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Research note

Diagnostic accuracy of SARS-CoV-2 rapid antigen self-tests in asymptomatic individuals in the omicron period: a cross-sectional study

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ABSTRACT

Objectives: To assess the performances of three commonly used antigen rapid diagnostic tests used as self-tests in asymptomatic individuals in the Omicron period.
Methods: We performed a cross-sectional diagnostic test accuracy study in the Omicron period in three public health service COVID-19 test sites in the Netherlands, including 3600 asymptomatic individuals aged ≥ 16 years presenting for SARS-CoV-2 testing for any reason except confirmatory testing after a positive self-test. Participants were sampled for RT-PCR (reference test) and received one self-test (either Acon Flowflex [Flowflex], MP Biomedicals (MPBio), or Siemens-Healthineers CLINITEST [CLINITEST]) to perform unsupervised at home. Diagnostic accuracies of each self-test were calculated.
Results: Overall sensitivities were 27.5% (95% CI, 21.3–34.3%) for Flowflex, 20.9% (13.9–29.4%) for MPBio, and 25.6% (19.1–33.1%) for CLINITEST. After applying a viral load cut-off (≥5.2 log10 SARS-CoV-2 E-gene copies/mL), sensitivities increased to 48.3% (37.6–59.2%), 37.8% (22.5–55.2%), and 40.0% (29.5–51.2%), respectively. Specificities were >99% for all tests in most analyses.
Discussion: The sensitivities of three commonly used SARS-CoV-2 antigen rapid diagnostic tests when used as self-tests in asymptomatic individuals in the Omicron period were very low. Antigen rapid diagnostic test self-testing in asymptomatic individuals may only detect a minority of infections at that point in time. Repeated self-testing in case of a negative self-test is advocated to improve the diagnostic

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yield, and individuals should be advised to re-test when symptoms develop. **Roderick P. Venekamp, Clin Microbiol Infect 2023;29:391.e1–391.e7**

Introduction

SARS-CoV-2 antigen rapid diagnostic tests (Ag-RDTs) perform adequately when conducted by symptomatic individuals [1,2]. Self-testing by asymptomatic persons, if sufficiently reliable, may also be useful. Individuals could screen themselves before visiting others if they want to minimize posing a risk. Also, it could be used for screening asymptomatic individuals, for example before admission in crowded places. Current evidence suggests that SARS-CoV-2 Ag-RDTs perform sub-optimally in asymptomatic individuals because of lower viral loads in this population [1,3,4]. However, previous studies were small, and either applied professional sampling or were conducted in the pre-Omicron period. We, therefore, studied the accuracy of three Ag-RDTs with unsupervised self-sampling in asymptomatic individuals in the Omicron period, using RT-PCR as the reference standard.

Methods

This study was embedded within the Dutch public testing infrastructure [2]. Formal ethical approval was not required because the study was judged outside the scope of the Dutch Medical Research Involving Human Subjects Act by the METC Utrecht (21-818/C). During the study period (12 January to 30 March 2022), public SARS-CoV-2 testing was conducted by RT-PCR, free-of-charge, for government-approved indications (supplementary material 1 Details on Study Methods). The estimated share of Omicron was >90% of circulating SARS-CoV-2 on 12 January 2022, and >99.5% from 31 January onwards [5–7].

Specimen collection and testing

Individuals aged ≥16 years without symptoms suggestive of SARS-CoV-2 infection were recruited consecutively at three public health service COVID-19 test sites. Trained test site staff took a swab for routine RT-PCR testing [2]. These samples were tested in off-site laboratories on Cobas 6800/8800 platforms. Participants were asked to perform all other study procedures at home within 3 hours of the test site visit: provide informed consent electronically, perform one Ag-RDT self-test (either Acon Flowflex ['Flowflex'], MP Biomedicals ['MPBio'], or Siemens-Healthineers CLINITEST ['CLINITEST']) using nasal self-sampling according to the manufacturer's instructions, and complete an online questionnaire (supplementary material 2). Participants interpreted their self-test results visually before receiving their RT-PCR test result from the public health service, and the self-test result was not available to the laboratories conducting the RT-PCR tests. Those with a negative RT-PCR received an online follow-up questionnaire after 10 days (supplementary material 3).

