AVIS SUR L'UTILISATION DES TESTS AG RAPIDES ET LE TYPE D'ÉCHANTILLONNAGE POUR LE DÉPISTAGE DU VARIANT SARS-COV-2 OMICRON

RAG subgroup Testing – 10 janvier 2022

> Note : Les recommandations actuelles sont susceptibles d'être modifiées en fonction de nouvelles informations et/ou de l'évolution de l'épidémie.

Recommandations:

- Commencer dès que possible la validation des tests Ag rapides disponibles sur le marché belge :
  - La validation doit être effectuée par Sciensano en collaboration avec le Centre national de référence (NRC).
  - La priorité doit être donnée aux tests les plus couramment utilisés.
  - Il convient d'utiliser au maximum les résultats déjà disponibles dans d'autres pays.
  - La validation devrait de préférence être effectuée avec d'autres pays européens.
  - Une liste des tests évalués comme ayant des performances suffisantes et une liste des tests évalués comme ayant des performances insuffisantes doivent être publiées sur le site Web de Sciensano.
- Dans l'attente des résultats de la validation, les lignes directrices actuelles concernant l'utilisation des tests Ag rapides et des autotests doivent être maintenues.
- L'attention des professionnels de santé et du grand public doit être attirée sur la nécessité de faire preuve d'une prudence particulière lorsque le résultat d'un test Ag rapide/autotest est négatif et de prendre toutes les mesures de précaution même lorsque le résultat est négatif. L'objectif principal d'un autotest est d'écarter la possibilité qu'une personne soit hautement contagieuse, mais pas de confirmer qu'elle ne l'est pas.
- Dans la mesure du possible, les professionnels de santé doivent préférer temporairement un écouvillon combiné nez-gorge à un écouvillon nasopharyngé pour la détection du COVID-19 (quel que soit le type de test effectué).

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CONTEXT

There are concerns about the performance of rapid Ag tests to detect the new SARS-CoV-2 variant, Omicron, and about the use of nasal samples. The use of rapid Ag tests, both administered by a health professional (mostly at pharmacies) and as at-home self-tests, is currently strongly promoted to reduce the burden on the RT-PCR testing capacity. A possible lesser sensitivity for detecting Omicron, compared to previous variants, could result in a large number of infections remaining undetected. In addition, the current standard is to detect SARS-CoV-2 in nasopharyngeal samples (NPS) and, in the event of self-tests, on mid-turbinate or anterior nasal samples. As the Omicron variant may have different kinetics, and could be present in the nasopharynx and nose at a later stage during the infection than previous variants, this could further increase the number of undetected infections. An advice was therefore requested on the use of rapid Ag tests and the type of specimen to collect, now that Omicron has become the dominant variant.

DISCUSSION

Use of rapid Ag tests

- What was known about the performance of rapid Ag tests before Omicron:
    - Their specificity is high (although not 100%)
    - They perform well in detecting highly infectious individuals and infections with high viral load (sensitivity of around 95%)
    - They perform poorly in detecting infections with low viral load (<50%)
    - Therefore, they can miss infections in the early (pre-symptomatic) phase
    - They do not perform sufficiently well on saliva samples
    - Self-administered rapid Ag tests have a higher risk of failure than provider-administered tests

- What is known about their performance for detecting Omicron, compared to previous variants
    - One in-vitro study found an on average lower analytical sensitivity to detect Omicron compared to other variants
    - On the other hand, another in-vitro study evaluated one rapid Ag test (Abbott) and concluded it was sufficiently effective in detecting Omicron, similar to other variants.
    - Two clinical studies found a low sensitivity in detecting positive Omicron samples, **even when viral load was high or viral culture positive**, particularly in the early phase of infection. Another clinical study found, however, a similar sensitivity as was observed in prior variants.
    - Results from evaluations by specific countries are inconclusive. The UK and the Netherlands report reassuring preliminary results, while the US reports a potentially reduced sensitivity.
    - As far as known, no agency has as yet updated its guidance on the use of rapid Ag tests.

- There is a need to validate the rapid Ag tests currently sold in Belgium, or at least the ones that are most commonly sold in Belgium. The objective of this validation is double: (1) to validate which brands have an acceptable performance, and which brands don't; (2) to validate their performance in the detection of Omicron, compared to previous variants.

- The commissariat has already requested Sciensano and the FAGG/AFMPS to initiate such a validation process. It was agreed that this is best done in collaboration with the National Reference Centre.

