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Neutralizing antibody responses following natural SARS-CoV-2 infection: Dynamics and correlation with commercial serologic tests.

Isabel Montesinos [a,*], Hafid Dahma [a], Fleur Wolff [b], Nicolas Dauby [c,d,f], Sabrina Delaunoy [a], Magaly Wuyts [a], Cedric Detemmerman [a], Cecile Duterme [b], Olivier Vandenberg [e,f,g], Charlotte Martin [c], Marie Hallin [a,e]

[a] Department of Microbiology, Laboratoire Hospitalier Universitaire de Bruxelles - Universitair Laboratorium Brussel (LHUB-ULB). Université Libre de Bruxelles. Rue Haute 322, 1000 Brussels, Belgium
[b] Department of Clinical Biochemistry, Laboratoire Hospitalier Universitaire de Bruxelles - Universitair Laboratorium Brussel (LHUB-ULB). Université Libre de Bruxelles. Rue Haute 322, 1000 Brussels, Belgium
[c] Department of Infectious Diseases, CHU Saint Pierre- Université Libre de Bruxelles (ULB). Brussels, Belgium & Institute for Medical Immunology (ULB), Belgium
[d] Institute for Medical Immunology. Université Libre de Bruxelles, Brussels, Belgium
[e] Innovation and Business Development Unit, Laboratoire Hospitalier Universitaire de Bruxelles - Universitair Laboratorium Brussel (LHUB-ULB), Université Libre de Bruxelles, Rue Haute 322, 1000 Brussels, Belgium
[f] Center for Environmental Health and Occupational Health, School of Public Health, Université Libre de Bruxelles, Rue Haute 322, 1000 Brussels, Belgium
[g] Division of Infection and Immunity, Faculty of Medical Sciences, University College London, London, United Kingdom

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ABSTRACT

The prediction of SARS-CoV-2 immunity by commercially available serologic tests will be crucial to assess the efficacy of vaccination. We used plaque reduction neutralization testing as the reference standard to evaluate the diagnostic performance of six commercial serologic tests for monitoring SARS-CoV-2 neutralizing antibodies. Euroimmun ELISA anti-spike 1 IgG, Euroimmun anti-spike 1 IgG QuantiVac ELISA, Elecsys Anti-nucleocapsid protein total antibodies, Elecsys Anti-receptor-binding domain total antibodies, VIDAS anti-spike subdomain IgG, and Microblot-Array COVID-19 IgG assay were performed on 228 sera from 89 healthcare workers who participated in a six-month seroprevalence survey. Although all immunoassays demonstrated similar performances, VIDAS SARS-CoV-2 IgG and Euroimmun QuantiVac IgG (area under the curve 0.96 and 0.95 respectively) showed the better ability to detect Nabs. Except for the Elecsys Anti-SARS-CoV-2 and the Elecsys Anti-SARS-CoV-2 S assays, the commercial serologic tests evaluated here showed a significant decrease of antibody titers in the 6-month follow-up samples. Depending on the immunoassay, 21% to 33% of the participants became seronegative, and 16.9% had a loss of neutralizing antibodies. Microblot-Array assay results showed cross-reactivity with HCoVNL63 in only one sample, and this sample showed SARS-CoV-2 neutralizing capacity. In conclusion, our results support the use of VIDAS SARS-CoV-2 IgG, Euroimmun Anti-SARS-CoV-2 ELISA IgG, Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA IgG and Microblot-Array COVID-19 IgG assays to monitor neutralizing antibody response following natural SARS-CoV-2 infection. These immunoassays could facilitate the prediction of post-vaccine protection in the long term and the allocation of booster doses.

1. Introduction

Since the beginning of the COVID-19 pandemic, several commercial SARS-CoV-2 serologic tests have been developed and widely used as complementary diagnostic tools and for seroprevalence studies [1–5]. Various methodologies and automated analytical platforms are now available for assessing the immune response to SARS-CoV-2 infections. These assays measure different classes of immunoglobulins, most of them detecting IgG or total antibodies that recognize the most important SARS-CoV-2 immunogenic antigens: the nucleocapsid protein (NC) or the spike glycoprotein (S) [6–8]. Van Elslanden et al. demonstrated a 2 days faster seroconversion for assays detecting anti-NC IgG or total Ig than for assays detecting anti-S IgG [9].