Outcomes and statistical analyses

We performed a complete case analysis because the number of missing values was low (Fig. 1). Confirmatory testers (13% of the study population) were excluded from our primary analyses. Primary outcomes were the diagnostic accuracies of each self-test with RT-PCR test result as the reference standard. Secondary outcomes were diagnostic accuracies stratified by COVID-19 vaccination status, prior SARS-CoV-2 infection, gender, and age. Diagnostic accuracies were also determined after applying a viral load cut-off (≥5.2 log10 SARS-CoV-2 E-gene copies/mL) [8]. Finally, we assessed self-reported infections that may have been missed initially.

Results

Of 4202 participants, 3635 were non-confirmatory testers (Fig. 1). The Ag-RDT self-test and the RT-PCR test result were available for 3600 non-confirmatory testers (99.0%) (Fig. 1). Most participants (83.5%) provided the self-test result within 3 hours of visiting the test site; the median time intervals were 0.96 (interquartile range (IQR), 0.62–1.8), 0.97 (IQR, 0.61–1.9), and 0.69 (IQR,

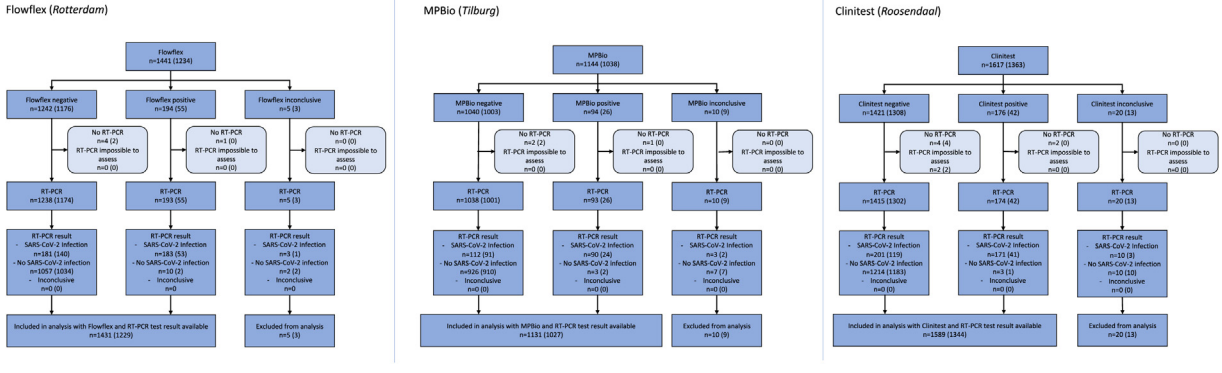

Fig. 1. Flow of study participants of the full study population and primary analysis population between brackets. CLINITEST, the Siemens-Healthineers CLINITEST Rapid covid-19 Antigen Test; Flowflex, the Acon Labs Flowflex COVID-19 Antigen Home Test; MPBio, the MP Biomedicals Rapid SARS-CoV-2 Antigen Test Card. "Ag-RDT inconclusive" is a combination of Ag-RDTs that showed no control line, test tubes that were dropped, and Ag-RDTs that provided results participants had difficulties interpreting (e.g. the very light line at the "T"). Ag-RDT, antigen rapid diagnostic tests.

0.24–1.9) hours for Flowflex, MPBio, and CLINITEST, respectively. Characteristics of the primary and full analysis populations by self-test group are described in Table 1 and Table S1, respectively.

Ag-RDT self-test accuracies: primary analysis population

Overall sensitivities were 27.5% (21.3–34.3%) for Flowflex, 20.9% (13.9–29.4%) for MPBio, and 25.6% (19.1–33.1%) for CLINITEST (Table 2, Fig. 2). Viral load distributions in RT-PCR–positive individuals show especially false-negative Ag-RDT test results in the lower viral load range (Fig. 3). After applying a viral load cut-off, sensitivities increased to 48.3% (37.6–59.2%), 37.8% (22.5–55.2%), and 40.0% (29.5–51.2%), respectively (Table S2, Fig. S1). Specificities were >99%, positive predictive values > 92%, and negative predictive values > 88% for all self-tests in overall primary analyses (Table 2).

