirmatory RT-PCR remains negative, those results should be reported negative even if the rapid antigen test result would be positive. If a rapid antigen test 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.

The countries applying rapid antigen tests would need to ensure that at the minimum a representative sample of specimens are shipped to national reference laboratories to ensure characterisation of circulating viruses for surveillance purposes.

Conclusions

Rapid antigen tests 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 RT-PCR testing capacity is reduced. Together, these benefits of rapid antigen tests can contribute to more efficient interruption of transmission through more timely identification of cases and faster contact tracing. The currently available data show that rapid antigen tests can best be used in settings where the time of symptom onset is known and is up to five days after symptom onset. After that, it becomes increasingly unlikely that rapid antigen tests will perform well.

There are currently several rapid antigen tests on the EU/EEA market, but data on their clinical performance are limited and many of those data are based on a limited number of mainly symptomatic individuals. In addition, many of the reports are still preprints, and the data should therefore be interpreted cautiously.

The validation studies conducted to date show variable performance between tests. ECDC recommends Member States perform independent validations of the rapid antigen tests against RT-PCR on specimens collected from patients around the onset of disease or within seven days after exposure and to conduct setting-specific validation of tests before deciding on any rapid test to be used. From such validation studies, ECDC suggests the use of tests that have a sensitivity of 90% or above and minimum specificity of 97%.

If testing by rapid antigen test 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 rapid antigen tests, depending on the prevalence. This risk needs to be taken into account when considering the use of rapid antigen tests in specific settings. The use of rapid antigen tests also changes the logistical arrangements for testing, including resources and procedures needed for confirmatory testing, thus posing a possible challenge for Member States.

A test that is able to detect the majority of infectious cases whether symptomatic or not, and that is sufficiently rapid to maximise the effectiveness of case isolation and contact tracing, would significantly improve COVID-19 prevention and control strategies. Further clinical validation studies, especially in asymptomatic persons and with different specimen types and comparing head-to-head with quantitative RT-PCR test, need to be conducted urgently.

Contributing ECDC experts (in alphabetical order)

