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STATEMENT

MANY RAPID TESTS DETECT OMICRON

Results from the Paul-Ehrlich-Institut and Robert Koch-Institut (RKI) on the Ability of Rapid Antigen Tests to Detect the Omicron Variant

High quality rapid antigen testing is an important tool in the fight against the SARS-CoV-2 pandemic. In October 2020, the Federal Ministry of Health (BMG) gave the Paul-Ehrlich-Institut the task of assessing the sensitivity of SARS-CoV-2 antigen tests that are reimbursable under the Coronavirus Test Ordinance (Coronavirus-Testverordnung, TestV)¹, because the performance data communicated in the manufacturer's package leaflets was heterogeneous and in some cases incomprehensible.

The evaluation of antigen tests by the Paul-Ehrlich-Institut and the Robert Koch-Institut (RKI) was based on the detection of defined viral loads, regardless of the clinical diagnostic background, and strictly followed a standardised procedure.

The nucleocapsid protein (N protein) is the target antigen for the vast majority of antigen tests (> 98%). The Omicron variant of the SARS-CoV-2 coronavirus, which is now the dominant variant in Germany, differs from previous variants in just a few of the N protein sites. Antigen tests were therefore carried out to determine whether the Omicron SARS-CoV-2 virus variant is detected analogously to previous virus variants, thereby ensuring the reliability of the test results against the currently dominant variant in Germany (see "Background" below). This analysis was not about a re-evaluation of the previously extensively tested sensitivity of the tests.

Twenty different SARS-CoV-2 rapid antigen tests were selected for the study to determine whether they recognise the Omicron variant as well as they recognise the original variant (wild-type virus) and the Delta variant. The results could then be transferred to similarly designed rapid antigen tests, provided that test design

¹www.bundesanzeiger.de/pub/publication/CvI8dVfWlcljyQheioc/content/CvI8dVfWlcljyQheioc/BAAnz%20AT%2030.03.2022%20V1.pdf (German only)



information was available for each test. This is scientifically possible because the test composition of many of the more than 600 tests offered on the European market is identical or at least very similar. The tests can thus be grouped together, in particular with regard to the binding sites (epitopes) of the antibodies used to detect the N protein.

The analysis with focus on the SARS-CoV-2 Omicron variant included:

1. Determination of the detection limit of 20 rapid antigen tests, each with six dilutions of inactivated cell culture virus of the Omicron variant or of the original variant with a defined virus concentration of around 10^6 copies per ml (corresponding to Ct=25), which was determined by means of RT-PCR.
2. Comparison of the ability to detect Omicron variant (N=11) and Delta variant (N=4) in pooled clinical swab samples with a defined viral concentration.
3. Comparison of the sensitivity differences determined for the Omicron variant between the 20 tests with the sensitivity data previously determined in a comparative evaluation with pre-Omicron variants conducted by the Paul-Ehrlich-Institut.
4. Bridging test on the basis of the binding sites of the antibodies (epitopes) used on the N protein of SARS-CoV-2 as specified by the manufacturers. Transfer of the results to analogous tests.

Summary of Results

Overall, the results of the experimental analysis showed no evidence of a reduced sensitivity to Omicron in the rapid antigen tests examined, regardless of the sample type. In the 20 rapid antigen tests selected to be tested, the sensitivity differences between the tests determined in the previous evaluation by the Paul-Ehrlich-Institut and RKI with earlier SARS-CoV-2 variants were also confirmed for the Omicron variant.

During this time, the Federal Institute for Drugs and Medical Devices (BfArM), which was still responsible up to and including 25 May 2022, asked the manufacturers of the SARS-CoV-2 rapid antigen tests on the market in Germany to provide details of their test designs, in particular the recognition sequence in the SARS-CoV-2 N protein. This data made it possible to transfer the results of the exemplary study on the sensitivity of the Omicron test from the 20 tests analysed to additional tests with a similar test design (bridging). When transferring results, each test design is checked to determine whether the binding sites of the antibodies are directly affected by the amino acid changes of the N protein of the

Omicron variant, which are in any case very rare, or whether they could be indirectly affected, meaning that they are closely located to a mutation.

Analysis of the test design of the antigen tests showed that the vast majority of tests (> 90%) use target regions on the N protein that are not affected by the Omicron mutations.² For most rapid antigen tests, there is therefore no concern that Omicron should be less well detected because of design-related mutations. Manufacturers must prove through additional studies that any tests that may be affected by mutations of the N protein are suitable for detecting Omicron.