Stratified sensitivities were comparable, with all 95% CIs overlapping substantially (Table 2, Fig. 2). After applying the viral load cut-off, all stratified sensitivities increased but the 95% CIs still overlapped substantially (Table S2, Fig. S1).

Ag-RDT self-test accuracies: primary versus full analysis population

The largest differences in RT-PCR positivity percentages and sensitivities were between non-confirmatory and confirmatory testers (Table S2, Fig. S2). In the full analysis population, consistently lower sensitivities were found in participants with a prior SARS-CoV-2 infection than in those without a prior infection,

Table 1
Baseline characteristics of the primary analysis population, stratified by a rapid antigen test

Test results available from the reference test and …	Flowflex	MPBio	Clinitest
Test site location	Rotterdam	Tilburg	Roosendaal
Inclusion dates Omicron period (>90% Omicron)	Jan 12–March 14	Jan 12–March 29	Jan 12–March 29
Sample size	N = 1229	N = 1027	N = 1344
SARS-CoV-2 infections based on RT-PCR test result, n (%)	193 (15.7)	115 (11.2)	160 (11.9)
Age [yrs], mean (SD)	39 (14)	38 (15)	43 (15)
Range (min-max)	16–80	16–89	16–81
Sex, female, n (%)	655 (53.3)	623 (60.7)	797 (59.4)
Self-reported reasons for testing, n (%)[a]			
Symptoms	40 (3.3)	42 (4.1)	43 (3.2)
Close contact	1035 (84.2)	888 (86.5)	1213 (90.3)
Other reason	154 (12.5)	97 (9.4)	88 (6.5)
Vaccination status			
Not vaccinated	89 (7.2)	52 (5.0)	73 (5.4)
Vaccinated with at least one dose, n (%)	1140 (92.8)	975 (95.0)	1271 (94.6)
Number of vaccinations received, n (%)[b]			
1	68 (6.0)	69 (7.1)	80 (6.3)
2	361 (31.7)	413 (42.4)	496 (39.0)
3	710 (62.3)	493 (50.6)	686 (54.0)
4	1 (0.1)	0 (0)	9 (0.7)
Unknown	0 (0)	0 (0)	0 (0.0)
Type of initial vaccination series, n (%)[b]			
Pfizer	−893 (78.3)	669 (68.6)	797 (62.7)
Moderna	88 (7.7)	105 (10.8)	228 (17.9)
Astra Zeneca	67 (5.9)	116 (11.9)	149 (11.7)
Janssen	85 (7.5)	79 (8.1)	87 (6.9)
Unknown/Other	7 (0.6)	6 (0.6)	10 (0.8)
Type of booster vaccine, n (%)[b]			
Pfizer	486 (42.6)	301 (30.9)	470 (37.0)
Moderna	263 (23.1)	224 (23.0)	262 (20.6)
No booster received	373 (32.7)	433 (44.4)	516 (40.6)
Unknown	19 (1.7)	18 (1.9)	24 (1.9)
At least one prior SARS-CoV-2 infection, n (%)	368 (29.9)	251 (24.5)	311 (23.2)
<2 mos ago	58 (15.8)	22 (8.8)	24 (7.7)
2–6 mos ago	102 (27.7)	50 (19.9)	81 (26.0)
6–12 mos ago	111 (30.2)	93 (37.1)	106 (34.1)
>12 mos ago	96 (26.1)	85 (33.9)	100 (32.2)
Unknown	1 (0.3)	1 (0.4)	0 (0)
Previous experience with using self-tests, n (%)	1185 (96.5)	991 (96.5)	1300 (96.8)
Performed last self-test, n (%)[b]			
<7 d ago	895 (75.5)	819 (82.6)	1038 (79.9)
1–4 wks ago	188 (15.9)	115 (11.6)	162 (12.5)
>1 mo ago	98 (8.3)	55 (5.6)	99 (7.6)
Unknown	4 (0.3)	2 (0.2)	1 (0.1)
Number of ever-performed self-tests, n (%)			
1–3	147 (12.4)	146 (14.7)	220 (16.9)
4–6	260 (21.9)	235 (23.7)	363 (27.9)
7–10	310 (26.2)	245 (24.7)	323 (24.9)
>10	465 (39.2)	356 (35.9)	390 (30.0)

CLINITEST, Siemens-Healthineers CLINITEST Rapid COVID-19 Antigen Test; Flowflex, Acon Labs Flowflex COVID-19 Antigen Home Test; MPBio, MP Biomedicals Rapid SARS-CoV-2 Antigen Test Card;; SD, standard deviation.