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

References

1. European Commission (EC). Commission Recommendation of 28.10.2020 on COVID-19 testing strategies, including the use of rapid antigen tests. 2020. Available from: https://ec.europa.eu/health/sites/health/files/preparedness_response/docs/covid19_testingstrategies_recommendation_en.pdf?utm_source=POLITICO.EU&utm_campaign=69a23e6b64-EMAIL_CAMPAIGN_2020_10_28_01_50&utm_medium=email&utm_term=0_10959edeb5-69a23e6b64-190636236&utm_source=POLITICO.EU&utm_campaign=08df23d4e5-EMAIL_CAMPAIGN_2020_10_28_02_29&utm_medium=email&utm_term=0_10959edeb5-08df23d4e5-190588983
2. European Centre for Disease Prevention and Control (ECDC). COVID-19 testing strategies and objectives.15 September 2020. . Stockholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-testing-strategies-and-objectives
3. European Centre for Disease Prevention and Control (ECDC). Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19, 8 April 2020. Stokcholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation
4. Rijskinstituut voor Volksgezondheid en Milieu (RIVM). Advies antigeen(snel)testen: Government of the Netherlands; 2020 [cited 8 November 2020]. Available from: https://www.rijksoverheid.nl/onderwerpen/coronavirus-covid-19/documenten/rapporten/2020/10/14/advies-antigeensneltesten
5. Ministry of Health Labour and Welfare (MHLW). Clinical Management of Patients with COVID-19. Tokyo: Ministry of Health Labour and Welfare; 2020 [cited 8 November 2020]. Available from: https://www.mhlw.go.jp/content/000646531.pdf
6. Haute Autorité de santé (HAS). Revue rapide sur les tests de détection antigénique du virus SARS-CoV-2: HAS; 2020 [cited 8 November 2020]. Available from: https://www.has-sante.fr/jcms/p_3213483/fr/revue-rapide-sur-les-tests-de-detection-antigenique-du-virus-sars-cov-2
7. Bundesministerium für Soziales Gesundheit Pflege und Konsumentenschutz (BMSGPK). Österreichische Teststrategie SARS-CoV-2. Wien: Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz; 2020 [cited 8 November 2020]. Available from: https://www.sozialministerium.at/Informationen-zum-Coronavirus/Neuartiges-Coronavirus-(2019-nCov).html
8. Robert Koch Institut (RKI). Nationale Teststrategie SARS-CoV-2. Berlin: RKI; 2020. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Teststrategie/Nat-Teststrat.html
9. Robert Koch Institut (RKI). Hinweise zur Testung von Patienten auf Infektion mit dem neuartigen Coronavirus SARS-CoV-2. Berlin: RKI; 2020. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.html
10. Servicio Nacional de Saude (SNS). Estratégia Nacional de Testes para SARS-CoV-2. Lisboa: Governo da República Portuguesa – Ministério da Saúde; 2020 [cited 9 November 2020]. Available from: http://www.insa.min-saude.pt/covid-19-estrategia-nacional-de-testes-para-sars-cov-2
11. World Health Organization (WHO). Coronavirus disease (COVID-19) Pandemic – Emergency Use Listing Procedure (EUL) open for in vitro diagnostics. Geneva: WHO; 2020 [cited 26 October 2020]. Available from: https://www.who.int/diagnostics_laboratory/EUL/en
12. Government of Canada. Interim guidance on the use of rapid antigen detection tests for the identification of SARS-CoV-2 infection. Government of Canada; 2020 [cited 10 November 2020]. Available from: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/use-rapid-antigen-detection-tests.html
13. US Centers for Disease Control and Prevention (CDC). Interim Guidance for Rapid Antigen Testing for SARS-CoV-2. Atlanta: CDC; 2020 [updated 4 September 2020; cited 9 November 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html
14. Van Walle I, Leitmeyer K, Broberg EK. Meta-analysis of the clinical performance of commercial SARS-CoV-2 nucleic acid, antigen and antibody tests up to 22 August 2020. medRxiv. 2020.09.16.20195917.
15. World Health Organization (WHO). Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. Interim guidance.11 September 2020. Geneva: WHO; 2020 [cited 22 October 2020]. Available from: https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays
16. European Commission (EC). Commission Recommendation of 18.11.2020 on the use of rapid antigen tests for the diagnosis of SARS-CoV-2 infection. 2020. Available from: https://ec.europa.eu/health/sites/health/files/preparedness_response/docs/sarscov2_rapidantigentests_recommendation_en.pdf
17. Foundation for Innovative New Diagnostics (FIND). FIND Evaluation of SD Biosensor, Inc. STANDARD™ F COVID-19 Ag FIA. External Report Version 1.0, 16 October 2020. Geneva: FIND; 2020 [cited 26 October