With the update of the "Minimum criteria for SARS-CoV-2 antigen tests pursuant to section 1 para 1 sentence 1 of the TestV: Rapid antigen tests"³ from 15 March 2022, detailed information on the test design is now required. This information also makes conclusions on test sensitivity for future dominant circulating SARS-CoV-2 variants possible.

It is also possible to use this approach to check whether future variants can be detected by the antigen test.

Overall, antigen detection for the Omicron variant also seems to correlate directly with the viral load, with positive antigen findings reflecting the replication capacity in cell culture and thus potential infectivity [1].

The Paul-Ehrlich-Institut's results correspond to the results from analyses presented in other publications, which gave no indication of reduced sensitivity for the rapid antigen tests studied in their detection of the Omicron variant [literature references 1-13].

Background – Discussion On The Reliability of Antigen Tests For Detection of the SARS-CoV-2 Omicron Variant

A precautionary warning from the US Food and Drug Administration (FDA) on 28 December 2021 had led to concerns that some SARS-CoV-2 diagnostics (PCR tests, antigen tests) were not sensitive enough with regard to the detection of the Omicron variant and that the presence of an Omicron infection could lead to false negative test results in many cases. This was later confirmed for some PCR tests.⁴ The US FDA later stated that initial laboratory tests with heat-inactivated samples

² www.pei.de/SharedDocs/veranstaltungen-events/EN/2022/2022-03-24-press-briefing-antigen-tests.html

³ www.pei.de/SharedDocs/Downloads/EN/newsroom-en/dossiers/minimum-criteria-for-rapid-sars-cov2-antigen-tests.pdf

⁴ www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-december-28-2021

for some of the antigen tests available in the USA provided detection of the Omicron variant that was comparable to other virus variants, whereby investigations with patient samples with intact viruses were announced. A published study by the National Institute of Health (NIH), with which the FDA cooperates closely, following the warning mentioned above, has now made the conclusion that the Omicron variant is detected by the tests examined just as well as the Delta variant. [2]

Other publications describe a reduced sensitivity to the Omicron variant for individual rapid antigen tests. For example, a publication by a working group from Geneva showed a reduced sensitivity to the Omicron variant in individual rapid antigen tests both for cell culture samples and for clinical samples [14], while the publication by a group from Munich found an analogous test sensitivity for clinical samples (in contrast to that in cell culture samples) for additional tests. A group from Würzburg summarised their experience in the multi-year routine use of three different rapid antigen tests and reported an underestimation of Omicron in samples of high virus concentrations. However, these observations were not differentiated by test.

Various studies on the sensitivity of SARS-CoV-2 diagnostics often produce different conclusions. [15;16] Widely varying results on the sensitivity of rapid antigen tests in particular have been published.

The reasons for this can be manifold, e.g. differences in the study population from which clinical samples were examined, motivation for testing, differences in the method of sampling, sample characterisation (PCR method(s) and their calibration), conditions of sample storage and preparation and/or in the test procedure itself.

In order to be able to compare results in a serious manner, the Paul-Ehrlich-Institut believes that a standardised test approach is necessary, as was chosen in the previous investigations of rapid antigen tests by the Paul-Ehrlich-Institut together with the RKI. Such an approach includes well-characterised study populations, a uniform examination methodology (same PCR method, standardised calibration), uniform sample storage and uniform test procedure.

Several publications confirm the experience of the Paul-Ehrlich-Institut that, in particular, non-uniform storage conditions and freezing/thawing cycles of the samples can lead to variability in the results [17;18,19,20]. From the point of view of the Paul-Ehrlich-Institut, this could explain the discrepancies in some published studies.

Furthermore, the Paul-Ehrlich-Institut has observed quite large fluctuations in test sensitivity between different batches of the same rapid antigen test. This could be a further explanation for discrepancies in the results of particular tests in different studies (different working groups).

Due to the legal situation up to and including 25 May 2022, pursuant to the IVD Directive⁵ or the Medical Devices Act⁶, there was no independent batch testing of SARS-CoV-2 tests planned (see below for background – legal framework conditions). Manufacturers were able to make changes to the test themselves at any time and without verification.

The evaluation by the Paul-Ehrlich-Institut and the Robert Koch-Institut is based on a coordinated and standardised approach that ensures the best possible comparability of the data. More than 250 antigen tests have been evaluated since October 2020.⁷ Tests that are structurally identical to the evaluated tests are additionally marked within the online list.⁸ This means that over 329 of the 610 registered tests are covered by the Paul-Ehrlich-Institut's evaluation. (As of 21 April 2022) These include tests available in Germany to give consumers a selection to choose from and to guarantee an adequate supply.