[a] All individuals who did not have any symptoms suggestive of SARS-CoV-2 at the actual time of visiting the Covid-19 test site and undergoing the RT-PCR were eligible for study participation. This, however, does not necessarily mean that study participants were asymptomatic at the time of scheduling the test.

[b] Percentage calculated as the proportion of those vaccinated, or those that had previous experience in performing a self-test, respectively.

Table 2
Diagnostic accuracy parameters for the three Ag-RDTs in the primary analysis population. Values are percentages (95% CI) unless stated otherwise

	N	RT-PCR test positivitya [%]	Sensitivity [%] (95%CI)	Specificity [%] (95%CI)	PPV [%] (95% CI)	NPV [%] (95% CI)
Flowflex						
Primary analysis	1229	15.7	27.5 (21.3–34.3)	99.8 (99.3–100)	96.4 (87.5–99.6)	88.1 (86.1–89.9)
Secondary (stratified) analyses:						
Viral load cut-off[b]	1221	7.3	48.3 (37.6–59.2)	99.2 (98.5–99.6)	82.7 (69.7–91.8)	96.1 (94.8–97.1)
Vaccinated (at least once):						
Yes	1140	15.1	28.5 (21.9–35.9)	99.8 (99.3–100)	96.1 (86.5–99.5)	88.7 (86.7–90.5)
No	88	23.9	19.0 (5.4–41.9)	100 (94.6–100)	100 (39.8–100)	79.8 (69.6–87.7)
Previous SARS-CoV-2 infection:						
Yes	368	16.3	26.7 (16.1–39.7)	99.7 (98.2–100)	94.1 (71.3–99.9)	87.5 (83.5–90.7)
No	861	15.4	27.8 (20.4–36.3)	99.9 (99.2–100)	97.4 (86.2–99.9)	88.3 (85.9–90.4)
Sex:						
Female	655	16.0	30.5 (21.9–40.2)	99.8 (99.0–100)	97.0 (84.2–99.9)	88.3 (85.5–90.7)
Male	569	15.3	23.0 (14.6–33.2)	99.8 (98.8–100)	95.2 (76.2–99.9)	87.8 (84.7–90.4)
Age [yrs]:						
16–40	711	16.7	23.5 (16.2–32.2)	99.8 (99.1–100)	96.6 (82.2–99.9)	86.7 (83.9–89.1)
>40	518	14.3	33.8 (23.2–45.7)	99.8 (98.8–100)	96.2 (80.4–99.9)	90.0 (87.0–92.5)
MPBio						
Primary analysis	1027	11.2	20.9 (13.9–29.4)	99.8 (99.2–100)	92.3 (74.9–99.1)	90.9 (89.0–92.6)
Secondary (stratified) analyses:						
Viral load cut-off[b]	1026	3.6	37.8 (22.5–55.2)	98.8 (97.9–99.4)	53.8 (33.4–73.4)	97.7 (96.6–98.5)
Vaccinated (at least one):						
Yes	975	10.3	18.0 (11.0–26.9)	99.8 (99.2–100)	90.0 (68.3–98.8)	91.4 (89.5–93.1)
No	51	29.4	40.0 (16.3–67.7)	100 (90.3–100)	100 (54.1–100)	80.0 (65.4–90.4)
Previous SARS-CoV-2 infection:						
Yes	251	14.3	16.7 (6.4–32.8)	100 (98.3–100)	100 (54.1–100)	87.8 (83.0–91.6)
No	775	10.2	22.8 (14.1–33.6)	99.7 (99.0–100)	90.0 (68.3–98.8)	91.9 (89.7–93.8)
Sex:						
Female	623	10.8	13.4 (6.3–24.0)	99.8 (99.0–100)	90.0 (55.5–99.7)	90.5 (87.9–92.7)
Male	404	11.9	31.2 (18.7–46.3)	99.7 (98.4–100)	93.8 (69.8–99.8)	91.5 (88.3–94.1)
Age [yrs]:						
16–40	582	12.4	25.0 (15.5–36.6)	99.8 (98.9–100)	94.7 (74.0–99.9)	90.4 (87.7–92.7)
>40	444	9.7	14.0 (5.3–27.9)	99.8 (98.6–100)	85.7 (42.1–99.6)	91.5 (88.5–94.0)
CLINITEST						
Primary analysis	1344	11.9	25.6 (19.1–33.1)	99.9 (99.5–100)	97.6 (87.4–99.9)	90.9 (89.2–92.4)
Secondary (stratified) analyses:						
Viral load cut-off[b]	1340	6.3	40.0 (29.5–51.2)	99.5 (99.0–99.8)	85.0 (70.2–94.3)	96.1 (94.9–97.1)
Vaccinated (at least one):						
Yes	1271	12.0	24.8 (18.2–32.5)	99.9 (99.5–100)	97.4 (86.5–99.9)	90.7 (88.9–92.2)
No	72	8.3	50.0 (11.8–88.2)	100 (94.6–100)	100 (29.2–100)	95.7 (87.8–99.1)
Previous SARS-CoV-2 infection:						
Yes	311	9.3	20.7 (8.0–39.7)	99.6 (98.0–100)	85.7 (42.1–99.6)	92.4 (88.9–95.1)
No	1032	12.7	26.7 (19.4–35.2)	100 (99.6–100)	100 (90.0–100)	90.4 (88.4–92.1)
Sex:						
Female	797	11.7	17.2 (10.2–26.4)	100 (99.5–100)	100 (79.4–100)	90.1 (87.8–92.1)
Male	544	12.1	37.9 (26.2–50.7)	99.8 (98.8–100)	96.2 (80.4–99.9)	92.1 (89.4–94.3)
Age [yrs]:						
16–40	568	12.1	24.6 (15.1–36.5)	99.8 (98.9–100)	94.4 (72.7–99.9)	90.5 (87.8–92.9)
>40	775	11.7	26.4 (17.7–36.7)	100 (99.5–100)	100 (85.8–100)	91.1 (88.8–93.0)