An accurate assessment of neutralizing antibodies (Nabs) responses

* Corresponding author.
E-mail address: carlota.montesinos@lhub-ulb.be (I. Montesinos).

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against SARS-CoV-2 is critical to assess the efficacy of vaccination. Antibodies binding the SARS-CoV-2 receptor-binding domain (RBD) of S glycoprotein have been identified as the most potently neutralizing and protective ones [10–17]. However, the longevity of the Nabs response after SARS-CoV-2 infection or vaccination needs further investigation. Published data regarding the durability of Nabs responses are conflicting: some studies suggest that antibody titers may diminish over time after SARS-CoV-2 infection as observed with coronaviruses while others have shown stable titers for at least 8 months [18–25].

The correlation between the antibody measurements by commercial serologic tests and their neutralizing activity using the Plaque Reduction Neutralization Test (PRNT) as the reference method has been confirmed in some studies [21, 26–28]. Given that PRNT is laborious and time-consuming and requires a high level of expertise, being able to use commercially available serologic test results with confidence to predict immunity will be crucial in the imminent post-vaccine era for monitoring the immune response after vaccination.

In this perspective, we describe here the diagnostic performance of six different commercial serologic tests for identifying neutralizing capacity of SARS-CoV-2 antibodies.

2. Material and methods

2.1. Patients and serums samples

Between April 15th and December 7th, 2020, a total of 532 healthcare workers (HCWs) working at the centre Hospitalier Universitaire Saint-Pierre (CHU Saint-Pierre) in Brussels, Belgium, participated in a six months survey of SARS-CoV-2 carriage and seroprevalence [5]. For each HCW, the Euroimmun Anti-SARS-CoV-2 IgG (Euroimmun, Lübeck, Germany) (Euroimmun IgG) assay was carried out at precise time points during 6 months: Day1 (baseline) - Day15- Day30- Month2- Month3- Month6. Presence of recent or current symptoms was assessed by a questionnaire at each visit. Mild or moderate symptoms were defined when one or more following symptoms where present: fever, cough, sore throat, headache, mild dyspnea and hypoxemia, tiredness, myalgia, nausea, diarrhea, conjunctivitis, loss of smell and/or taste. Severe dyspnea and hypoxemia requiring hospitalization, acute respiratory distress syndrome, confusion, coma or other neurological symptoms, were considered severe symptoms. The participants were considered asymptomatic when no symptoms were present currently or in the last month. The Ethical committee of CHU Saint Pierre approved this study (CE/20–04/17) and written informed consent was obtained from the participants.

At Day1 visit, 89 HCWs were Euroimmun IgG positive (baseline seroprevalence of 16,7%). A total of 202 serum samples from these 89 IgG-positive participants were selected to evaluate the presence of Nabs and their correlation with six commercial serologic tests. The sample selection was focused on the presence and the titer of antibodies at baseline and at least at the Month6 visit. Some participants were lost-to-follow-up throughout the study. In more detail this cohort of samples included: 89 Euroimmun IgG positive samples at Day1 visit, 70 samples from the Month6 visit (54 Euroimmun IgG positive and 16 Euroimmun IgG negative (seroreversion) samples), 37 last Euroimmun IgG positive samples of the participant showing a total seroreversion or lost at any time of the study (19 Euroimmun IgG positive samples at Month3 visit; 8 Euroimmun IgG positive samples at Month2 visit; 8 Euroimmun IgG positive samples at Month1 visit; 2 Euroimmun IgG positive samples at Day15 visit), 6 Euroimmun IgG negative samples from seroreverted patients before the Month6 visit (2 samples at Month2 visit and 4 samples at Month3 visit). We also selected twenty-six serum samples from non-seroconverted participants at baseline visit used as negative controls.

