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

To the Editor:

A number of antigen-detecting rapid diagnostic tests (Ag-RDTs) for severe acute respiratory syndrome coronavirus 2 (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 World Health Organization (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 clinical reality, with a possible consequence for test sensitivity. Evidence supports the use of alternative sampling methods for RT-PCR, including nasal swabs collected by patients, and some tests have received regulatory approval with nasal samples [5, 6]. The term nasal sampling is often not used uniformly but can be differentiated in anterior nasal and nasal mid-turbinate sampling [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 nasal mid-turbinate (NMT) swab sample with a healthcare 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 coronavirus disease 2019 (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 NMT 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 s against the nasal walls on each side. Deviations from the instructed technique were recorded. Subsequently, a combined OP/NP swab (eSwab from Copan with 1mL Amies medium) as per institutional

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Supervised nasal self-sampling 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. https://bit.ly/3mup0hS

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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 min. The manufacturer's instructions for use were followed. The Ag-RDTs were performed directly after sampling (within 60 min) at point of care by study physicians. The Ag-RDT results were interpreted

TABLE 1 Antigen-detecting rapid diagnostic test (Ag-RDT) results with a supervised self-collected nasal mid-turbinate (NMT) swab and with a professional-collected nasopharyngeal (NP) swab in RT-PCR positive patients from combined NP/oropharyngeal (OP) swab

Number	NMT swab self-collected SD Q Ag-RDT	NP swab professional-collected SD Q Ag-RDT	OP/NP swab RT-PCR		Symptom duration days
			CT value	Viral load[+]	
1	pos. (+++)	pos. (+++)	17.33[#]	9.59	2
2	pos. (++)	pos. (+++)	17.86[#]	9.43	1
3	pos. (+++)	pos. (+++)	18.01[#]	9.38	1
4	pos. (++)	pos. (+++)	18.31[#]	9.29	3
5	pos. (+++)	pos. (+++)	18.40[#]	9.27	3
6	pos. (+++)	pos. (+++)	18.76[#]	9.16	4
7	pos. (+++)	pos. (+++)	18.77[#]	9.16	5
8	pos. (+++)	pos. (+++)	18.78[#]	9.16	5
9	pos. (+++)	pos. (+++)	19.05[#]	9.08	3
10	pos. (+++)	pos. (+++)	19.40[#]	8.97	2
11	neg.	pos. (+++)	19.66[#]	8.90	1
12	pos. (+++)	pos. (+++)	20.32[#]	8.70	3
13	pos. (+++)	pos. (+++)	17.81[¶]	8.68	4
14	pos. (++)	pos. (+++)	20.44[#]	8.67	2
15	pos. (++)	pos. (++)	20.54[#]	8.63	5
16	pos. (+++)	pos. (+++)	21.09[#]	8.47	4
17	pos. (+++)	pos. (+)	18.62[¶]	8.44	4
18	pos. (+)	pos. (++)	21.87[#]	8.24	7
19	pos. (++)	pos. (+++)	19.34[¶]	8.23	5
20	pos. (++)	pos. (+++)	22.05[#]	8.19	2
21	pos. (+++)	pos. (+++)	19.47[¶]	8.19	6
22	pos. (+++)	pos. (+++)	22.60[#]	8.03	6
23	pos. (+++)	pos. (++)	23.66[#]	7.71	6
24	pos. (+)	pos. (++)	26.42[#]	6.90	5
25	pos. (+++)	pos. (+++)	26.77[#]	6.79	5
26	neg.	neg.	24.25[¶]	6.78	10
27	pos. (++)	pos. (+++)	24.77[¶]	6.62	4
28	pos. (+++)	pos. (++)	25.29[¶]	6.46	2
29	pos. (+)	pos. (++)	29.33[#]	6.03	5
30	neg.	neg.	29.56[#]	5.97	3
31	neg.	neg.	29.95[#]	5.85	3
32	pos. (+)	pos. (+)	30.25[#]	5.76	4
33	neg.	neg.	27.81[¶]	5.72	8
34	pos. (++)	pos. (+)	31.20[#]	5.48	8
35	neg.	pos. (+)	31.61[#]	5.36	10
36	neg.	neg.	32.58[#]	5.07	10
37	neg.	neg.	32.86[#]	4.99	2
38	neg.	neg.	34.62[#]	4.47	7
39	neg.	neg.	35.53[#]	4.20	14
Sensitivity	29/39 (74.4%)	31/39 (79.5%)			
Positive percent agreement[§]	90.6% (95% CI 75.8–96.8%)				