Ag-RDT, antigen rapid diagnostic tests; CLINITEST, Siemens-Healthineers CLINITEST Rapid covid-19 Antigen Test; Flowflex, Acon Labs Flowflex covid-19 Antigen Home Test; MPBio, MP Biomedicals Rapid SARS-CoV-2 Antigen Test Card; NPV, negative predictive value; PPV, positive predictive value.
aSARS-CoV-2 infections based on RT-PCR test results.
[b] Defined as viral load above which 95% of individuals with a positive RT-PCR test result had a positive viral culture [7] which was 5.2 $\log_{10}$ SARS-CoV-2 E-gene copies/mL.

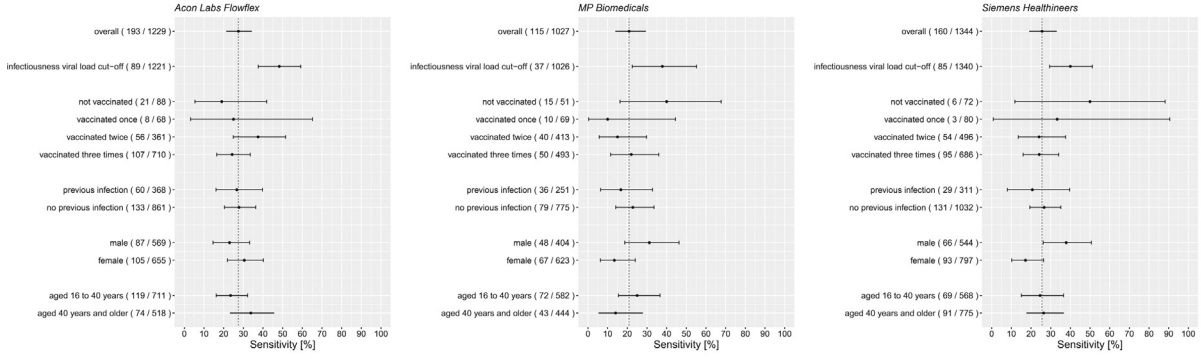