2.2. Plaque reduction neutralization test (PRNT)

PRNT was performed and considered as the reference method to determine the neutralization capacity of SARS-CoV-2 antibodies. Briefly, 100 µL of wild SARS-CoV-2 suspension (around 90 plaque-forming units (PFU) final titer) was mixed with 100 µL of heat-inactivated serum sample at 1:80 dilution. The virus-serum mixture was incubated at 37 °C for 1 h. Then, 100 µL of this mixture was transferred onto washed Vero cell monolayers in 24-well tissue culture plates and incubated at 37 °C in 5% CO2 for 1 h. After incubation, cell monolayers were overlaid with 1% agarose in Opti-MEM™ medium (Thermo Fisher Scientific; Waltham, Ma, USA). The plates were re-incubated at 37 °C in 5% CO2 for 3 to 4 days, then the agarose was removed and the cells were fixed and stained. PFU were counted using an inverted transmitted light microscope. A serum was considered positive for Nabs if its 1:80 dilution reduced the number of plaques by more than 50% (PRNT50) compared to the negative control.

2.3. Enzyme-linked immunoassays (ELISA)

The Euroimmun Anti-SARS-CoV-2 ELISA IgG (Euroimmun IgG) and the Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA IgG (Euroimmun QuantiVac IgG) (Euroimmun, Lübeck, Germany) were performed on serum samples according to the manufacturer's instructions for the ELISA automated system ETI-MAX 3000 (DiaSorin, Saluggia, Italy). The microplate wells are coated with recombinant S1 structural protein. Euroimmun IgG results are evaluated semi-quantitatively by calculation of the ratio of the samples' extinction value over the calibrator's extinction. The ratio interpretation was as follows: < 0.8 = negative, ≥ 0.8 to < 1.1 = borderline, ≥ 1.1 = positive. Euroimmun QuantiVac IgG is a specific ELISA for the quantitative detection of anti-SARS-CoV-2 IgG by means of a 6-point calibration curve. Euroimmun recommends interpreting results as follows: <8 Ratio Unit/mL (RU/mL) = negative, ≥8 to <11 RU/mL borderline, ≥11 RU/mL positive. Borderline data for both tests were considered as positive for statistical analyses.

2.4. Chemiluminescent immunoassay (CLIA)

The Elecsys Anti-SARS-CoV-2 (Elecsys NC) and Elecsys Anti-SARS-CoV-2 S (Elecsys S) assays are immunoassays for in vitro determination of total antibodies, and were performed on a Cobas e801 analyzer (Roche Diagnostics, Vilvoorde, Belgium). Elecsys NC uses a SARS-CoV2 specific recombinant nucleocapsid antigen, and the qualitative results are interpreted either as negative (cut-off index; COI <1) or positive (COI ≥1). Elecsys S uses a recombinant protein comprising the RBD of the S antigen, and the quantitative results are interpreted as follows: <0.8 U/mL: negative or ≥0.8 U/mL: positive.

2.5. Enzyme linked fluorescence assays (ELFA)

The VIDAS SARS-CoV2 IgG (VIDAS IgG) is a two-step sandwich ELFA performed on a VIDAS analyzer (bioMérieux, Marcy-l'Etoile, France). A recombinant SARS-CoV2 sub-domain spike antigen is coated on a solid phase and a soluble anti-human IgG labeled with alkaline phosphatase recognizes the immunoglobulins. After adding the substrate, the intensity of the fluorescence measured at 450 nm is proportional to the level of antibody. An index ratio between the relative fluorescence value (RFV) measured in the sample and the RFV obtained for the calibrator (humanized recombinant anti SARS-CoV2 IgG) is calculated and interpreted as negative (index <1) or positive (index ≥1).

