Clinica Chimica Acta 529 (2022) 104–108

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

# Two rapid SARS-CoV-2 disposable devices for semi-quantitative S-RBD antibody levels determination compared with CLIA and ELISA assays at different protective thresholds

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ARTICLE INFO

*Keywords:*
SARS-CoV-2
Antibodies
Point of care device
iRapid
CLIA
ELISA
Rapid antibody test
Protective thresholds

ABSTRACT

*Background and aims:* Performance of two disposable devices for identifying subjects with low anti-SARS-CoV-2 protection was compared with that of automated enzyme-linked immunosorbent (ELISA) and chemiluminescent (CLIA) assay.

*Materials and Methods:* In July 2021, 123 healthcare workers (HCW), twice vaccinated by BNT162b2/Comirnaty mRNA (BioNTech-Pfizer), underwent Ab iRapid COVID-19 Quant "Neutralizing" Self-test (iRapid Self-test) and "Neutralizing" Professional-use (iRapid pro) (DIESSE, Diagnostica Senese, Siena, Italy). Simultaneously, serum Ab were determined by Maglumi 2000 plus (anti S-RBD CLIA assay, Snibe Diagnostics, Shenzhen, China) and SARS-CoV-2 "Neutralizing" Ab Chorus ELISA (DIESSE, Siena, Italy). Results were evaluated against two "protective-thresholds", 90 kBAU/L and 506 kBAU/L.

*Results:* HCW mean age, 46.2 (±12.6) years; 26 (20.5%), males, 101 (79.5%), females. The mean time interval (and standard deviation) between the first vaccine dose and Ab determination was 129.5 (±36.4) days and was neither gender ($p = 0.879$) nor age ($p = 0.341$) related. With Maglumi, 114 (89.7%) and 43 (33.8%) HCW presented Ab ≥ 90 kBAU/L and Ab ≥ 506 kBAU/L, respectively; with Chorus, 96 (75.6%) presented Ab values ≥506 kBAU/L. CLIA and ELISA agreement was 56.7%. At 90 kBAU/L, iRapid self-test and Pro sensitivities were 98.2% (95% CI: 92.7–99.8), specificity 69.2% (95% CI: 38.6–90.9%) and 76.9% (46.2–95%), respectively. At 506 kBAU/L, iRapid sensitivities were 58.1–91.6%, and specificities, 89–96.6%. On evaluating Ab at <4 and ≥4 months, protective titers had decreased.

*Conclusions:* iRapid semi-quantitative devices had very good overall agreements of 95.1% and 95.9% for detecting individuals with low anti-SARS-CoV-2 protection.

## 1. Introduction

The current coronavirus disease 2019 (COVID-19) pandemic continues to threaten human health. Among the efforts made to control the pandemic, vaccination is considered the most promising strategy [1]. Although the elicitation of neutralizing antibodies (Nab) by vaccination protects cells from viral intrusion, the protective immunity thresholds conferred might differ depending on individuals' Nab levels. Nab titer determination is therefore of fundamental importance in designing risk-based surveillance programs, and identifying subjects likely to benefit from additional vaccine doses, fragile patients in particular [2].

Disposables devices might be an appropriate tool for achieving accurate, timely and cost-effective determination of Nabs as a correlate of immune protection, and for allowing assays to be performed outside clinical laboratories, with self-testing [3]. However, neutralization tests cannot easily be implemented using disposables devices, while the point-of-care (POC) determination of antibodies (Ab) anti Spike Receptor-Binding Domain (S-RBD) portion of SARS-CoV-2 represents an alternative method, particularly when adopting lateral flow immunoassays [3,4]. In addition, since anti S-RBD Ab serum levels have been demonstrated to closely correlate with Nab, it might be possible to achieve protective thresholds conferring immune protection [5,6].