2020]. Available from: https://www.finddx.org/wp-content/uploads/2020/10/SDF_Ag-INTERIM-Public-Report_20201016-v1.pdf
18. World Health Organization (WHO). WHO Emergency Use Listing for In vitro diagnostics (IVDs) Detecting SARS-CoV-2. Geneva: WHO; 2020 [updated 2 October 2020; cited 8 November 2020]. Available from: https://www.who.int/diagnostics_laboratory/201002_eul_sars_cov2_product_list.pdf?ua=1
19. US Food and Drug Administration (FDA). In Vitro Diagnostics EUAs. Silver Spring: FDA; 2020 [cited 26 October 2020]. Available from: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-antigen
20. World Health Organization (WHO). Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. Geneva: WHO; 2020 [updated 11 September 2020; cited 8 November 2020]. Available from: https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays
21. World Health Organization (WHO). COVID-19 Target product profiles for priority diagnostics to support response to the COVID-19 pandemic v.1.0. Geneva: WHO; 2020 [cited 16 November 2020]. Available from: https://www.who.int/publications/m/item/covid-19-target-product-profiles-for-priority-diagnostics-to-support-response-to-the-covid-19-pandemic-v.0.1
22. European Commission (EC). Current performance of COVID-19 test methods and devices and proposed performance criteria - Working document of Commission services. 2020 [cited 10 November 2020]. Available from: https://ec.europa.eu/docsroom/documents/40805
23. Foundation for Innovative New Diagnostics (FIND). Comparative evaluation of lateral flow assay tests that directly detect antigens of SARS-CoV-2. Geneva: FIND; 2020 [cited 10 November 2020]. Available from: https://www.finddx.org/wp-content/uploads/2020/04/20200421-COVID-Ag-RDT-Evaluation-Synopsis.pdf.
24. European Centre for Disease Prevention and Control (ECDC) and World Health Organization Regional Office for Europe. Operational considerations for influenza surveillance in the WHO European Region during COVID-19: interim guidance. Copenhagen: WHO Regional Office for Europe; 2020 [cited 13 November 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/operational-considerations-influenza-surveillance-european-region-during-covid-19
25. European Centre for Disease Prevention and Control (ECDC). Surveillance of COVID-19 at longterm care facilities in the EU/EEA. Stockholm: ECDC; 2020 [cited 16 November 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-COVID-19-long-term-care-facilities-EU-EEA
26. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. New England Journal of Medicine. 2020;382(22):2081-90.
27. La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2020;39(6):1059-61.
28. Health Information and Quality Authority (HIQA). Rapid health technology assessment (HTA) of alternatives to laboratorybased real-time RT-PCR to diagnose current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Dublin: HIQA; 2020 [cited 10 November 2020]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/rapid-hta-alternative-tests-detect-current
29. European Centre for Disease Prevention and Control (ECDC). Strategy for the external quality assessment of public health microbiology laboratories. Stockholm: ECDC; 2020 [cited 11 November 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/strategy-external-quality-assessment-public-health-microbiology-laboratories
30. European Centre for Disease Prevention and Control (ECDC). Case definition for coronavirus disease 2019 (COVID-19), as of 29 May 2020. Stockholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition
31. BD. BD Veritor™ Plus System for rapid COVID-19 (SARS-CoV-2) testing. BD; 2020 [cited 26 October 2020]. Available from: https://www.bd.com/en-us/offerings/capabilities/microbiology-solutions/point-of-care-testing/bd-veritor-plus-system-for-rapid-covid-19-sars-cov-2-testing
32. Young S, Taylor SN, Cammarata CL, Varnado KG, Roger-Dalbert C, Montano A, et al. Clinical evaluation of BD Veritor SARS-CoV-2 point-of-care test performance compared to PCR-based testing and versus the Sofia 2 SARS Antigen point-of-care test. Journal of clinical microbiology. 2020.
33. Van der Moeren N, Zwart V, Lodder E, Van den Bijllaardt W, Van Esch H, Stohr J, et al. Performance evaluation of a SARS-COV-2 rapid antigen test: test performance in the community in the Netherlands. medRxiv. 2020:2020.10.19.20215202.
34. RapiGen. BIOCREDIT COVID-19 Ag. RapiGen; 2020 [cited 26 October 2020]. Available from: https://www.biovendor.com/file/13419/1-2%20IFU_Covid-19_Ag_Antigen_Multi%20Language%20SEP2020Watermarked.pdf?version=202009300841
35. Weitzel T, Legarraga P, Iruretagoyena M, Pizarro G, Vollrath V, Araos R, et al. Head-to-head comparison of four antigen-based rapid detection tests for the diagnosis of SARS-CoV-2 in respiratory samples. bioRxiv. 2020:2020.05.27.119255.