Cycle threshold (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 NMT and NP samples on Ag-RDT, as well as the respective sensitivities compared to RT-PCR are shown. SD Q: STANDARD Q COVID-19 Ag Test (SD Biosensor); neg.: negative; pos. (+): weak positive; pos. (++): positive; pos. (+++): strong positive. [#]: Roche Cobas SARS-CoV-2 assay (E-gene, T2 target); [¶]: TibMolbiol assay, E-gene target; [+]: $\log_{10}$ RNA SARS-CoV-2 per swab; [§]: including two false-positives on NMT and one on NP.

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 readout of the Ag-RDT test band was categorised on a semi-quantitative scale as negative, weak positive, positive and strong positive.

The Roche Cobas SARS-CoV-2 assay (Pleasanton, CA, USA) 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 cycle threshold values, based on external calibration 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 mean±SD age of participants was 34.7±11.0 years; 42.9% were 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±2.7 days. 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 NMT or NP samples. Two patients were detected by NP but not by NMT sampling. No patient was detected by NMT sampling only. The positive percent agreement was 90.6% (95% CI 75.8–96.8%; including two false-positive results with NMT and one with NP). The negative percent agreement was 99.2% (95% CI 97.2–99.8%). Inter-rater reliability was near perfect with kappa of 0.98 for NMT and 1.0 for NP samples. The semi-quantitative read-out was more often higher for the NP samples (nine higher on NP, four higher on NMT). Of the two patients detected by NP but not by NMT sampling, one patient collected the NMT 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 NMT sampling showed a sensitivity of 74.4% (29/39 PCR positives detected; 95% CI 58.9–85.4%) and specificity of 99.2% (95% CI 97.1–99.8%) compared to RT-PCR. The sensitivity with NP sampling was 79.5% (31/39 PCR positives detected; 95% CI 64.5–89.2%) and specificity was 99.6% (95% CI 97.8–100%). In patients with high viral load (>7.0 $\log_{10}$ RNA SARS-CoV-2/swab), the sensitivity of the Ag-RDT with NMT sampling was 95.7% (22/23 PCR positives detected; 95% 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 nose appeared unpleasant due to a tickling sensation and led to frequent sneezing.

The strengths of the study are the rigorous methods, including standardised 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%; 95% 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 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 optimised 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.

Andreas K. Lindner[1,8], Olga Nikolai[1,8], Franka Kausch[1], Mia Wintel[1], Franziska Hommes[1], Maximilian Gertler[1], Lisa J. Krüger[2], Mary Gaeddert[2], Frank Tobian[2], Federica Lainati[2], Lisa Köppel[2], Joachim Seybold[3], Victor M. Corman[4,5], Christian Drosten[4,5], Jörg Hofmann[6], Jilian A. Sacks[7], Frank P. Mockenhaupt[1,9] and Claudia M. Denkinger[2,9]

[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, Heidelberg, 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), Berlin, Germany. [6]Labor Berlin – Charité Vivantes GmbH, Berlin, Germany. [7]Foundation for Innovative New Diagnostics, Geneva, Switzerland. [8]Authors contributed equally. [9]Authors contributed equally.

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

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This study is registered at the German Clinical Trial Registry (DRKS00021220). All raw data and analysis code are available upon a request to the corresponding author; data will be available to researchers who provide a sound proposal and all if study sites agree to sharing the data, for 5 years after publication of the article.

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