- Some countries, such as Germany, have already done this type of validation exercise. Possibly their findings could be used for the Belgian validation, and possibly this validation could be done in conjunction with other neighboring countries.

- A similar validation exercise has been done in the past for rapid antibody tests.

- FAGG/AFMPS cannot prohibit the use of rapid Ag tests that received CE-marking. Sciensano can, on the other hand, always publish a list of the tests that have been validated as sufficiently performant and a list of the tests that have been shown as insufficiently performant. This list can then serve as guidance for GPs, pharmacists and supermarkets.

- While awaiting the results of this validation exercise, there is no need to change the current indications for the use of rapid Ag tests/ self-tests. However, health providers and the public need to be made aware that they perform poorly in detecting infections with low viral load.

- There is a risk of false negative results in case of lower excretion and inadequate sampling. Therefore, a negative result can never be a reason to stop respecting the precautionary measures in place.

Type of specimens to use for Omicron detection

- What was known about the use of different specimens before Omicron:
  - Nasopharyngeal and combined nose-throat swabs have the highest sensitivity (although not 100%)
  - RT-PCR on saliva specimens, in particular if obtained through enhanced collection, performs similarly when viral load is high, but somewhat less when it is low (asymptomatic individuals).
  - Rapid Ag tests do not perform well on saliva specimens.
  - Nasal swabs perform well when viral load is high and in symptomatic people. In asymptomatic people they have probably a lower, but still acceptable, sensitivity than nasopharyngeal swabs.
  - Self-collected nose-throat swabs perform probably slightly less well compared to health care provider collected nose-throat swabs.

- What is known about the use of different specimens for the detection of Omicron:
  - One study found a better sensitivity for detecting Omicron by RT-PCR on saliva swabs than by RT-PCR on mid-turbinate nasal swabs, while for the detection of

Delta it was the opposite. The study was, however, small with large overlapping confidence intervals.

- o Anecdotal evidence is circulating on Twitter about a higher chance of testing positive when using throat samples compared to nasal samples (mostly in a context of self-testing).
- o As far as known, no agency has as yet updated its guidance on the type of specimen to use.

- The evidence of different kinetics of the Omicron variant, compared to previous variants, and a later presentation in the nasal area is still very limited.

- Nevertheless, caution has to be taken and wherever possible a combined nose-throat swab should be temporarily (until there is more evidence) preferred above a nasopharyngeal swab.

- For self-testing this recommendation is not possible, because self-tests are only approved to be used according the manufacturer's instructions. In addition, it is not sure if the provided swab is appropriate for throat swabbing.

RECOMMENDATIONS

- To initiate as soon as possible the requested validation exercise of the rapid Ag tests/self-tests available on the Belgian market.
    - o The validation should be done by Sciensano in collaboration with the National Reference Centre.
    - o Priority should be given to the most commonly used tests.
    - o Results already available from other countries should be used as much as possible.
    - o The validation is preferably done together with some of the other European countries.
    - o A list of tests evaluated as sufficiently performant and a list of tests evaluated as insufficiently performant should be published on the Sciensano website.

- While awaiting the results of the validation exercise, maintain the current indications for the use of rapid Ag tests and self-tests.

- Issue an alert for health care providers and communicate to the general public that special care has to be taken when the result of a rapid Ag test/ self-test is negative and that even with a negative result all precautionary measures still need to be respected. The main purpose of a self-test is to exclude that a person is highly contagious, but not to confirm that he/she is not infected.

- To issue an alert for health care providers that, as much as possible, temporarily a combined nose-throat swab is preferred above a nasopharyngeal swab for the detection of COVID-19 (regardless of the type of test performed).

BACKGROUND

Current guidelines

The current **indications for rapid Ag tests** are available at the Sciensano website[1]. In summary:

- They are recommended in patients with symptoms<=5 days
- They can be used, by or under supervision of a health care provider:
    - in returning and arriving travelers, and departing travelers if allowed by the country of destination
    - for obtaining a CST and for pre-event screenings
    - in repetitive screening programs
- They can be used as self-tests:
    - out of courtesy before contacts with people outside the household
    - after an at-risk contact, including in partially or non-vaccinated high-risk contacts to terminate quarantine earlier

The current guidelines on the use of different specimens is also available at the Sciensano website[2]. In summary:

- The preferred sample is either a (health care provider-administered) nasopharyngeal or a combined nose-throat swab
- Saliva specimens are acceptable, but <u>only if tested with RT-PCR</u>:
    - in patients with symptoms<=5 days
    - in repetitive screenings
    - for obtaining a CST and for pre-event screenings, if under supervision of a health care provider
    - if a nasopharyngeal or combined nose-throat swab is impossible or very difficult (for example very young children, too much pain or discomfort…)
- Nasal swabs (anterior or mid-turbinate) are acceptable:
    - in patients with symptoms<=5 days in which a nasopharyngeal or combined nose-throat swab is impossible or very difficult
    - for self-testing

Scientific evidence

Performance of rapid Ag tests, pre-Omicron

A review of the literature with regards to the performance of rapid Ag tests and self-tests was done for the recent advice on the use of self-tests (20211223_Advice_RAG_update indications for self-testing_NL.pdf (sciensano.be)).

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[1] Snelle antigeen (Ag) testen | Coronavirus Covid-19 (sciensano.be) or Tests rapides antigéniques (Ag) | Coronavirus Covid-19 (sciensano.be)
[2] Staalafname | Coronavirus Covid-19 (sciensano.be) or Prélèvement d'échantillons | Coronavirus Covid-19 (sciensano.be)

In brief, multiple studies have been published validating the performance of specific rapid Ag tests, and several systematic reviews and meta-analyses of these studies have already been done (1–4). In addition, some countries have validated large number of brands before authorizing them in the country (5,6). Overall, performance of tests in clinical practice differs markedly from the manufacturers reported performance, and varies substantially across studies and across brands. The main determinant of the sensitivity of the tests is viral load, with on average an overall sensitivity around 70-75%, a sensitivity of around 96% when viral load is very high (Ct<20), and of around 50% when viral load is low (Ct>=25). Specificity is on average around 99%.

A study by the NRC, comparing the performance of a breath test with PCR and rapid Ag tests on NPS, prospectively followed high-risk contacts from an early phase onwards and found that rapid Ag tests performed poorly in the early and late stages of infection (7). During the 2 days prior to onset of symptoms, rapid antigen tests only detected half of the positive patients.
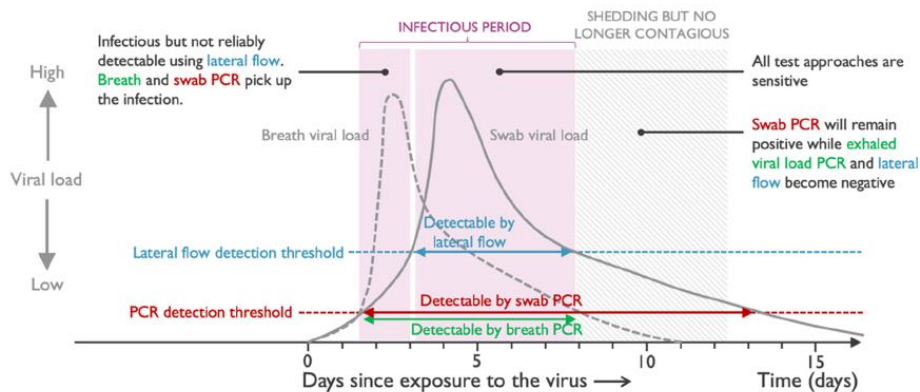
Source: Adapted from FT and Michael Mina et al., "Rethinking Covid-19 test Sensitivity – A Strategy for Containment", N Engl J Med 2020; 383:e120
Note: lateral flow test = rapid antigen test

Several studies have, prior to Omicron, shown reduced sensitivity when using saliva specimens, sometimes to alarmingly low levels (8–15); and sensitivity is less when the test is self-administered compared to administered by a health professional (8,16,17).

Performance of rapid Ag tests for the detection of Omicron

In-vitro studies

A study in Switzerland evaluated in-vitro analytical sensitivity of 7 rapid Ag tests using cultured SARS-CoV-2 Omicron variant, and compared this to earlier data on previous variants (18). **Analytical sensitivity to detect Omicron was lower than for the other variants in most tests** evaluated, although with considerable heterogeneity across variants and between individual assays. As possible explanation, the authors mention the different epitopes used in each test, potentially affected by the mutations in the nucleocapsid.