The value of the comparative evaluation is also demonstrated by the fact that many of the results were included in the EU Health Committee's HSC list of Mutually Recognised Rapid Antigen Tests in the EU (91% of all tests)⁹. (as of 8 April 2022)

Possible differences in sensitivity in Omicron diagnosis due to biological changes in comparison to earlier variants (infection, replication kinetics, replication sites, localisation) are not directly related to the performance of the antigen tests.

Overall, antigen detection for the Omicron variant also seems to correlate directly with the viral load, with positive antigen findings reflecting the replication capacity in cell culture and thus potential infectivity. [8]

Background – Legal Framework

Pursuant to the EU IVD Directive valid up to and including 25 May 2022, the manufacturers of SARS-CoV-2 antigen tests were able to affix a CE marking to their test themselves without official inspection. Any changes, such as the possibility of or obligation for an official review, was only possible beginning on 26

⁵ <https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A31998L0079>

⁶ www.gesetze-im-internet.de/mpg/ (German only)

⁷ www.pei.de/antigen-tests

⁸ www.bfarm.de/EN/Medical-devices/Tasks/Special-topics/Antigen-tests/_node.html

⁹ https://ec.europa.eu/health/system/files/2022-05/covid-19_rat_common-list_en.pdf

May 2022, the date of application of the IVD Regulation¹⁰. However, a further transitional period of three years is planned (27.05.2025). There is currently a shortage of notified bodies and the EU reference laboratories provided for in the regulation have not yet been nominated.¹¹ The Paul-Ehrlich-Institut will apply as soon as possible as one of these EU reference laboratories.

Bibliography

Sources

1. Deearain et al Dec 21 2022
Assessment of the Analytical Sensitivity of 10 Lateral Flow Devices against the SARS-CoV-2 Omicron Variant. J Clin Microbiol. 2022 Feb 16;60(2)
<https://journals.asm.org/doi/10.1128/jcm.02479-21>
2. Apurv Soni et al Febr 2022
Comparison of Rapid Antigen Tests' Performance between Delta (B.1.61.7; AY.X) and Omicron (B.1.1.529; BA1) Variants of SARS-CoV-2: Secondary Analysis from a Serial Home Self-Testing
www.medrxiv.org/content/10.1101/2022.02.27.22271090v1
3. James Regan et al Dec 2021
Detection of the omicron variant virus with the Abbott BinaxNow SARS-CoV-2 Rapid Antigen Assay
www.medrxiv.org/content/10.1101/2021.12.22.21268219v1
4. Statens Serum Institute, Copenhagen, DK. 08 Mar 2022
Testing of SARS-CoV-2 rapid antigen tests detection of variants (Delta and Omicron BA.1 and BA.2)
<https://en.ssi.dk/-/media/arkiv/subsites/covid19/diagnostik/afprvning-af-sars-cov-2-antigentests-for-pvisning-af-varianter.pdf>
5. Goderski G et al (RIVM, NL) 16 Dec 2021
Technical evaluation of SARS-CoV-2 antigen self-tests with Omicronvariant
www.rivm.nl/sites/default/files/2021-12/Technical-evaluation-of-SARS-CoV-2-Self-test-with-omicron-variant_Final.pdf
6. UK Health Security Agency. Technical briefing 32. 17 Dec 2021
SARS-CoV-2 variants of concern and variants under investigation in England –

¹⁰ <https://eur-lex.europa.eu/eli/reg/2017/746/oj>

¹¹ https://lexparency.org/eu/32017R0746/ART_100/

Technical briefing 32

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042046/Technical_Briefing_32.pdf