Fig. 2. Sensitivities with 95% CIs of the Ag-RDT-RT-PCR reference standard test comparisons stratified according to COVID-19 vaccination status, previous infection status, sex, and age. The vertical line indicates the sensitivity of the Ag-RDT in the respective overall study population and the number of positive RT-PCR tests out of the total or subgroup between parentheses. Ag-RDT, antigen rapid diagnostic tests.

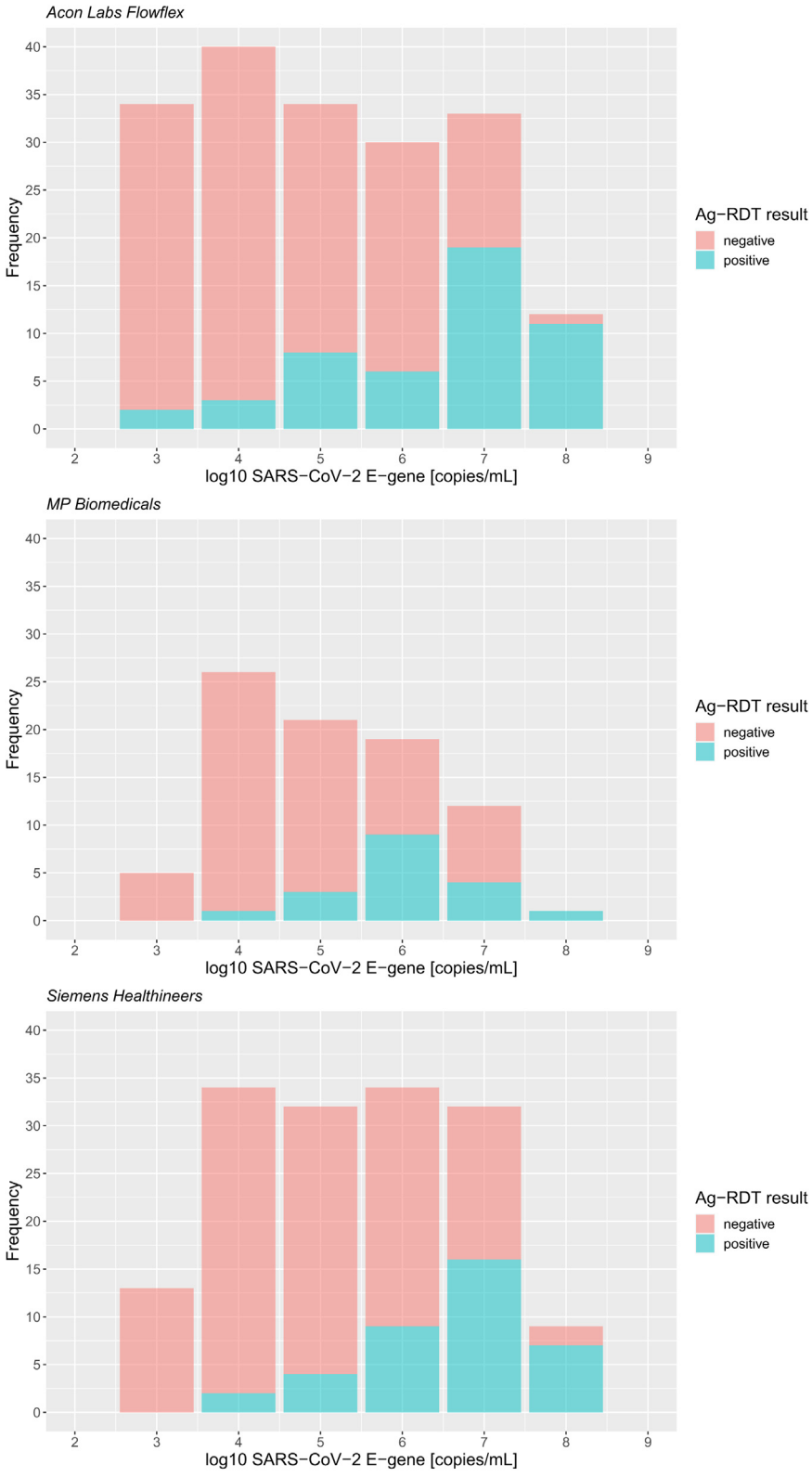

Fig. 3. Viral load distribution of reverse transcriptase polymerase chain reaction positive individuals across the three Ag-RDTs, stratified by Ag-RDT self-test result. Ag-RDT, antigen rapid diagnostic tests.