In addition, the authors evaluated retrospectively the sensitivity of five rapid Ag tests on 10 nasopharyngeal specimens that had tested positive for Omicron with RT-PCR (19). With exception of one test, **all tests had failures in detecting infections with high viral load and positive on culture.**

A study in the US validated the Abbott BinaxNow assay on anterior nasal swabs that had tested positive with RT-PCR (20). They tested two omicron variant specimens and two delta variant specimens and the results were interpreted by three different readers. The four specimens **with concentrations of 100,000 copies/swab or greater were positive with both the delta and omicron variant specimens**. Assay sensitivity was diminished below that, with positive results in 1/4 omicron specimens and 1/3 of delta specimens (with the fourth delta specimen resulting in discordant reads between reviewers). All specimens with 2,500 copies/swab were interpreted as negative. The authors conclude that **the results are qualitatively similar to results with previous variants** suggesting that the BinaxNow assay can detect the Omicron variant.

The USA's FDA monitors the potential impact of genetic variants on antigen tests in collaboration with the NIH. On 28 December 2021, the FDA reported that they recently performed preliminary studies evaluating some antigen tests using patient samples containing live virus, and that early data suggests that antigen tests **do detect the omicron variant but may have reduced sensitivity** (21). This was in contrast with initial laboratory tests using heat-inactivated samples, in which the performance was similar to previous variants. The FDA stresses that this needs to be confirmed by clinical studies and continues to authorize the use of rapid Ag tests.

In its Technical briefing of 17 December 2021, the UK Health Security Agency reports that preliminary results of a laboratory evaluation of the rapid Ag tests in use by NHS Test and Trace indicate a **comparable sensitivity to that observed for previous strains** of SARS-CoV-2 including Delta (22).

The RIVM of the Netherlands assessed the analytical sensitivity of 7 rapid Ag self-tests using cultured Omicron samples (23). At high viral load (>=1.35E+04 TCID50/ml; ~Ct<19.5) samples from all RATs tested positive in triplicate. At a concentration of 2.70E+03 TCID50/ml, 3 RATS had weak positive results, and at a concentration of <=5.41E+02 TCID50/ml (~Ct>24.5) no samples tested positive. The authors conclude that 4 RATS meet the pre-established criteria without discussion, and that the reason for the weak positive results was probably due to the smaller tip of the swab that was used. They conclude that the performance of the tested rapid Ag self-tests is **similar to evaluations with previous clades and not affected by the Omicron variant**, and therefore meeting the pre-set criteria.

Clinical studies

A study in the US compared the performance of rapid Ag tests (Quidel QuickVue At-Home OTC COVID-19 Test and Abbott BinaxNOW COVID-19 Antigen Self-Test) on self-collected nasal swabs with RT-PCR on saliva, in Omicron outbreaks at the workplace during December 2021 (24). 62 matched pairs of 30 individuals were compared. Viral dynamics and discordance in test results are shown in the figure below. **The rapid Ag tests were mostly negative in the first 3 days after the first positive RT-PCR test, including in several cases where the viral load was already high.** In four cases transmission during this early phase was confirmed. The authors conclude that rapid Ag tests may not be as fit-for-purpose in routine workplace screening to prevent asymptomatic spread of Omicron, compared to prior variants, given the

shorter time from exposure to infectiousness and lower infectious doses sufficient for transmission.

A)
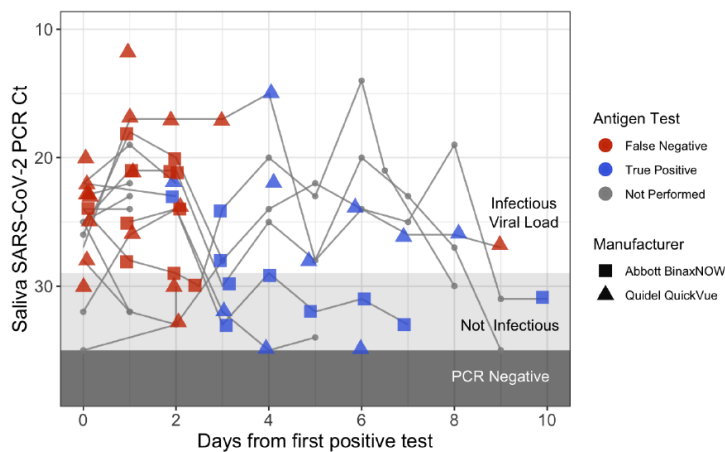
In a study in San Francisco (US), 731 nasal samples of test center attendees that had been tested for different reasons with RT-PCR were retested with a rapid Ag test (Abbott BinaxNow) (25). Of the 296 samples that had tested positive 97% were estimated to be Omicron. Sensitivity of the Ag test was 95.2% (95% CI 92-98%); 82.1% (95% CI 77-87%) and 65.2% (95% CI 60-70%) for Ct thresholds of < 30, < 35 and no threshold, respectively. The authors conclude that sensitivity is similar to that observed for prior variants.

