



Early View

Research letter

Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected anterior nasal swab *versus* professional-collected nasopharyngeal swab

Andreas K. Lindner, Olga Nikolai, Franka Kausch, Mia Wintel, Franziska Hommes, Maximilian Gertler, Lisa J. Krüger, Mary Gaeddert, Frank Tobian, Federica Lainati, Lisa Köppel, Joachim Seybold, Victor M. Corman, Christian Drosten, Jörg Hofmann, Jilian A. Sacks, Frank P. Mockenhaupt, Claudia M. Denkinger

Please cite this article as: Lindner AK, Nikolai O, Kausch F, *et al.* Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected anterior nasal swab *versus* professional-collected nasopharyngeal swab. *Eur Respir J* 2020; in press (<https://doi.org/10.1183/13993003.03961-2020>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected anterior nasal swab versus professional-collected nasopharyngeal swab

Andreas K. Lindner^{1*}, Olga Nikolai^{1*}, Franka Kausch¹, Mia Wintel¹, Franziska Hommes¹, Maximilian Gertler¹, Lisa J. Krüger², Mary Gaeddert², Frank Tobian², Federica Lainati², Lisa Köppel², Joachim Seybold³, Victor M. Corman^{4,5}, Christian Drosten^{4,5}, Jörg Hofmann⁶, Jilian A. Sacks⁷, Frank P. Mockenhaupt^{1§} and Claudia M. Denkinger^{2,§}

^{*,§}Authors contributed equally

¹ Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health; Institute of Tropical Medicine and International Health, Berlin, Germany.

² Division of Clinical Tropical Medicine, Center of Infectious Diseases, Heidelberg University Hospital, Germany.

³ Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health; Medical Directorate, Berlin, Germany.

⁴ Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health; Institute of Virology, Berlin, Germany.

⁵ German Centre for Infection Research (DZIF), partner site Charité, 10117 Berlin, Germany.

⁶ Labor Berlin - Charité Vivantes GmbH, Berlin, Germany

⁷ Foundation for Innovative New Diagnostics, Geneva, Switzerland

Correspondence: Claudia M. Denkinger, Division of Clinical Tropical Medicine, Heidelberg University Hospital, Im Neuenheimer Feld 672, 69120 Heidelberg, Germany. E-mail: claudia.denkinger@uni-heidelberg.de

Take-Home Message: Supervised self-sampling from the anterior nose is a reliable alternative to professional nasopharyngeal sampling using a WHO-listed SARS-CoV-2 antigen-detecting rapid test. Self-sampling and potentially patient self-testing may be a future use case.

To the Editor:

A number of antigen-detecting rapid diagnostic tests (Ag-RDTs) for SARS-CoV-2 are now commercially available and can result in rapid decisions on patient care, isolation and contact tracing at the point-of-care [1]. Two Ag-RDTs using nasopharyngeal (NP) swab samples meet WHO targets and are now approved through the WHO Emergency Use Listing procedure [2-4].

NP swab samples are frequently perceived as uncomfortable by patients and must be collected by trained healthcare personnel with protective equipment. A more complex sampling technique could also result in an incorrect performance in the clinical reality with a possible consequence on test sensitivity. Evidence supports the use of alternative sampling methods for RT-PCR, including anterior nasal (AN) swabs collected by patients and some tests have received regulatory approval with AN samples [5, 6]. Considering the ease-of-use of Ag-RDTs, a reliable simple sampling method would not only allow self-sampling, but may also pave the way for self-testing.

The primary objective of this prospective diagnostic accuracy study was a head-to-head comparison (positive and negative percent agreement) of a supervised, self-collected AN swab sample with a health care worker (professional)-collected NP swab sample, using a WHO-listed SARS-CoV-2 Ag-RDT against the reference standard RT-PCR collected from a NP/oropharyngeal (OP) swab. The secondary objective was to assess sensitivity and specificity for different sampling techniques with Ag-RDT. The study was continued until at least 30 positive NP swab samples according to Ag-RDT were obtained, as it was requested by the WHO to approve a novel sample type. This manufacturer-independent study was conducted in partnership with the Foundation of Innovative New Diagnostics (FIND), the WHO collaborating centre for COVID-19 diagnostics.