2.6. Microblot-Array assay

The Microblot-Array COVID-19 IgG assay (TestLine CliniCal Diagnostics s.r.o, Brno, Czech Republic) (Microblot-Array) for the determination of specific anti-SARS-CoV-2 antibodies was performed

according to the manufacturer's instructions. This Microblot-Array enables simultaneous detections of SARS-CoV-2 antibodies against recombinant and highly purified native antigens as NC, RBD, subunit Spike 2 (S2), Envelope protein (E), papain-like protease (PLpro) and anti-Angiotensin-converting enzyme (ACE2) antibodies. This kit also contains antigens aiming at excluding cross-reactivities with the following endemic coronaviruses: Middle East Respiratory Syndrome coronavirus (MERS-CoV): S1 protein, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV): NC, Human coronavirus 229E (HCoV 229E): NC, Human coronavirus NL63 (HCoV NL63): NC. Recombinant and highly purified native antigens are spotted on a nitrocellulose membrane that is fixed onto a plastic pad at the bottom of each microplate well. The wells contain also calibration spots that are necessary for quantitative results. The reading and the interpretation are performed using the Microblot-Array reader and software and are reported and interpreted as follows: <185 U/mL = negative, 185–210 U/Ml = borderline, >210 U/mL = positive. The overall interpretation is taking into account the presence or absence of reaction against at least 1 antigen from the main group of antigens (NC, RBD, S2) and/or at least 1 antigen from the group of other antigens (E, ACE2, PLPro). A positive reaction against other coronaviruses antigens indicates a possible cross-reactivity.

2.7. Statistical analyses

Results were analyzed using the Graph Pad Prism software version 5.0 (La Jolla, USA). The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. These later were reported using the median and the range. Receiver operator characteristic (ROC) curve was calculated, the area under the curve (AUC) obtained with the confidence interval at 95% (CI 95%) was reported for each assay. Categorical variables were compared using the Fisher's exact test. Sensitivity, specificity, positive (PPV) and negative predictive (NPV) values were reported. Differences in baseline antibody titers between asymptomatic and symptomatic patients were evaluated using the Mann-Whitney test. The evolution of antibody levels between the samples drawn during the first month following SARS-CoV-2 infection and six month later was assessed with the Wilcoxon-signed rank test. The variation of antibody titers observed between baseline and 6-month follow-up sera (expressed in percent) were compared between asymptomatic and symptomatic HCWs using a Mann-Whitney test. A p-value lower than 0.05 was considered statistically significant.

3. Results

Using the PRNT50 at a dilution 1/80, the presence of Nabs was demonstrated in 82 out of 89 HCWs who had positive results by Euroimmun IgG assay at the baseline visit. Based on the sera chosen from these participants, 157 (87.2%) of the 180 positive or borderline results by Euroimmun IgG assay showed Nabs. Seven (31.8%) of the 22 negative sera collected during the follow-up visit of seroreverted HCWs showed a neutralizing capacity (median index = 0.6). However, none of the 26 negative sera from non-seroconverted HCWs (negatives controls) showed Nabs. Sensitivity, specificity, PPV, and PNV of the commercial serologic tests using manufacturer cut-off value to detect Nabs are shown in Table 1, along with the AUCs.

Only 65 of the 82 HCWs showing Nabs at the baseline visit completed the 6-month follow-up. The neutralizing activity was lost in 11 of 65 (16.9%) HCWs. Fig. 1 shows the number of participants who had neutralizing antibodies and positive serologic results at the baseline visit and at the 6-month follow-up. Regarding the evolution of the antibody titers detected by serologic tests, a significant decrease was observed for Euroimmun G, Euroimmun QuantiVac IgG, VIDAS IgG, Microblot-Array NC, and RBD antigen, with a respective median decrease percentage of −56.3%, −59.8%, −54.2% and −57% (P value < 0.05). No significant decrease of antibody titers was observed for Elecsys NC and Microblot-Array anti-S2 antigen (−21,4% and −1,2% respectively). A significant rise of antibody titers was observed for Elecsys S (+ 96,7%). No significant decrease of antibody titers was observed according to the presence or the absence of symptoms before or at the baseline visit (Table 2).

Only one cross-reaction (with HCoVNL63: 464 U/mL) was observed by the Microblot-Array assay on a serum sample collected from an asymptomatic participant. PRNT results showed SARS-CoV-2 neutralizing capacity in this sample. It was also positive for Euroimmun G (index 1.3); Euroimmun QuantiVac IgG (18.45 RU/mL), Elecsys S (7.7 U/mL), VIDAS IgG (Index 1.4) and the Microblot-Array RBD antigen (241 U/mL), but negative for Elecsys NC and Microblot-Array assay NC and S2 antigens. No reactivity to the other minor antigen nor to other coronaviruses antigens was observed for the remaining 227 sera.