36. Mak GC, Cheng PK, Lau SS, Wong KK, Lau CS, Lam ET, et al. Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. J Clin Virol. 2020;129:104500-.
37. Foundation for Innovative New Diagnostics (FIND). FIND Evaluation of RapiGEN Inc. BIOCREDIT COVID-19 Ag. External Report Version 1.0, 16 October 2020. Geneva: FIND; 2020 [cited 26 October 2020]. Available from: https://www.finddx.org/wp-content/uploads/2020/10/Rapigen_Ag-INTERIM-Public-Report_20201016-v1.pdf
38. Shenzhen Bioeasy Biotechnology. BIOEASY Novel coronavirus (2019-nCoV) test kits. Shenzhen, Guangdong Province, China: Shenzhen Bioeasy Biotechnology; 2020 [cited 26 October 2020]. Available from: http://en.bioeasy.com/?page_id=1002
39. Krüger LJ, Gaeddert M, Köppel L, Brümmer LE, Gottschalk C, Miranda IB, et al. Evaluation of the accuracy, ease of use and limit of detection of novel, rapid, antigen-detecting point-of-care diagnostics for SARS-CoV-2. medRxiv. 2020:2020.10.01.20203836.
40. Porte L, Legarraga P, Vollrath V, Aguilera X, Munita JM, Araos R, et al. Evaluation of a novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. Int J Infect Dis. 2020;99:328-33.
41. CORIS Bioconcept. COVID-19 Ag Respi-Strip. CorisBioconcept SPRL; 2020 [cited 26 October 2020]. Available from: https://www.corisbio.com/Products/Human-Field/Covid-19.php#
42. Mertens P, De Vos N, Martiny D, Jassoy C, Mirazimi A, Cuypers L, et al. Development and Potential Usefulness of the COVID-19 Ag Respi-Strip Diagnostic Assay in a Pandemic Context. Frontiers in medicine. 2020;7:225.
43. Lambert-Niclot S, Cuffel A, Le Pape S, Vauloup-Fellous C, Morand-Joubert L, Roque-Afonso A-M, et al. Evaluation of a Rapid Diagnostic Assay for Detection of SARS-CoV-2 Antigen in Nasopharyngeal Swabs. Journal of clinical microbiology. 2020;58(8):e00977-20.
44. Blairon L, Wilmet A, Beukinga I, Tré-Hardy M. Implementation of rapid SARS-CoV-2 antigenic testing in a laboratory without access to molecular methods: Experiences of a general hospital. Journal of Clinical Virology. 2020;129:104472.
45. Veyrenche N, Bollore K, Pisoni A, Bedin A-S, Mondain A-M, Ducos J, et al. Diagnosis value of SARS-CoV-2 antigen/antibody combined testing using rapid diagnostic tests at hospital admission. medRxiv. 2020:2020.09.19.20197855.
46. Scohy A, Anantharajah A, Bodéus M, Kabamba-Mukadi B, Verroken A, Rodriguez-Villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. Journal of Clinical Virology. 2020;129:104455.
47. Foundation for Innovative New Diagnostics (FIND). FIND Evaluation of Coris BioConcept COVID-19 Ag Respi-Strip. External Report Version 1.0, 18 September 2020. Geneva: FIND; 2020 [cited 26 October 2020]. Available from: https://www.finddx.org/wp-content/uploads/2020/09/Coris-RespiStrip-Ag_Public-Report_20200918.pdf
48. Fujirebio. Lumipulse® G SARS-CoV-2 Ag. Fujirebio; 2020 [cited 26 October 2020]. Available from: https://www.fujirebio.com/en/products-solutions/lumipulse-g-sars-cov2-ag
49. Hirotsu Y, Maejima M, Shibusawa M, Nagakubo Y, Hosaka K, Amemiya K, et al. Comparison of automated SARS-CoV-2 antigen test for COVID-19 infection with quantitative RT-PCR using 313 nasopharyngeal swabs including from 7 serially followed patients. Int J Infect Dis. 2020.
50. Abbott. PANBIO™ COVID-19 Ag rapid test device. Abbott; 2020 [cited 26 October 2020]. Available from: https://www.globalpointofcare.abbott/en/product-details/panbio-covid-19-ag-antigen-test.html
51. Albert E, Torres I, Bueno F, Huntley D, Moya E, Fernandez-Funtes MA, et al. Field evaluation of a rapid antigen test (Panbio COVID-19 Ag Rapid Test Device) for the diagnosis of COVID-19 in primary healthcare centers. medRxiv. 2020:2020.10.16.20213850.
52. Gremmels H, Winkel BMF, Schuurman R, Rosingh A, Rigter NAM, Rodriguez O, et al. Real-life validation of the Panbio COVID-19 Antigen Rapid Test (Abbott) in community-dwelling subjects with symptoms of potential SARS-CoV-2 infection. medRxiv. 2020:2020.10.16.20214189.
53. Linares M, Pérez Tanoira R, Romanyk J, Pérez García F, Gómez-Herruz P, Arroyo T, et al. Panbio antigen rapid test is reliable to diagnose SARS-CoV-2 infection in the first 7 days after the onset of symptoms. medRxiv. 2020:2020.09.20.20198192.
54. SD BIOSENSOR. SD BIOSENSOR. SD BIOSENSOR; 2020 [cited 26 October 2020]. Available from: http://www.sdbiosensor.com/xe
55. ROCHE. Roche to launch SARS-CoV-2 Rapid Antigen Test in countries accepting CE mark, allowing fast triage decisions at point of care. Basel: F. Hoffmann-La Roche Ltd; 2020 [cited 26 October 2020]. Available from: https://www.roche.com/media/releases/med-cor-2020-09-01b.htm
56. Cerutti F, Burdino E, Milia MG, Allice T, Gregori G, Bruzzone B, et al. Urgent need of rapid tests for SARS CoV-2 antigen detection: Evaluation of the SD-Biosensor antigen test for SARS-CoV-2. J Clin Virol. 2020;132:104654.
57. Liotti FM, Menchinelli G, Lalle E, Palucci I, Marchetti S, Colavita F, et al. Performance of a novel diagnostic assay for rapid SARS-CoV-2 antigen detection in nasopharynx samples. Clin Microbiol Infect. 2020:S1198-743X(20)30583-8.
58. Quidel Corporation. Sofia SARS Antigen FIA. Quidel Corporation; 2020. Available from: https://www.quidel.com/immunoassays/rapid-sars-tests/sofia-sars-antigen-fia