The study protocol was approved by the ethical review committee at Heidelberg University Hospital for the study site in Berlin (registration number S-180/2020). The study took place at the ambulatory SARS-CoV-2 testing facility of Charité University Hospital (Charité-Universitätsmedizin Berlin, Germany) from 23 September to 14 October 2020. The study enrolled adults at high risk for SARS-CoV-2 infection according to clinical suspicion. Participants were excluded if either of the swabs for the Ag-RDT or the RT-PCR reference standard could not be collected.

Participants underwent first an instructed, self-collected bilateral AN swab for the Ag-RDT. Verbal instruction was given to insert the swab horizontally 2-3 cm into the nostril and rotate it for 15 seconds against the nasal walls on each side. Deviations from the instructed technique were recorded.

Subsequently, a combined OP/NP swab (eSwab from Copan with 1 ml Amies medium) as per institutional recommendations for RT-PCR, and a separate NP swab for the Ag-RDT were taken from different sides of the nose. The samples for the Ag-RDTs were collected using the swab provided by the manufacturer within the test kit.

The Ag-RDT evaluated in this study was the STANDARD Q COVID-19 Ag Test (SD Biosensor, Inc. Gyeonggi-do, Korea; henceforth called STANDARD Q) [7], which is also being distributed by Roche [8]. The test uses the lateral flow assay principle in a cassette-based format with a visual read-out after 15-30 minutes. The manufacturer's instructions for use were followed. The Ag-RDTs were performed directly after sampling (within 60 minutes) at point-of-care by study physicians. The Ag-RDT results were interpreted by two operators, each blinded to the result of the other. The second reader was also blinded to the second Ag-RDT results of individual patients. The visual read out of the Ag-RDT test band was categorized on a semi-quantitative scale as negative, weak positive, positive and strong positive.

The Roche Cobas SARS-CoV-2 assay (Pleasanton, CA United States) or the SARS-CoV-2 E-gene assay from TibMolbiol (Berlin, Germany) were performed for RT-PCR according to routine procedures at the central laboratory. Viral RNA concentrations were calculated using assay specific CT-values, based on external calibrations curves [9, 10]. Staff performing the Ag-RDTs were blinded to results of RT-PCR tests and vice versa.

Of 303 patients invited, 289 (95.4%) consented to participate. Two patients were excluded as both swabs for the Ag-RDT could not be obtained. The average age of participants was 34.7 years (Standard Deviation [SD] 11.0) with 42.9% female and 19.0% having comorbidities. On the day of testing, 97.6% of participants had one or more symptoms consistent with COVID-19. Duration of symptoms at the time of presentation on average was 4.4 days (SD 2.7). Among the 289 participants, 39 (13.5%) tested positive for SARS-CoV-2 by RT-PCR (Table 1).

No invalid tests were observed on either AN or NP samples. Two patients were detected by NP but not by AN sampling. No patient was detected by AN sampling only. The positive percent agreement was 90.6% (CI 75.8-96.8; including 2 false positive results with AN and 1 with NP). The negative percent agreement was 99.2% (CI 97.2-99.8). Inter-rater reliability was near perfect with kappa of 0.98 for AN and 1.0 for NP samples. The semi-quantitative read-out was more often higher for the NP samples (9 higher on NP, 4 higher on AN). Of the two patients detected by NP but not by AN sampling, one patient

collected the AN swab only with gentle rotation, the second presented 10 days post symptom onset with a low viral load (Table 1).

The STANDARD Q Ag-RDT with AN sampling showed a sensitivity of 74.4% (29/39 PCR positives detected; CI 58.9-85.4) and specificity of 99.2% (CI 97.1-99.8) compared to RT-PCR. The sensitivity with NP sampling was 79.5% (31/39 PCR positives detected; CI 64.5-89.2) and specificity was 99.6% (CI 97.8-100). In patients with high viral load ($>7.0 \log_{10}$ RNA SARS-CoV2/swab), the sensitivity of the Ag-RDT with AN sampling was 95.7% (22/23 PCR positives detected; CI 79.0-99.8) and 100% (23/23 PCR positives detected; CI 85.7-100) with NP sampling. In contrast, the Ag-RDT frequently did not detect patients with lower viral load or with symptoms >7 days (Table 1). For most patients, the application of the flexible swab (meant for NP swab collection) in the anterior nose appeared unpleasant due to a tickling sensation and led to frequent sneezing.