Table 1
Analytical sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serologic tests for detecting SARS-CoV-2 neutralizing antibodies (Nabs) assessed by PRNT in 228 sera from 89 HCWs.

	Recombinant antigen	Type of Ig	Sensitivity (IC 95%)	Specificity (IC 95%)	PPV (IC 95%)	NPV (IC 95%)	AUC (IC 95%)
ELISA							
Euroimmun Anti-SARS-CoV-2	S1	IgG	95,7% (91,5–98)	64,1% (51,8-74,7)	87,2% (81,6–91,3)	85,4% (72,8–92,8)	0,93 (0.90-0.96)
Euroimmun Anti-SARS-CoV-2 QuantiVac	S1	IgG	92,1% (86,9–95,3)	79,7% (68,3–87,7)	92,1% (86,9–95,3)	79,7% (68,3–87,7)	0.95 (0.92–0.98)
CLIA							
Elecsys Anti-SARS-CoV-2	NC	Total IgG	98,8% (95,7–99,7)	54,7% (42,6–66,3)	84,8% (79–89,2)	94,6% (82,3–98,5)	0.87 (0.81–0.92)
Elecsys Anti-SARS-CoV-2 S	RBD	Total IgG	98,8% (95,7–99,7)	54,7% (42,6–66,3)	84,8% (79–89,2)	94,6% (82,3–98,5)	0.88 (0.84–0.93)
ELFA							
VIDAS SARS-CoV2 IgG	S Sub-domain	IgG	86% (79,8–90,5)	89,1% (79,1–94,6)	95,3% (90,6–97,7)	71,3% (60,5–80)	0.96 (0.93–0.98)
Microblot-Array COVID-19 assay							
Overall interpretation			95,1% (90,7–97,5)	62,5% (50,3–63,3)	86,7% (80,9–90,9)	83,3% (70,4–91,3)	
Main group of antigens	NC	IgG	93,3% (88,4–96,2)	60,9% (48,7–71,9)	86% (80,1–90,3)	78% (64,8–87,2)	0.89 (0.84–0.93)
	RBD	IgG	82,9% (76,4–87,9)	82,8% (71,8–90,1)	92,5% (87,1–95,8)	65,4% (54,6–74,9)	0.94 (0.91–0.97)
	S2	IgG	52,4% (44,8–59,9)	89,1% (79,1–94,6)	92,5% (85,3–96,3)	42,2% (34,2–50,7)	0.87 (0.81–0.92)