In this study we evaluated the performances of two different disposable self-testing devices for the determination of anti S-RBD Ab

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https://doi.org/10.1016/j.cca.2022.02.014
Received 9 February 2022; Received in revised form 17 February 2022; Accepted 17 February 2022
Available online 21 February 2022

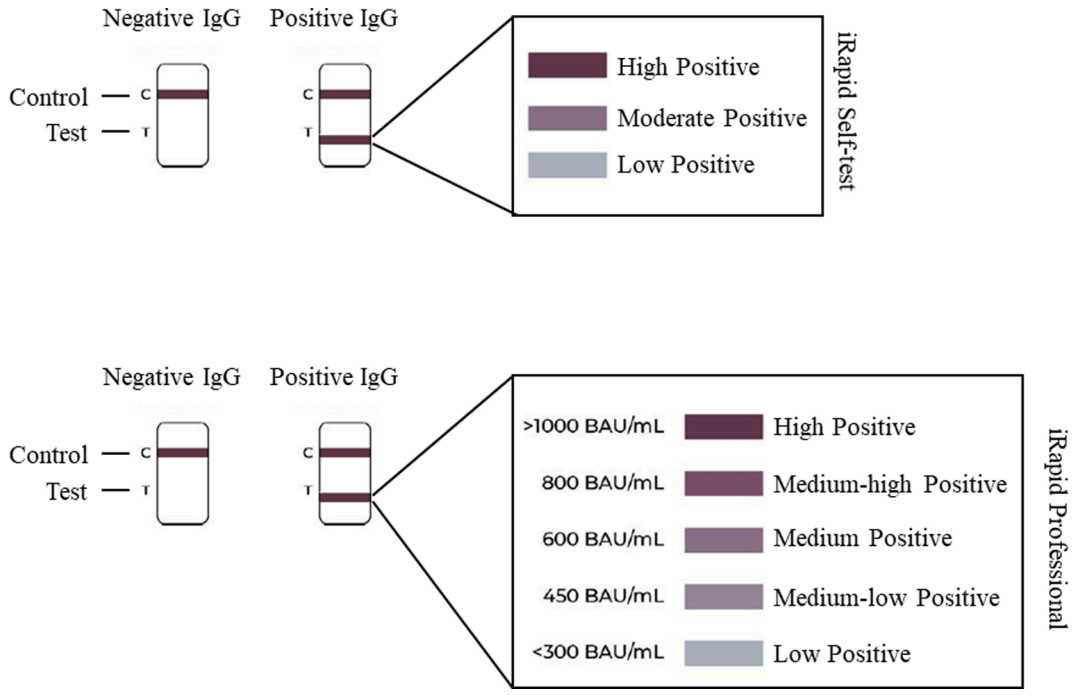


**Fig. 1.** iRapid self-test and iRapid professional use results interpretation schemes, as suggested by manufacturer's inserts. Both tests are composed by anti-RBD recombinant monoclonal antibodies. Only tests with a positive control line (C) are valid.

"Neutralizing" antibodies, with respect to two Ab "protective-thresholds", recently reported in the literature, and compared results with anti S-RBD Ab values obtained from an automated enzyme-linked immunosorbent assay (ELISA) and a chemiluminescent (CLIA) assay.

## 2. Materials and methods

The study population consisted of 127 healthcare workers (HCW), enrolled at the University-Hospital of Padova in July 2021. Four HCW were not vaccinated, and were excluded from the analyses, and the remaining 123 had two BNT162b2 (BNT162b2/Comirnaty mRNA, BioNTech-Pfizer) doses between January and June 2021. All individuals were instructed to self-test Ab levels by the iRapid COVID-19 Quant "Neutralizing" Self-test Report (iRapid Self Test) (DIESSE, Diagnostica Senese, Siena, Italy). Subsequently, all subjects underwent an additional test with the iRapid SARS-CoV-2 Quant "Neutralizing" Professional-use (iRapid Professional) Ab assay, performed by a trained operator. Both these device work with capillary blood samples. iRapid self-test is equipped with a finger stick to facilitate the self-collection of whole blood. Rapid semi-quantitative results refer to anti S-RBD IgG, and were obtained from the coloured test line region following the manufacturer's recommendations (IFU 70102, rev 210630 for iRapid self-test and IFU 70100, 290621 for iRapid Professional). For the iRapid professional, intensities were interpreted as Binding Antibody Units (kBAU/L) as referred to the first international standard WHO 20/136 for anti-SARS-CoV-2 (Fig. 1). The limit of detection for the iRapid professional device, based on the manufacturer's instructions, was found to be 279 kBAU/L. iRapid cards coloured results were evaluated by two different operators (LG and CC) and discrepancies were resolved by a third operator (AP).