7. Zachary A. Weishampel et al 9 Feb 2022
OraSure IntelliSwab™ Rapid Antigen Test Performance with the SARS-CoV-2 Variants of Concern - Alpha, Beta, Gamma, Delta, and Omicron
www.mdpi.com/1999-4915/14/3/543
8. John Schrom et al 10 Jan 2022
Direct Comparison of SARS Co-V-2 Nasal RT- PCR and Rapid Antigen Test (BinaxNOW™) at a Community Testing Site During an Omicron Surge
www.medrxiv.org/content/10.1101/2022.01.08.22268954v4
9. Molenkamp, R & Igloi, Z. 2022
Evaluation of Antigen rapid test and PCR test to Omicron variant
www.erasmusmc.nl/-/media/erasmusmc/pdf/1-themaspecifiek/viroscience/2021-evaluation-omicron-in-pcr-and-ag-assays.pdf
10. Barbara L Goodall et al. 21 Jan 2022
Investigating sensitivity of nasal or throat (ISNOT): A combination of both swabs increases sensitivity of SARS-CoV-2 rapid antigen tests.
www.medrxiv.org/content/10.1101/2022.01.18.22269426v1
11. Kanjilal et al. 19 Feb 2022
Performance of three rapid antigen tests against the SARS-CoV-2 Omicron variant.
www.medrxiv.org/content/10.1101/2022.02.17.22271142v1
12. de Michelena P et al 22 Feb 2022
Real-life performance of a COVID-19 rapid antigen detection test targeting the SARS-CoV-2 nucleoprotein for diagnosis of COVID-19 due to the Omicron variant.
[www.journalofinfection.com/article/S0163-4453\(22\)00110-4/fulltext](http://www.journalofinfection.com/article/S0163-4453(22)00110-4/fulltext)
13. Bayart, J.-L. et al 01 Mar 2022
Analytical Sensitivity of Six SARS-CoV-2 Rapid Antigen Tests for Omicron Versus Delta Variant
www.preprints.org/manuscript/202203.0010/v1

14. Eckerle et al 17 Jan 2022
Sensitivity of SARS-CoV-2 antigen-detecting rapid tests for Omicron variant
www.medrxiv.org/content/10.1101/2021.12.18.21268018v2
15. Cochrane COVID-19 Diagnostic Test Accuracy Group, 24 Mar 2021
Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection
www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013705.pub2/full
16. Denking et al Aug 2021 eCollection
Accuracy of novel antigen rapid diagnostics for SARS-CoV-2: A living systematic review and meta-analysis
<https://pubmed.ncbi.nlm.nih.gov/34383750/>
17. Navarro et al; 22 Feb 2022
Real-life performance of a COVID-19 rapid antigen detection test targeting the SARS-CoV-2 nucleoprotein for diagnosis of COVID-19 due to the Omicron variant; The Journal of Infection 84(5): e64-e66
<https://europepmc.org/article/pmc/pmc8863328>
18. Related Articles zu Nr.18
[www.journalofinfection.com/article/S0163-4453\(22\)00110-4/fulltext#relatedArticles](https://www.journalofinfection.com/article/S0163-4453(22)00110-4/fulltext#relatedArticles)
19. Premsrirut et al; 05 Jan 2022
Discordant SARS-CoV-2 PCR and Rapid Antigen Test Results When Infections: A December 2021 Occupational Case Series
www.medrxiv.org/content/10.1101/2022.01.04.22268770v1
20. Klimek-Tulwin Rapid Reviews 03 Mar 2022
Review 2: Sensitivity of SARS-CoV-2 antigen-detecting rapid tests for Omicron variant
<https://rapidreviewscovid19.mitpress.mit.edu/pub/inotpnls/release/1>

Key Findings from Publications [1] to [13]

[1] Deerrain et al; Feb 16 2022
Assessment of the Analytical Sensitivity of 10 Lateral Flow Devices against the SARS-CoV-2 Omicron Variant. J Clin Microbiol; 60(2)
<https://journals.asm.org/doi/10.1128/jcm.02479-21>
The analytical sensitivities of the 10 antigen kits were similar for both the Delta and Omicron variants.

[2] Apurv Soni et al Feb 2022

Comparison of Rapid Antigen Tests' Performance between Delta (B.1.61.7; AY.X) and Omicron (B.1.1.529; BA1) Variants of SARS-CoV-2: Secondary Analysis from a Serial Home Self-Testing Study

www.medrxiv.org/content/10.1101/2022.02.27.22271090v1

The performance of Ag-RDT is not inferior among individuals infected with the SARS-CoV-2 Omicron variant as compared to the Delta variant. The improvement in sensitivity of Ag-RDT noted with serial testing is consistent between Delta and Omicron variant.

[3] James Regan et al Dec 2021

Detection of the omicron variant virus with the Abbott BinaxNow SARS-CoV-2 Rapid Antigen Assay

www.medrxiv.org/content/10.1101/2021.12.22.21268219v1

All Omicron and delta specimens with concentrations of 100,000 copies/swab or greater were positive by the BinaxNow Assay, a concentration similar to previously reported limits of detection for this assay.