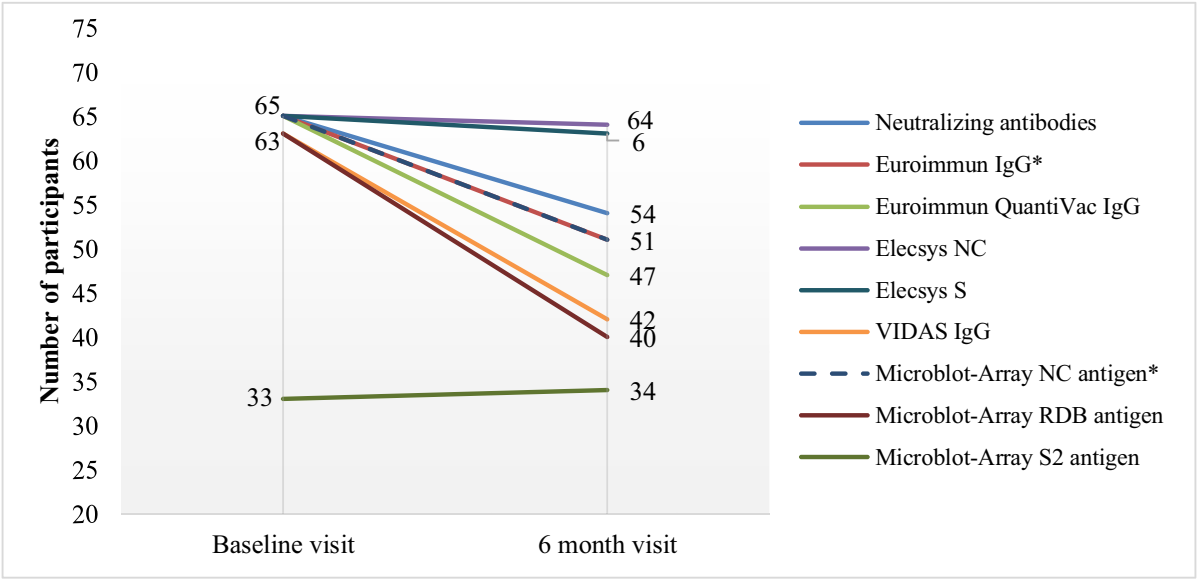

Fig. 1. Evolution of the 65 participants who had neutralizing antibodies and positive results at the baseline visit and at the 6-month follow-up *Overlapping lines for Euroimmun IgG and Microblot-Array NC.

Table 2
Six-month follow-up evolution of serologic tests results from 65 symptomatic and asymptomatic HCWs who developed SARS-CoV-2 neutralizing antibodies at the baseline visit.

	Baseline Overall Sympto/Asympto[1]	6 month Overall Sympto/Asympto[1]	P value
ELISA			
Euroimmun Anti-SARS-CoV-2: median ratio	3.9 4.1/3.1	1.5 1.5/1.4	<0.05 =0.3[5]
Euroimmun Anti-SARS-CoV-2 QuantiVac : median U/mL	50.7 51.3/33.2	17 18.2/15.4	<0.05 =0.4[5]
CLIA			
Elecsys Anti-SARS-CoV-2: median COI[2]	42 42/41.5	37.1 37.1/37.1	= 0.29 =0.06[5]
Elecsys Anti-SARS-CoV-2 S: median RU/mL[3]	50.8 69.7/32.7	105 123/84.2	<0.05 =0.1[5]
ELFA			
VIDAS SARS-CoV2 IgG: median RFV[4]	6.9 7.2/5.9	1.65 1.6/1.4	<0.05 =0.4[5]
Microblot-Array assay main antigens: median U/mL			
NC antigen	954 951/964	388 370/415	<0.05 =0.7[5]
RBD antigen	780 791/735	254 280/208	<0.05 =0.7[5]
S2 antigen	213 256/126	194 199/140	=0.61 =0.9[5]

[1]Symptomatic subjects ($n = 47$)/Asymptomatic subjects ($n = 18$). [2]COI: cut-off index. [3]RU: ratio units. [4]RVF: relative fluorescence value. [5]The P value was calculated comparing the variation of antibodies titers (baseline and 6-month follow-up sera) observed in symptomatic HCWs to the titers variation in asymptomatic ones.

4. Discussion

The protective character of SARS-CoV-2 neutralizing antibodies has been demonstrated in animal models and humans [14, 22, 29, 30]. Nowadays, many serologic immunoassays are available for monitoring SARS-CoV-2 antibodies using automated platforms, allowing larger tests capacities. In the context of vaccine performance evaluation, the ability of the commercial immunoassays to detect Nabs has been highlighted and several reports demonstrating the neutralizing capacity of the antibodies detected by these immunoassays have been published. However, a consensual cut-off titer of Nabs to predict protection has not been defined yet [31]. High titers of Nabs (>1:160) are recommended for COVID-19 convalescent plasma use in therapy [21, 31, 32]. However, other studies consider Nabs from 1:20 [27, 28]. The minimal titer suggested for immunotherapy (1:80) was chosen in this study as the cut-off value for Nabs [26, 33].