All subjects underwent withdrawal of a blood sample, which was centrifuged at 3500gx5 min, serum being collected for anti S-RBD measurement. Anti S-RBD IgG was measured by the validated chemiluminescent (CLIA) assay Maglumi 2000 plus (Snibe Diagnostics, Shenzhen, China, hereafter called the reference method) [7]. Anti S-RBD total Ab levels were measured in collected sera using an automated enzyme-linked immunosorbent competitive assay (ELISA) SARS-CoV-2 "Neutralizing" Ab Chorus (REF 81408) (DIESSE, Diagnostica Senese, Siena, Italy) (highly correlated with Nab titers [8]) and results compared with that of the reference method. Chorus determines the total Ab capable of competing with a monoclonal antibody direct against an epitope of the wild type S-RBD portion of SARS-CoV-2.

Two different "protective-thresholds" of anti-SARS-CoV-2 Ab were evaluated, based on recently published data: 90 kBAU/L, representing the minimum threshold of protective Nab ($PRNT_{50} \leq 20$) [5], and 506 kBAU/L, corresponding to a vaccine efficacy of 80% against symptomatic COVID-19 (high protection threshold) [9]. Both thresholds (CLIA) or the high protective threshold only (ELISA) were used to dichotomize quantitative anti-SARS-CoV-2 Ab. Dichotomized results were then used to evaluate the performance of both iRapid devices. However, to avoid troubles in results interpretation, only the 123 subjects with two BNT162b2 doses were included in these performances analyses.

Statistical analyses were performed using Stata v16.1 (Statacorp LLC, Lakeway drive, TX, USA). The Kruskal-Wallis equality-of-populations rank test was used to evaluate differences between median values of anti S-RBD IgG, and Fisher's exact test, to estimate differences between iRapid test results. The "DIAGT" Stata module was used to calculate the sensitivities and the specificities and their 95% CI by the Wilson method [10].

All subjects gave their fully informed written consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki and the Institutional Review Board of the University of Padua (protocol nr 7862).

## 3. Results

The mean age of subjects (±SD) included in the study was 46.2 years (±12.6 years); 26/127 (20.5%) were males, and 101/127 (79.5%) females. Among vaccinated individuals, the mean time interval (and standard deviation) between the first vaccine dose and Ab determination of 129.5 (±36.4) days was neither associated with gender (Kruskal-Wallis $\chi^2 = 0.023$, $p = 0.879$) nor with age (Spearman's $r = 0.086$, $p = 0.341$).

Of the 127 individuals, 114 (89.7%) presented anti S-RBD IgG Ab above 90 kBAU/L, as measured by the reference method. Moreover, on

**Table 1**
iRapid self-test and iRapid professional performances results, reported at different protective thresholds, estimated either by a CLIA assay (Maglumi) or by an ELISA assay (Chorus). Confidence intervals at 95% levels were estimated by the Wilson score confidence method.