Annex 1. Overview of available clinical validation results by antigen test by 06 November 2020

Antigen test	Manufacturer	Type of interpretation	Authorization/ certification	Country tested	Type of specimen	Population	Stratified analysis	Sensitivity %[a] (95%CI)	Specificity % (95%CI)	Ref
BD Veritor™ System for Rapid Detection of SARS-CoV-2	Becton, Dickinson and Company, BD Life Sciences—Integrated Diagnostics Solutions, Sparks, MD, USA [31]	NR	CE-IVD Brazil ANVISA FDA-USA	United States	Nasopharyngeal or oropharyngeal swabs	Symptomatic (n= 251)	 By symptoms onset 1 dpo 2 dpo 3 dpo 4 dpo 5 dpo 6 dpo ≤ 7 dpo	76.3 (60.8-87.0) 87.5 (52.9 – 97.8) 85.0 (64.0 – 94.8) 81.8 (61.5 – 92.7) 85.2 (67.5 – 94.1) 83.9 (67.4 – 92.9) 82.4 (66.5 – 91.7) 76.3 (60.8 – 87.0)	99.5 (97.7-99.9) 100 (88.6 – 100) 100 (95.1 – 100) 100 (97.1 – 100) 100 (97.7 – 100) 100 (98.1 – 100) 99.5 (97.4 – 99.9) 99.5 (97.4 – 99.9)	[32]
				The Netherlands	Nasal swabs	Symptomatic adults (n=352)	 By symptoms onset < 7 dpo ≥ 7 dpo By symptoms onset and Ct values < 7 dpo, Ct < 20 < 7 dpo, Ct 20-25 < 7 dpo, Ct 25- 30 < 7 dpo, Ct ≥ 30 < 7 dpo, Ct < 30 ≥ 7 dpo, Ct < 20 ≥ 7 dpo, Ct 20-25 ≥ 7 dpo, Ct 25- 30 ≥ 7 dpo, Ct ≥ 30 < 7 dpo, Ct < 30	80.7 (73.2-86.9) **91.0** (82.4-96.3) 67.2 (53.7 - 79.0) **100** (85.2-100) **100** (89.7- 100) **92.3** (64.0 – 99.8) 25.0 (3.2 – 65.1) **98.6** (92.3 -100) **100** (29.2 -100) 81.3 (54.4- 96.0) 87.0 (66.4- 97.2) 18.8 (4.1 – 45.7) 85.7 (71.5 – 94.6)	100(98.9-100) NR NR NR NR NR NR NR NR NR NR NR NR	[33]

Antigen test	Manufacturer	Type of interpretation	Authorization/ certification	Country tested	Type of specimen	Population	Stratified analysis	Sensitivity %[a] (95%CI)	Specificity % (95%CI)	Ref
RapiGen Biocredit COVID-19 Ag One 90 Step SARS-CoV-2	RapiGEN Inc., Anyang-si, Gyeonggi-do, Republic of Korea [34]	Visual	CE-IVD Brazil Philippines	Chile	Nasopharyngeal or oropharyngeal swabs	Symptomatic (n=111)	By Ct values Ct < 25 Ct > 25	62.0 (51.0-71.9) 84.9 (72 - 92) 15.4 (6 - 34)	100 (88.7-100) NR NR	[35]
				Hong Kong	Respiratory samples	NR (n= 336) NPA-TS (n=81) NPS-TS (n=103) Sputum(n= 62) Saliva(n= 122)	By type of samples NPA-TS NPS-TS Sputum Saliva By type of samples and Ct values [b] NPA-TS, Ct < 18.57 NPS-TS, Ct < 18.57 Sputum, Ct < 18.57 Saliva, Ct < 18.57 NPA-TS, Ct >18.57 NPS-TS, Ct > 18.57 Sputum, Ct > 18.57 Saliva, Ct > 18.57	34.3 (NR) 45.7 (NR) 11.1 (NR) 40.0 (NR) 81.8 (NR) 80.0 (NR) 28.6 (NR) 53.8 (NR) 12.5 (NR) 0 [c] 7.9 (NR) 21.1 (NR)	 NR NR NR NR NR NR NR NR NR NR NR NR	[36]
				Brazil	Nasopharyngeal swabs	Symptomatic (n=476)	By symptoms onset ≤ 7 dpo By Ct values Ct < 25 Ct < 33	74.4 (65.8-81.4) 77.6 (68.3-84.7) **90.9** (80.5-96.1) 82.5 (73.7-88.8)	98.9 (97.2-99.6) NR NR NR	[37]