Although all immunoassays evaluated here demonstrate similar performances, VIDAS IgG and Euroimmun QuantiVac IgG (AUC 0.96 and 0.95 respectively) showed a better ability to detect Nabs. In agreement with previously reported studies, the weakest correlation was observed for Elecsys NC (AUC 0.87) [34–36]. The new quantitative anti-RBD serologic test recently developed by Roche, Elecsys S, does not seem to perform better than the original assay (AUC 0.88). To our knowledge, this is the first evaluation of Elecsys S for detecting Nabs. The longevity of the protective character of SARS-CoV-2 antibodies is unknown for the time being. Although preliminary evidence suggested a rapid decline of Nabs, more recent large prospective cohorts have found persistent IgG response at least after 6–8 months of follow-up [18, 19, 22, 24, 25, 37–40]. Moreover, a recent report indicates an increase in the number of circulating memory B cells eight months after infection [18]. In the present study, only a minority (16.9%) of the participants lost Nabs within in at least 6 months.

Except Elecsys NC, Elecsys S, and Microblot-Array S2 antigens, the commercial serologic tests evaluated in this study showed a significant decrease of antibody titers. The competitive design of the Roche assays could explain the stability or increase in the antibody rates. The decrease in the total amount of antibodies might be compensated by the affinity increase resulting from the antibody's maturation over time. The unexpected antibody dynamic of Elecsys NC and Elecsys S limits their use to predict neutralizing antibody's evolution over time. The S2 subunit is a highly conserved epitope and this characteristic might explain the stability of anti-S2 antibodies titers. The Micro-Array S2 antigen could be detecting not only SARS-COV-2 antibodies but also antibodies against other coronaviruses. The low sensitivity of antibodies anti-S2 antigen by Microblot-Array test needs further investigation by the manufacturer.

Seow et al. observed that the magnitude of the decline of SARS-COV-2 antibodies was dependent on disease severity [41]. Although the antibody decline depending on the clinical status is not statistically significant, a declining trend was observed in the present study. A full seroreversion was observed in 21% to 33% of participants depending on the assay. Interestingly, the seroreversion observed by some commercial

serologic tests did not always correlate with the absence of antibody neutralizing capacity. Lumley et al. demonstrated a faster wane of anti-NC IgG than anti-S IgG titers in a cohort of HCWs, particularly in younger adults and following asymptomatic infection [42].

Microblot-Array assay results showed cross-reactivity with other coronaviruses only in one sample, towards HCoVNL63. Cross-reactivity with other seasonal coronavirus has been observed by others [43–45]. Simula et al. have recently demonstrated that pre-existing HCoVNL63 antibodies cross-react with SARS-CoV-2 in pre- and mid- COVID-19 pandemic individuals [45]. Some studies suggest less severe COVID-19 in patients with a previous infection with other endemic coronaviruses [44, 46]. Interestingly, this sample showed SARS-CoV-2 neutralizing capacity. Larger studies are warranted to better demonstrate this potential neutralizing capacity.

With the ongoing vaccination campaigns, questions remain regarding the durability of protection and the identification of a correlate of protection would be crucial [46]. Some experts suggest that serologic assay could guide the prioritization of vaccine uptake. Given the fact that past SARS-CoV-2 infection and seropositivity has been associated with protection, priority could be given to subject with low or absent Nabs based on commercial serologic assays in particular contexts [47].

This study has some limitations. First, the loss or decrease of neutralizing antibodies and titers may correspond to a period longer than 6 months, given that the participants of this study were enrolled on a voluntary basis and not on having suspicion of SARS-CoV-2 infection. Second, because only asymptomatic and mild or moderate symptomatic HCWs were included, our observations should also be assessed including patients suffering of severe COVID-19 infection. Lastly, the borderline results were considered as positive for statistical analyses and may correspond to both falsely positive results and/or low SARS-CoV-2 antibodies titers.

In conclusion, our results support the use of VIDAS SARS-CoV-2 IgG, Euroimmun Anti-SARS-CoV-2 ELISA IgG, Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA IgG or Microblot-Array COVID-19 IgG assays to monitor neutralizing antibody response following natural SARS-CoV-2 infection. These assays could facilitate the evaluation of possible waning protection of vaccines in the long term and the allocation of booster doses.

Declaration of Competing Interest

bioMérieux has partly sponsored this study. EuroImmun (Euroimmun Anti-SARS-CoV-2 IgG QuantiVac ELISA) and TestLine CliniCal Diagnostics (Microblot-array COVID-19 IgG assay) have offered reagents for validation. The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

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