| | Maglumi | | | | Chorus | |
|---|---|---|---|---|---|---|
| | iRapid self-test | | iRapid Professional | | High protection threshold[#] | |
| | Minimum threshold[*] | High protection threshold[#] | Minimum threshold[*] | High protection threshold[#] | iRapid Self-test | iRapid Professional |
| Antibody concentration from colour intensity scheme[§] | Low positivity | High positivity | 300 kBAU/L | 800 kBAU/L | Moderate positivity | 450 kBAU/L |
| Sensitivity (%) and 95% CI | 98.2 (93.7–99.8) | 58.1 (42.1–73.0) | 98.2 (93.7–99.8) | 72.1 (56.3–84.7) | 91.7 (84.2–96.3) | 89.6 (81.7–94.9) |
| Specificity (%) and 95% CI | 55.6 (21.2–86.3) | 97.4 (91.0–99.7) | 66.7 (29.9–92.5) | 88.5 (79.2–94.6) | 84.0 (63.9–95.5) | 96.0 (79.6–99.9) |
| Positive Predictive value (%) and 95% CI | 96.5 (91.3–99.0) | 92.6 (75.7–99.1) | 97.3 (92.4–99.4) | 77.5 (61.5–89.2) | 95.7 (89.2–98.8) | 98.9 (93.8–100.0) |
| Negative Predictive value (%) and 95% CI | 71.4 (29.1–96.3) | 80.9 (72.7–99.1) | 75.0 (34.9–96.8) | 85.2 (76.6–92.1) | 72.4 (52.8–87.3) | 70.6 (52.5–84.9) |
| Overall agreement (%) | 95.1 | 83.4 | 95.9 | 82.6 | 90.1 | 90.9 |

[*] Minimum threshold corresponds to anti S-RBD IgG Ab above 90 kBAU/L.
[#] High protection threshold to a vaccine efficacy of 80% against symptomatic COVID-19 (506 kBAU/L).
[§] From interpretation of colours result (IFU 70100 ed 290621).

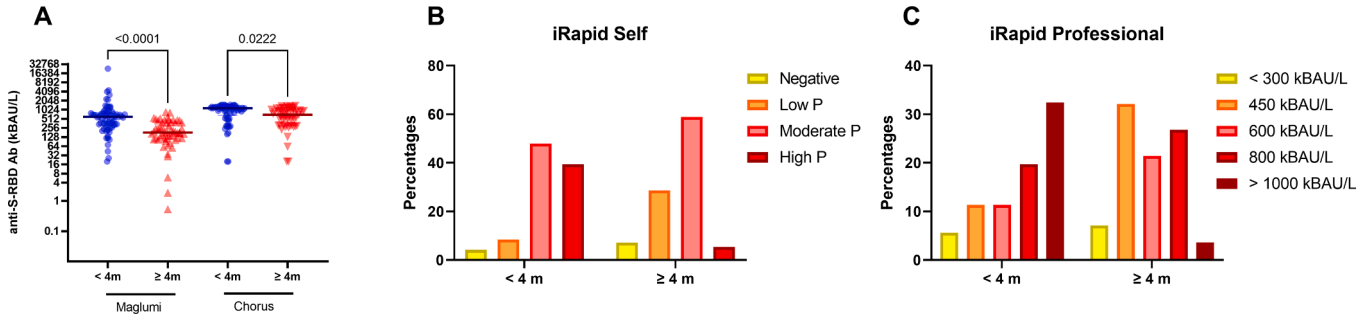


**Fig. 2.** CLIA (Maglumi), ELISA (Chorus), iRapid self-test and iRapid Professional results. Analyses were performed considering the time from first dose of vaccine and serological determinations, subdividing data in two periods <4 months and ≥4 months. Panel A) quantitative anti-S-RBD Ab results, expressed in kBAU/L, obtained by CLIA (Maglumi) and ELISA (Chorus) assays; Panel B) percentages of Negative, Low positive (Low P), Moderate positive (Moderate P) and High positive (High P) for iRapid self-tests results; Panel C) iRapid Professional positive (>1000 kBAU/L, 800 kBAU/L, 600 kBAU/L, 450 kBAU/L) and negative results (<300 kBAU/L), expressed as percentages.