Antigen test	Manufacturer	Type of interpretation	Authorization/ certification	Country tested	Type of specimen	Population	Stratified analysis	Sensitivity %[a] (95%CI)	Specificity % (95%CI)	Ref
Bioeasy 2019-nCoV Ag Fluorescence Rapid Test Kit	Shenzhen Bioeasy Biotechnology Co. Lt. Guangdong Province, China [38]	Reader	CE-IVD	Germany and the UK	Nasopharyngeal or oropharyngeal swabs	Symptomatic (n=727)	By Ct values Ct < 25 Ct ≥ 25	66.7 (41.7-84.8) 88.9 (56.5 -99.4) 33.3 (9.7-70.0)	93.1 (91.0-94.8) NR NR	[39]
				Chile	Nasopharyngeal or oropharyngeal swabs	Symptomatic (n=127)	By symptoms onset 0-7 dpo 8-12 dpo By Ct values [d] Ct < 25.1 Ct ≥ 25.1	**93.9** (86.5-97.4) **94.7** (87.2 -97.9) 80.0 (37.6 – 96.4) **100** (89.8-100) 49.1 – 87.5	100 (92.1-100) 100 (NR) 100 (NR) NR NR	[40]
				Chile	Nasopharyngeal or oropharyngeal swabs	Symptomatic (n=111)	By Ct values Ct < 25 Ct > 25	85.0 (75.6-91.2) **100** (94 -100) 54 (35 - 71)	100 (89.0-100) NR NR	[35]
Coris COVID-19 Ag Respi-Strip	Coris Bioconcept, Gembloux, Belgium [41]	Visual	CE-IVD	Belgium	Nasopharyngeal swabs	Symptomatic (n= 328) HCW (n=53)	By Ct values Ct < 25 By sub-population and Ct values HCW, Ct < 25	57.6 (NR) 73.9 (NR) **92.9** (NR)	99.5 (NR) NR NR	[42]
				France	Nasopharyngeal swabs	NR (n= 138)	By Ct values Ct < 25	50.0 (39.5-60.5) 82.2 (NR)	100 (91.8-100) NR	[43]
				Belgium	Nasopharyngeal swabs	NR (n= 56)		30 (16.7–47.9)	100 (NR)	[44]
				France	Nasopharyngeal swabs	Symptomatic (n=45)	By Ct values Ct ≤ 25 Ct 25-34 Ct ≥ 35 By symptoms onset ≤ 7 dpo 7- 14 dpo > 14 dpo	29.0 (15.7-42.3) 87 (70-100) 0 0 41.0 (20.4 – 61.6) 29.0 (5.2 – 52.8) 0	100 (NR) 100 (NR) 100 (NR) 100 (NR) 100 (NR) 100 (NR) 100 (NR)	[45]