although only reaching statistical significance for Flowflex (Table S2, Fig. S2). Viral load cut-off application resulted in higher sensitivities, but all stratification trends remained similar (Fig. S3).

Positive SARS-CoV-2 tests during 10-day follow-up: primary analysis population

Follow-up information was available for 79.2% (2479/3132) of participants with an initial negative RT-PCR (Table S3). About half (1339/2443; 54.8%) reported having been re-tested within 10 days, with 24.6% of them (329/1339) testing positive.

Discussion

The sensitivities of three Ag-RDT self-tests for detecting the SARS-CoV-2 Omicron variant in asymptomatic individuals using nasal self-sampling were very low, varying between 20.7% and 27.5%, and increasing to only 37.8% to 48.3% after applying a viral load cut-off.

A review of pre-Omicron Ag-RDT evaluations, predominantly using professional sampling, found a pooled sensitivity of 52.5% (95% CI, 43.7–61.1) in asymptomatic individuals [1]. We previously found a sensitivity of 23% for the SD Biosensor self-test based on data from 31 RT-PCR–positive participants in the Delta period [4]. A U.S. study during an Omicron surge found a sensitivity of 52.5% (64/122) for the BinaxNOW Ag-RDT performed by professionals in asymptomatic individuals or those with symptom onset >7 days ago [9].

Sensitivities of Ag-RDTs may be lower in asymptomatic than in symptomatic individuals because of differences in viral load distributions [1,4,9]. Also, retrieving sufficient nasal fluid by self-swabbing might be hampered in asymptomatic individuals by the absence of rhinorrhea. The addition of oropharyngeal to nasal self-sampling might increase sensitivities [2,10]; however, it is unlikely that this would have achieved acceptable levels.

Study strengths include the large sample size, real-world context, completeness of data, and blinding of outcome assessment. The study also has some limitations. Firstly, estimates are less precise than anticipated because of the post hoc exclusion of asymptomatic confirmatory testers. Secondly, the viral load calculations were based on standard curves generated in a previous study and should therefore be considered the best estimates [8]. We used a cut-off above which 95% of people with a positive RT-PCR test result had a positive virus culture in that previous study [8]. Those experiments were performed when Alpha dominated and in a largely unvaccinated population.

We conclude that SARS-CoV-2 self-testing has limited value for asymptomatic individuals wishing to protect vulnerable persons and may even lead to a false sense of security. One should be aware of this, and better informed about other prevention options, such as physical distancing or mask use, on the other hand, all evaluated self-tests were highly specific. Therefore, self-testing regardless of symptoms is useful in other public health contexts because every positive test captured reduces the number of subsequent exposures. The high SARS-CoV-2 infection rate within 10 days of a negative RT-PCR test that we found in our study emphasizes the importance of re-testing over time, especially when symptoms develop, to reduce missed infections as much as possible.

Author contributions

KGMM initiated the study. ES, RPV, LH, IKV, WvdB, SDP, EL, MH, RM, CW, IV, CRSN-I, SvdH, JAJWK, JHHMvdW, and KGMM designed the study. ES, RPV, CRSN-I, and KGMM coordinated the study. WvdB, SDP, VFZ, LS, and MK were responsible for laboratory analyses and data processing. ES, RPV, and KGMM verified the underlying data. ES performed the statistical analysis and verified the underlying data in close collaboration with RPV and KGMM. RPV, ES, JHHMvdW, and KGMM drafted the first version of the manuscript. All authors critically read the manuscript and provided feedback. All authors approved the submission of the current version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency declaration

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.11.004.

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