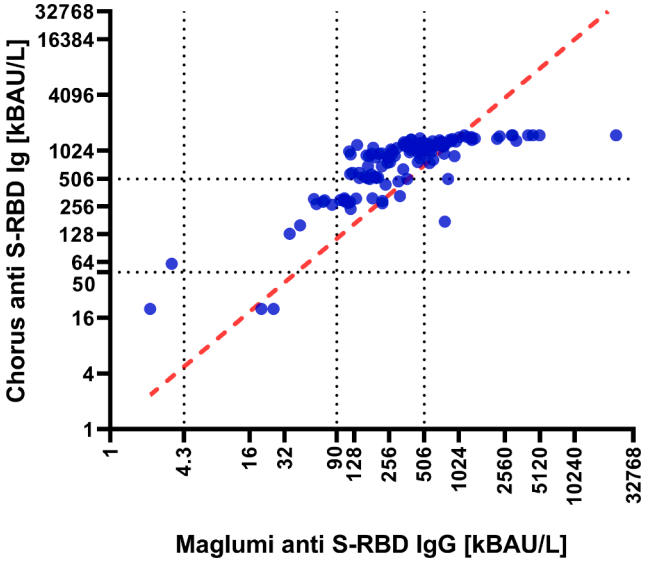


**Fig. 3.** Linear correlation between CLIA (Maglumi) and ELISA (Chorus). Spearman's correlation coefficient was r = 0.836 (p < 0.001).

using the same method, 43 (33.8%) presented anti S-RBD IgG Ab above 506 kBAU/L. Considering Chorus anti S-RBD Ab, 96 (75.6%) presented values above 506 kBAU/L, demonstrating a low agreement with the reference method (overall agreement = 56.7%, Cohen's κ = 0.250, SE = 0.0599).

The performances of iRapid devices were calculated with respect to the reference method (for both protective thresholds), and with respect to Chorus anti S-RBD Ab (for high protection threshold, only). The results are reported in Table 1.

Further analyses were performed considering the time interval between the first vaccine dose and serological determinations, and data were subdivided according to two periods of time (<4 and ≥4 months); the results are reported in Fig. 2. As expected, anti S-RBD Ab median levels from the two periods differed, the value of decrease being greater with Maglumi than Chorus. Likewise, for both iRapid self ($p < 0.001$) and iRapid professional ($p < 0.001$), the levels measured in the two periods differed, highlighting decreased protective titers.

The comparison of Maglumi and Chorus quantitative anti S-RBD Ab is shown in Fig. 3. The two methods are linearly correlated (Spearman's $r = 0.836$, $p < 0.001$).

## 4. Discussion

The determination of anti-SARS-CoV-2 antibody levels is of fundamental importance in designing surveillance programs, especially in subjects at an enhanced risk of developing severe SARS-CoV-2 infection, and for personalized (patient-based) vaccinations schemes [2,11]. To these purposes, it is important to evaluate which Ab threshold confers immune protection against symptomatic SARS-CoV-2 infection [12]. However, consensus on thresholds conferring immune protection has not yet been achieved. Jeopardized thresholds are due to several factors, including poor method comparability, limited availability of clinical

studies evaluating the relationships between circulating Ab levels, breakthrough infections, and individuals' clinical outcomes [12]. Furthermore, the impact of SARS-CoV-2 strands (e.g., Omicron variant) on protective threshold should be considered and evaluated by neutralization experiments using live viruses.