Antigen test	Manufacturer	Type of interpretation	Authorization/ certification	Country tested	Type of specimen	Population	Stratified analysis	Sensitivity %[a] (95%CI)	Specificity % (95%CI)	Ref
				Belgium	Nasopharyngeal swabs	NR (n=148)	By Ct values Ct < 25 Ct < 30 Ct < 35	30.2 (21.7-39.9) **100** (NR) 70.6 (NR) 46.9 (NR)	100 (NR) NR NR NR	[46]
				Germany and the UK	Nasopharyngeal or combined nasopharyngeal and oropharyngeal swabs	Symptomatic (n=425)	By symptoms onset <7 dpo	50 (21.5-78.5) 42.9 (15.8-75.0)	95.8 (93.4-97.4) NR NR NR	[47]
LUMIPULSE SARS-CoV-2 Ag kit	Fujirebio, Japan [48]	NR	CE--IVD	Japan	Nasopharyngeal swabs	NR (n= 313)	By viral load > 100 copies 10-100 copies 1 – 10 copies < 1 copy	55.2 (41.5-68.2) 100 (NR) 60 (NR) 33 (NR) 26 (NR)	99.6 (97.8-99.9) NR NR NR NR	[49]
Abbott Panbio™ COVID-19 Ag Rapid Test	Abbott Rapid Diagnostics, Chicago, US [50]	Visual	CE-IVD WHO EUL	Spain	Nasopharyngeal swabs	Symptomatic (n= 412) Adults (n= 387) Children (n=85)	By sub-population Adults Children By symptoms onset < 5 dpo By Ct values Ct < 25	79.6 (67.0-88.8) 82.6 (69.3 -90.9) 62.5 (30.6-86.3) 80.4 (66.8-89.3) **100** (NR)	100 (98.7-100) NR NR NR NR	[51]
				The Netherlands	Nasopharyngeal swabs	Symptomatic (n= 1367)	By Ct value Ct < 32	72.6 (64.5-79.9) **95.2** (89.3-98.5)	100 (99.7-100) NR	[52]
				Aruba	Nasopharyngeal swabs	Symptomatic (n= 208)	By Ct value Ct < 32	81.0 (69.0 -89.8) **98.0** (89.2–99.95)	100 (97.5-100) NR	[52]
				Chile	Nasopharyngeal swabs	Symptomatic (n= 185) Asymptomatic (n= 55) Total (n= 240)	By symptoms onset < 7 dpo By Ct values Ct<25	73.3 (62.2-83.8) 86.5 (75.0 – 97.0) 100 (NR) 87.5 (NR)	100 (NR) NR NR NR	[53]

Antigen test	Manufacturer	Type of interpretation	Authorization/ certification	Country tested	Type of specimen	Population	Stratified analysis	Sensitivity %[a] (95%CI)	Specificity % (95%CI)	Ref
							Ct<30 Ct<35	25 (NR)	NR	
SD Biosensor Standard F COVID-19 Ag FIA	SD Biosensor, Inc. Gyeonggi-doo, Korea F. Hoffmann-La Roche LTD, Basel, Switzerland	Reader	CE-IVD	Brazil	Nasopharyngeal swabs	Symptomatic (n= 421) Asymptomatic (n=29) Total (n= 453)	By symptoms onset ≤ 7 dpo By Ct value Ct ≤ 25 Ct ≤ 33	77.5 (69.2-84.1) 80.2% (71.1, 86.7) 87.9% (77.9, 93.7) 80.9% (72.6, 87.2)	80.2 (71.1-86.7) NR NR NR	[17]
SD Biosensor Standard Q COVID-19 Ag Test	SD Biosensor, Inc. Gyeonggi-doo, Korea [54] F. Hoffmann-La Roche LTD, Basel, Switzerland [55]	Visual With F2400 device	CE-IVD Brazil WHO FDA USA - EUA	Germany and the UK	Nasopharyngeal or oropharyngeal swabs	Symptomatic (n=2417)	By type of specimen NPS OPS NPS/OPS (Berlin) NPS/ OPS (Liverpool) By symptoms onset 0-7 dpo 8- 14 dpo >14 dpo By disease severity Category 1 [f] Category 2 [g] Category 3 [h] By Ct values Ct < 25 Ct ≥ 25	76.6 (62.8-86.4) 57.1(25.0-84.1) NA[e] 79.5 (64.5 -89.2) NA 80.0 (64.1 -90.0) **100** (51.0- 100) NA 58.8 (36.0 -78.4) 85.7 (65.4 -95.0) **100** (51.0-100) **100** (82.4 -100) 62.1 (44.0 -77.3)	99.3 (98.6-99.6) 97.9 (95.6 -99.1) 100 (90.1 -100) 99.7 (99.0-99.9) 100 (83.2 -100) 99.2 (98.4 -99.6) 100 (93.0 – 100) 100 (74.1 -100) 99.2 (97.9 -99.7) 99.2 (98.2 – 99.7) 100 (84.5 – 100) NR NR	[39]
				Italy	Nasopharyngeal swabs	Symptomatic (n= 185) Travellers (n= 145) Total (n= 330)	By Ct value Ct < 28 Ct < 28-30 Ct < 31-34 Ct > 34	70.6 (NR) **100** (NR) 38.5 (NR) 26.7 (NR) 9.1 (NR)	100 (NR) NR NR NR NR	[56]