[4] Statens Serum Institut, Copenhagen, DK. 08.03.2022

Testing of SARS-CoV-2 rapid antigen tests detection of variants (Delta and Omicron BA.1 and BA.2)

<https://en.ssi.dk/-/media/arkiv/subsites/covid19/diagnostik/afprvning-af-sars-cov-2-antigentests-for-pvisning-af-varianter.pdf?la=en>

The testing of the 23 tested antigen tests shows that all tests can detect Delta and Omicron BA.1 and BA.2 on a comparable level with the wild-type (Wuhan).

[5] Goderski G et al (RIVM, NL) 16 Dec 2021

Technical evaluation of SARS-CoV-2 antigen self-tests with Omicron variant

www.rivm.nl/sites/default/files/2021-12/Technical-evaluation-of-SARS-CoV-2-Self-test-with-omicron-variant_Final.pdf

In conclusion, the performance of all [7] self-tests is similar and not affected by the Omicron variant, and therefore meeting the pre-set criteria.

[6] UK Health Security Agency. Technical briefing 32. 17 Dec 2021

SARS-CoV-2 variants of concern and variants under investigation in England – Technical briefing 32

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042046/Technical_Briefing_32.pdf

Five different Ag RDT Lateral Flow Tests detect Omicron as accurately as Delta.

[7] Zachary A. Weishampel et al 9 Febr 2022

OraSure InteliSwab™ Rapid Antigen Test Performance with the SARS-CoV-2 Variants of Concern - Alpha, Beta, Gamma, Delta, and Omicron

www.mdpi.com/1999-4915/14/3/543

Ultimately, the OraSure InteliSwab™ COVID-19 Rapid Test showed no decrease in sensitivity between the ancestral SARS-CoV-2 strain and any VOCs including Omicron.

[8] John Schrom et al 10 Jan 2022

Direct Comparison of SARS Co-V-2 Nasal RT- PCR and Rapid Antigen Test (BinaxNOW™) at a Community Testing Site During an Omicron Surge

www.medrxiv.org/content/10.1101/2022.01.08.22268954v4

731 people found that the Abbott BinaxNOW rapid tests performed about as well with Omicron as they did with other variants when people were symptomatic and had high viral load.

[9] Molenkamp, R & Igloi, Z. 2022

Evaluation of Antigen rapid test and PCR test to Omicron variant

www.erasmusmc.nl/-/media/erasmusmc/pdf/1-themaspecifiek/viroscience/2021-evaluation-Omicron-in-pcr-and-ag-assays.pdf

Three rapid Ag-tests showed comparable sensitivity Omicron to Delta.

[10] Barbara L Goodall et al. 21 Jan 2022

Investigating sensitivity of nasal or throat (ISNOT): A combination of both swabs increases sensitivity of SARS-CoV-2 rapid antigen tests

www.medrxiv.org/content/10.1101/2022.01.18.22269426v1

Omicron detection, comparable to previous evaluations using other SARS-CoV-2 lineages.

[11] Kanjilal et al 19 Febr 2022

Performance of three rapid antigen tests against the SARS-CoV-2 Omicron variant

www.medrxiv.org/content/10.1101/2022.02.17.22271142v1

We found no change in the analytic sensitivity of all three RADTs for detection of Omicron versus Delta, but noted differences in performance between assays

[12] de Michelena P et al 22 Febr 2022

Real-life performance of a COVID-19 rapid antigen detection test targeting the SARS-CoV-2 nucleoprotein for diagnosis of COVID-19 due to the Omicron variant.

[www.journalofinfection.com/article/S0163-4453\(22\)00110-4/fulltext](https://www.journalofinfection.com/article/S0163-4453(22)00110-4/fulltext)

In our experience, the clinical performance of the Panbio™ COVID-19 assay for Omicron variant was comparable to previous reports for the Wuhan-Hu-1 G614 variant (100% specificity and sensitivity of 81.4% in non-vaccinated adult patients with a clinical course of <5 days).

[13] Bayart, J.-L. et al 01 Mar 2022

Analytical Sensitivity of Six SARS-CoV-2 Rapid Antigen Tests for Omicron Versus Delta Variant

www.preprints.org/manuscript/202203.0010/v1

Sensitivity across a wide range of Ct values (13.5 to 35.7; median = 21.3) were comparable and ranged from 70.0% to 77.1% for Delta strains and from 69.6% to 78.3% for Omicron strains.