The strengths of the study are the rigorous methods, including standardized sampling, two independent blinded readers and an additional semi-quantitative assessment of Ag-RDT results. The cohort was representative, judging from the comparable sensitivity observed in the recent independent validation study of STANDARD Q (sensitivity 76.6%; CI 62.8-86.4) [4]. The study is limited as it was performed in a single centre. Also, the NP swab was usually rotated against the nasopharyngeal wall for less time than recommended by the manufacturer, which may have a negative impact on the sensitivity of the Ag-RDT with NP sampling, but also reflects the difficulty of collection of this sample type.

In conclusion, this study demonstrates that supervised self-sampling from the anterior nose is a reliable alternative to professional nasopharyngeal sampling with STANDARD Q. The data will contribute to WHO recommendations for use of this test. Considering the ease-of-use of Ag-RDTs, self-sampling and potentially patient self-testing at home may be a future use case. If such testing could be repeated frequently and immediately ahead of situations when transmissions are likely to occur, self-testing with Ag-RDTs may have a significant impact on the pandemic. Further implementation studies on optimized self-sampling techniques and swabs (e.g. less flexible sponge swab) and the correct performance/interpretation of the test by patients themselves, are urgently needed to drive self-testing to scale.

TABLE 1 Antigen-detecting RDT results with a supervised self-collected anterior nasal (AN) swab and with a professional-collected nasopharyngeal (NP) swab in RT-PCR positive patients from combined oro-/nasopharyngeal swab. CT-values and viral load (in descending order) of the paired RT-PCR samples are shown, as well as the duration of symptoms per patient. The positive percent agreement between AN and NP samples on Ag-RDT, as well as the respective sensitivities compared to RT-PCR are shown.

No.	AN swab self-collected SD Q Ag-RDT	NP swab prof.-collected SD Q Ag-RDT	OP/NP swab RT-PCR		Symptom duration (days)
			CT value	Viral load ³	
1	pos (+++)	pos (+++)	17.33 ¹	9.59	2
2	pos (++)	pos (+++)	17.86 ¹	9.43	1
3	pos (+++)	pos (+++)	18.01 ¹	9.38	1
4	pos (++)	pos (+++)	18.31 ¹	9.29	3
5	pos (+++)	pos (+++)	18.40 ¹	9.27	3
6	pos (+++)	pos (+++)	18.76 ¹	9.16	4
7	pos (+++)	pos (+++)	18.77 ¹	9.16	5
8	pos (+++)	pos (+++)	18.78 ¹	9.16	5
9	pos (+++)	pos (+++)	19.05 ¹	9.08	3
10	pos. (+++)	pos. (+++)	19.40 ¹	8.97	2
11	neg.	pos (+++)	19.66 ¹	8.90	1
12	pos (+++)	pos (+++)	20.32 ¹	8.70	3
13	pos (+++)	pos (+++)	17.81 ²	8.68	4
14	pos (++)	pos (+++)	20.44 ¹	8.67	2
15	pos (++)	pos (++)	20.54 ¹	8.63	5
16	pos (+++)	pos (+++)	21.09 ¹	8.47	4
17	pos (+++)	pos (+)	18.62 ²	8.44	4
18	pos (+)	pos (++)	21.87 ¹	8.24	7
19	pos (++)	pos (+++)	19.34 ²	8.23	5
20	pos (++)	pos (+++)	22.05 ¹	8.19	2
21	pos (+++)	pos (+++)	19.47 ²	8.19	6
22	pos (+++)	pos (+++)	22.60 ¹	8.03	6
23	pos (+++)	pos (++)	23.66 ¹	7.71	6
24	pos (+)	pos (++)	26.42 ¹	6.90	5
25	pos (+++)	pos (+++)	26.77 ¹	6.79	5
26	neg.	neg.	24.25 ²	6.78	10
27	pos (++)	pos (+++)	24.77 ²	6.62	4
28	pos (+++)	pos (++)	25.29 ²	6.46	2
29	pos (+)	pos (++)	29.33 ¹	6.03	5
30	neg.	neg.	29.56 ¹	5.97	3
31	neg.	neg.	29.95 ¹	5.85	3
32	pos (+)	pos (+)	30.25 ¹	5.76	4
33	neg.	neg.	27.81 ²	5.72	8
34	pos (++)	pos (+)	31.20 ¹	5.48	8
35	neg.	pos (+)	31.61 ¹	5.36	10
36	neg.	neg.	32.58 ¹	5.07	10
37	neg.	neg.	32.86 ¹	4.99	2
38	neg.	neg.	34.62 ¹	4.47	7
39	neg.	neg.	35.53 ¹	4.20	14

Sensitivity 29/39 (74.4%)	Sensitivity 31/39 (79.5%)
Positive percent agreement⁴	

¹ Roche Cobas SARS-CoV-2 assay (E-gene, T2 target)

² TibMolbiol assay, E-gene target.