Disposable devices, promising POCT tools for assessing Ab levels that are less costly than immunometric assays, can be used without requiring specifically trained personnel (e.g., self-testing). However, tailored vaccination schemes call for the quantitative determination of Ab levels, whilst the majority of current POCT antibody tests offer only qualitative results. In this study, we evaluated two disposable devices: the iRapid COVID-19 Quant "Neutralizing" Self-test Report (iRapid Self-test) and iRapid COVID-19 Quant "Neutralizing" Professional-use (iRapid professional). Both were based on a semi-quantitative membrane containing monoclonal recombinant antibodies directed against the receptor binding domain (RBD) of SARS-CoV-2. The iRapid Professional offers different ranges of kBAU/L, based on the T line colour intensity, being proportional to the concentration of antibodies (Fig. 1), whilst the iRapid self-test identifies three ranges of Ab levels (low, moderate and high positivity). In this study we evaluated the performances of both iRapid devices with respect to the CLIA assay Maglumi anti S-RBD IgG, which has been extensively tested and demonstrated to be highly correlated ($R^2 = 0.820$) with the plaque reduction neutralization (PRNT) assay [5]. We identified a minimum protection level of 90 kBAU/L, which was the threshold obtained by receiver operating characteristic curve analysis (ROC) associated with a $PRNT_{50}$ titer of 1:20. In addition to 90 kBAU/L (defined here after minimum protective threshold for Maglumi assay), a secondary threshold of 506 kBAU/L identified by Feng et al., was used as the high protective threshold [9].

In addition, to the CLIA method, an automated ELISA assay was used to further compare the results of both iRapid devices with the high protective threshold. As expected, the iRapid results differ in comparison with the CLIA and the ELISA, whilst the overall agreement was better with the latter assay (Chorus).

Excellent results, especially in terms of sensitivity (98.2% for both iRapid devices) and overall agreement (95.1% and 95.9% for iRapid self-test and professional test, respectively) were found for the minimum protective threshold, measured by the CLIA assay (Table 1). Differently, a limited overall agreement of around 82% for the high protection cut-off was found. In addition, iRapid presented excellent results with respect to the ELISA assay at the high protective threshold, with sensitivity and specificity above 84% for both iRapid.

These results are in agreement with data recently reported by Broccolo et al., who compared iRapid with micro-neutralization assay, although in their study the data were evaluated in respect to the presence or absence of Nab, but not against quantitative thresholds [13].

The CLIA and the ELISA assays were then compared, and it was found that, with respect to Maglumi, Chorus overestimated anti S-RBD Ab. This might explain the discrepancy found in iRapid performances at the high protection threshold.

The vaccine elicited immune response has been demonstrated to wane rapidly after 4–6 months from inoculum. Our results for iRapid, CLIA and ELISA assays confirm the decline of Ab levels after 4 months from the first inoculum, despite the magnitude of the difference between CLIA and ELISA results (Fig. 3) [14]. Interestingly, on considering iRapid assays, no increase was found in the number of false negative results occurring before and after 4 months from the first inoculum.

This study presents also some limitations. The first limitation is the use of IgG anti S- RBD method (Maglumi) as a reference instead of a neutralization or pseudo-neutralization method. Second, the considered protective thresholds were not specific for the different SARS-CoV-2 strains, in particular omicron.

Currently, several qualitative POCT have been produced for the detection of anti-SARS-CoV-2 Ab, but at this stage of the pandemic, their utility seems to be rather limited. Recently developed semi-quantitative devices might represent a useful tool for mitigating the pandemic. Both iRapid self-test and professional present very good overall agreements for detecting individuals with low anti-SARS-CoV-2 protection, whilst results for the highest protection better correlate with the neutralizing assay. Therefore, these devices could aid to identify persons with low levels of protection, and to define personalized strategies for vaccination and/or risk-based strategies for fragile individuals.

## Funding

This research received no external funding.

### *CRediT authorship contribution statement*

**Andrea Padoan:** Conceptualization, Formal analysis, Writing – original draft. **Chiara Cosma:** Methodology. **Luisa Galla:** Writing – original draft. **Daniela Basso:** Visualization. **Mario Plebani:** Conceptualization, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

The Authors thank Daniela Rinaldi (medical laboratory scientist) for her valuable technical support, and Diesse, DiagnosticaSenese, Siena, Italyfor kindly supplying reagents without in any way influencing the study design and data analysis.

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