Antigen test	Manufacturer	Type of interpretation	Authorization/ certification	Country tested	Type of specimen	Population	Stratified analysis	Sensitivity %[a] (95%CI)	Specificity % (95%CI)	Ref
				Italy	Nasopharyngeal swabs	NR (n= 359)		47.1 (37.1-57.1)	98.4 (96.0-99.6)	[57]
				The Netherlands	Nasopharyngeal swabs	Mild symptomatic (n=521)	By Ct value Ct < 20 Ct < 25 Ct < 30	87.14 (77-93.95) **100** (NR) **95** (NR) 67 (NR)	100 (99.2- 100) NR NR NR	Pc[7]
				The Netherlands	Nasopharyngeal swabs	Mild symptomatic (n=798)	By Ct value Ct <30	83.6 (NR) **93.7** (NR)	99.5 NR	Pc[8]
				The Netherlands	Nasopharyngeal swabs	Total (n= 977) Symptomatic 92%	By symptoms onset and Ct values ≤3 dpo, Overall ≤3 dpo; Ct < 25 ≤3 dpo; Ct<30 ≤7 dpo; Overall; ≤7 dpo; Ct < 25; ≤7 dpo; Ct<30)	84.0 (78.1-88.6) **99.3** (84.1-97.4) **100** (92.1-100) **96.5** (88.1-99.0) 89.9 (83.5-94.0) **98.8** (93.7-99.9) **95.0** (89.4-97.7)	99.5 (98.7-99.8) 96.6 (97.9-100) NR NR 96.6 (95.9-98.6)	Pc[9]
				The Netherlands	Nasopharyngeal swabs	Mild symptomatic (n=628)	By Ct values: Ct < 20 Ct < 25	78.0 (69.4-85.1) **92.7** (NR) **90.3** (NR)	99.6 (98.6-99.9)	Pc[10]

[7] Chantal Reusken PhD, RIVM, the Netherlands (email communication, November 2020)
[8] Chantal Reusken PhD, RIVM, the Netherlands (email communication, November 2020)
[9] Clinical evaluation of the Roche/SD Biosensor rapid antigen test with symptomatic, non-hospitalized patients in a municipal health service drive-through testing site. Zsófia Igloi, Jans Velzing, Janko van Beek, David van de Vijver, Georgina Aron, Roel Ensing, Kimberley Benschop, Wanda Han, Timo Boelsums, Marion Koopmans, Corine Geurtsvankessel, Richard Molenkamp. (Manuscript in preparation)
[10] Chantal Reusken PhD, RIVM, the Netherlands (email communication, November 2020)

Antigen test	Manufacturer	Type of interpretation	Authorization/ certification	Country tested	Type of specimen	Population	Stratified analysis	Sensitivity %[a] (95%CI)	Specificity % (95%CI)	Ref
							Ct < 30	84.4 (NR)		
Quidel, SARS Ag Test with Sofia 2 device	Quidel Corporation, San Diego, US [58]	NR		The Netherlands	Nasopharyngeal swabs	Mild symptomatic (n=733)	By Ct values: Ct < 20 Ct < 25 Ct < 30	84.0 (77-89.6) **91.8** (NR) **93.5** (NR) 79.2 (NR)	99.0 (99.1-100)	Pc[10]

Pc: personal communication
CE-IVD = CE Marking according to the Requirements of European Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices (IVDD) or its successor Directive; Ct= cycle threshold; Brazil ANVISA= Brazil National Health Surveillance Agency; dpo= days post symptoms onset; FDA = United States Federal Drug Agency; NA = not applicable; NPA-TS= Nasopharyngeal aspirate and throat swab; NPS= Nasopharyngeal swab; NPS-TS= Nasopharyngeal swab and throat swab; NR= not reported, OPS= oropharyngeal swab;
[a] Results >90% sensitivity are presented in bold.
[b] The Ct threshold was defined by the limit of detection between the antigen test, viral culture and RT-PCR calculated in this study.
[c] None of the positive samples tested were detected by the antigen test.
[d] Ct values was defined by using the upper limit of the interquartile range of the Ct values of all samples tested.
[e] No positive PCR results in this category.
[f] Category 1: normal activity possible
[g] Category 2: light restrictions and able to walk
[h] Category 3: limited self-sufficiency and completely need of care