³ log₁₀ RNA SARS-CoV2/swab

⁴ including 2 false positives on AN and 1 on NP

90.6% (CI 75.8-96.8)

Abbreviations: No., patient number; SD Q, STANDARD Q COVID-19 Ag Test (SD Biosensor); Ag-RDT, antigen-detecting rapid diagnostic test; AN, anterior nasal; NP, nasopharyngeal; OP, oropharyngeal; CT, cycle threshold; RT-PCR, reverse transcription-polymerase chain reaction; neg., negative; pos (+), weak positive; pos. (++) , positive; pos. (+++) , strong positive.

Acknowledgements: Heike Rössig, Chiara Manon Rohardt, Claudia Hülso, Elisabeth Linzbach, Susen Burock, Katja von dem Busche, Stephanie Padberg, Melanie Bothmann, Zümrüt Tuncer, Stefanie Lunow, Beate Zimmer, Astrid Barrera Pesek, Sabrina Pein, Nicole Buchholz, Verena Haack, Oliver Deckwart.

Author contributions: AKL, LJK, FL and CMD designed the study and developed standard operating procedures. AKL and ON implemented the study design, enrolled patients, performed laboratory work and led the writing of the manuscript. FPM and JS coordinated and supervised the study site. FK, MW, FH enrolled patients. MGe coordinated the testing facility. MGa, LK and FT led the data analysis. VC, JH and CD were responsible for PCR testing and contributed to the interpretation of the data. JAS supported the study design setup and the interpretation of the data. CMD was the principle investigator of the study. All authors have reviewed the manuscript.

Data availability: All raw data and analysis code are available upon a request to the corresponding author.

Conflict of interest: None declared.

Support statement: The study was supported by FIND, Heidelberg University Hospital and Charité University Hospital internal funds, as well as a grant of the Ministry of Science, Research and the Arts of Baden-Württemberg, Germany. FIND provided input on the study design, and data analysis in collaboration with the rest of the study team.

References

1. Foundation of Innovative New Diagnostics (FIND). SARS-CoV-2 Diagnostics Pipeline 2020 <https://www.finddx.org/covid-19/pipeline/>. Date last accessed: October 15 2020.
2. World Health Organisation. WHO interim guidance 11 September 2020. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays 2020 https://apps.who.int/iris/bitstream/handle/10665/334253/WHO-2019-nCoV-Antigen_Detection-2020.1-eng.pdf?sequence=1&isAllowed=y. Date last accessed: October 15 2020.
3. World Health Organisation. WHO news release 28 September 2020. Global partnership to make available 120 million affordable, quality COVID-19 rapid tests for low-and middle-income countries. <https://www.who.int/news-room/detail/28-09-2020-global-partnership-to-make-available-120-million-affordable-quality-covid-19-rapid-tests-for-low--and-middle-income-countries>. Date last accessed: October 15 2020.
4. Krueger LJ, Gaeddert M, Koeppl L, Bruemmer L, 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.

5. Tu YP, Jennings R, Hart B, Cangelosi GA, Wood RC, Wehber K, et al. Swabs Collected by Patients or Health Care Workers for SARS-CoV-2 Testing. *N Engl J Med.* 2020;383(5):494-6.
6. CDC. Interim Guidelines for Collecting H, and Testing Clinical Specimens for COVID-19. <https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>. Date last accessed: October 15 2020.
7. SD Biosensor. COVID-19 Ag STANDARDTM Q COVID-19 Ag Test 2020. <http://sdbiosensor.com/xs/product/7672>. Date last accessed: October 15 2020.
8. Roche to launch SARS-CoV-2 Rapid Antigen Test in countries accepting CE mark, allowing fast triage decisions at point of care. <https://www.roche.com/media/releases/med-cor-2020-09-01b.htm>. Date last accessed: October 15 2020.
9. Matheeußen V, Corman VM, Donoso Mantke O, McCulloch E, Lammens C, Goossens H, et al. International external quality assessment for SARS-CoV-2 molecular detection and survey on clinical laboratory preparedness during the COVID-19 pandemic, April/May 2020. *Euro Surveill.* 2020;25(27).
10. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill.* 2020;25(3).