Performance of different type of specimens to detect SARS-CoV-2, pre-Omicron

A review of the literature on the performance of different type of specimens in the pre-Omicron era is available in previous advices (20210906_Advice_RAG_Update_use of saliva and anterior nasal samples NL.pdf (sciensano.be); 20210614 Advice RAG Saliva and self-collected nose-throat swabs_NL.pdf (sciensano.be); 20210517_Advice_RAG_Use_of saliva for rapid Ag testing_NL.pdf (sciensano.be); 20210517 Advice RAG Use of nasal swabs NL.pdf (sciensano.be)).

In summary:

With regards to **RT-PCR on saliva specimens**, several systematic reviews and meta-analyses have been published, including mostly studies among symptomatic patients and coming to same conclusions (26–34):

- RT-PCR on saliva samples in symptomatic people generally has a somewhat lesser sensitivity than on nasopharyngeal swabs (NPS) - a loss of about 2-5% - and detects about 85% of positive cases.
- Viral load in saliva samples is usually higher than in nasopharyngeal samples, indicating that it are mostly cases with a low viral load that are undetected.
- Sensitivity is almost equal to nasopharyngeal swabs in patients with recent/severe symptoms or high viral load.
- Most reviews conclude that saliva is an acceptable alternative specimen collection method in a context of diagnosis in ambulatory care.
- There is some evidence that sensitivity in self-collected samples is lower than in saliva specimens collected under supervision (35).

- Enhanced saliva collection, such as after deep throat clearing or gargling, performs better than simply spitting or drooling.

There is less evidence on the performance of RT-PCR on saliva specimens in asymptomatic people, but studies including both symptomatic and asymptomatic people consistently find a lower sensitivity in asymptomatic people (36–38), probably because of the lower viral load.

Studies on the performance of RT-PCR on saliva in children often have small sample sizes and are mostly in older (>6 years) and symptomatic children (39–43).

As mentioned above, several studies assessing **rapid Ag tests on saliva specimens** have shown alarmingly low sensitivity levels (8–15).

The performance of **self-collected combined nasal-throat swabs**, was only evaluated in a few studies, mostly among symptomatic people and always using RT-PCR, and often showed discrepant results (44–49). Overall, the conclusion is that the sensitivity is slightly less compared to a health care provider-collected nasal-throat or nasopharyngeal swab.

With regards to the performance of **self-collected nasal swabs**, most studies were among symptomatic people and many are of low quality or have a small sample size. Most assessed self-collection under supervision in a health setting and very few assessed at-home self-collection. There is sufficient evidence of good concordance between self-administered supervised nasal swabs and HCP-collected nasopharyngeal swabs among symptomatic outpatients (50–53). Only one study of good quality evaluated RT-PCR testing on at-home self-collected nasal swabs and found comparable results with HCP-collected nasopharyngeal swabs (54). Only one study of good quality evaluated at-home rapid Ag self-testing and found slightly lower sensitivity compared with PCR on HCP-collected nasopharyngeal swabs among patients with high viral load (17).

Performance of different specimens for the detection of Omicron

A study in South Africa recruited 382 symptomatic patients presenting for SARS-CoV-2 testing between August and December 2021 (55). Paired mid-turbinate nasal and saliva swabs were collected and tested by RT-PCR. The positive percent agreement (≈sensitivity) for the Delta variant was 71% (95% CI: 53-84%) for the saliva samples and 100% (95% CI: 89-100%) for the mid-turbinate samples, using being positive on either sample as reference. For the Omicron variant saliva and mid-turbinate swabs had a 100% (95% CI: 90-100%) and 86% (95% CI: 71-94%) PPA, respectively. The median time from symptom onset to positive test was 3 days (range: 1-10) for Delta and 2 days for Omicron (range: 0-7). The authors conclude that **Omicron has higher viral shedding in saliva relative to nasal samples**, in contrast to Delta.

One possible hypothesis for the low sensitivity of the rapid Ag tests on self-collected nasal swabs, compared to RT-PCR on saliva, in the early phase of infection, that was encountered in the above mentioned clinical study in the US (24), is that the low sensitivity is due to a later presentation of the virus in the nasal area.

International guidelines

No changes in recommendations by international agencies or countries with regards to the use of rapid Ag tests or nasal samples were identified.

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