Evaluation of high-throughput SARS-CoV-2 serological assays in a longitudinal cohort of patients with mild COVID-19: clinical sensitivity, specificity and association with virus neutralization test

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Background: The association between SARS-CoV-2 commercial serological assays and virus neutralization test (VNT) has been poorly explored in mild patients with COVID-19.

Methods: 439 serum specimens were longitudinally collected from 76 healthcare workers with RT-PCR-confirmed COVID-19. The clinical sensitivity (determined weekly) of nine commercial serological assays were evaluated. Clinical specificity was assessed using 69 pre-pandemic sera. Correlation, agreement and concordance with the VNT were also assessed on a subset of 170 samples. Area under the ROC curve (AUC) was estimated at 2 neutralizing antibody titers.

Results: The Wantai Total Ab assay targeting the receptor binding domain (RBD) within the S protein presented the best sensitivity at different times during the course of disease. The clinical specificity was greater than 95% for all tests except for the Euroimmun IgA assay. The overall agreement with the presence of neutralizing antibodies ranged from 62.2% (95%CI; 56.0-68.1) for bioMérieux IgM to 91.2% (87.0-94.2) for Siemens. The lowest negative percent agreement (NPA) was found with the Wantai Total Ab assay (NPA 33% (21.1-48.3)). The NPA for other total Ab or IgG assays targeting the S or the RBD was 80.7% (66.7-89.7) , 90.3 (78.1-96.1) and 96.8% (86.8-99.3) for Siemens, bioMérieux IgG and DiaSorin, respectively. None of commercial assays have sufficient performance to detect a neutralizing titer of 80 (AUC<0.76).

Conclusions: Although some assays show a better agreement with VNT than others, the present findings emphasize that commercialized serological tests including those targeting the RBD cannot substitute a VNT for the assessment of functional antibody response.

Introduction

The evaluation of the humoral immune response to SARS-CoV-2 with serological tests is crucial to further manage the coronavirus disease 2019 (COVID-19) pandemic. Serological testing represents an easy to implement and cost-effective method allowing rapid identification of individuals exposed to the virus (1,2). Over the last few months, a large number of SARS-CoV-2 commercial assays have been evaluated for their ability to detect specific antibodies (3–9). However, the detection of specific SARS-CoV-2 antibodies does not indicate whether or not the antibodies are functional for neutralizing the virus. In association with the assessment of other immune responses, such as cellular immunity, the exploration of the neutralizing antibody response is important to evaluate the protective immunity to SARS-CoV-2 after infection and therefore the risk of reinfection (10–13). To date, the association between SARS-CoV-2 commercial assay results and the presence of neutralizing antibodies has been mainly explored in hospitalized COVID-19 patients (14–18). Because conflicting findings have been reported, it is unclear whether the commercial serological assays could be useful to assess the protective immunity against SARS-CoV-2.

Virus neutralization test (VNT) is considered as the reference to assess the functional ability of antibodies to block the entry of the virus into human cells (19). However, such an assay requires living virus manipulated in a biosafety level 3 facility that needs trained staff and specific equipment, and which is a tedious and time-consuming method. The first study exploring the association of commercial serological assays and VNT claimed that the Wantai Total Ab assay detecting total antibodies directed against the SARS-CoV-2 receptor binding domain (RBD) had the best characteristics to detect functional antibodies at different stages and severity of disease (14). The RBD, within the sub-unit S1 of the spike protein, enables the viral entry into human cells by fixing to the angiotensin-converting enzyme 2 receptor (20). As emphasized in this study (14), there is an urgent need for further studies addressing the performance of

alternative high-throughput assays in correlation with VNT among persons with mild COVID-19, which is the most common form of the disease.

Thus, the aim of the present study was to evaluate widely-used SARS-CoV-2 serological tests and their potential association with VNT in a cohort of patients with mild mild COVID-19.

Methods

Study design and sample collection

A prospective longitudinal cohort study was conducted at the laboratory associated with the National reference center for respiratory viruses (University Hospital of Lyon, France)(21). Healthcare workers (HCW) with symptoms suggesting a SARS-CoV-2 infection requiring a RT-PCR test were included (visit 1, V1). Clinical data including date of symptom onset were recorded for all included HCWs using an electronic case report form by trained clinical research associate. Patients with a positive RT-PCR result at inclusion (V1) returned weekly for 6 additional visits (V2 toV7). Serum samples were prepared from 5 mL of whole blood collected in BD Vacutainer® Serum Separating Tubes II Advance Tube (Beckon Dickinson). After collection tubes were shaken gently and serum were allowed to clot for a minimum 30 min at room temperature to obtain total coagulation, followed by centrifugation at 2,500 g for 10 min. Removed supernatants were frozen at -80°C until the serological assays. Written informed consent was obtained from all participants; ethics approval was obtained from the national review board for biomedical research in April 2020 (*Comité de Protection des Personnes Sud Méditerranée I*, Marseille, France; ID RCB 2020-A00932-37), and the study was registered on ClinicalTrials.gov (NCT04341142). A total of 439 serum specimens were longitudinally collected from 76 HCW. Among them, 74 had mild COVID-19 related symptoms (fever, cough, loss of taste or smell, diarrhea) and did not require hospital admission. Two out of 76 HCW were admitted to the hospital (not in intensive care unit, ICU) due to the severity of their

symptoms. Among the 439 collected samples, 170 of them obtained at V2, V4, V7 from 57 patients were tested by VNT (for one patient the sample at V7 was missing). To compare neutralizing antibody titers between patients with mild and severe COVID-19 patients, 117 sera collected longitudinally from 44 patients with severe COVID-19 were also tested by VNT. These patients have been admitted to ICU at the University Hospital of Saint-Etienne and serum were collected longitudinally between March and May 2020. The median age was 70.4 y and 20% were female. All patients were sampled by nasal swab and had tested positive for SARS-CoV-2 RNA by RT-qPCR assay.

In addition, to evaluate clinical specificity, we selected retrospectively 69 prepandemic sera (collected between April and July 2019) from 30 healthy volunteers (52% females, median age of 28 y, IQR: 21-34), 30 patients with autoimmune disorders, and 9 patients with a positive serological result for *M. pneumonia*e. The patients with autoimmune disorders (F: M ratio of 1.7; mean age 42.7 y) included 10 patients with antinuclear antibodies at a titer ≥ 320, 10 patients with rheumatoid factor associated (n=2) or not (n=8) with anti-citrullinated protein antibodies, and 10 patients with inflammatory bowel disease, 7 of whom exhibited anti-neutrophil cytoplasmic antibodies (n=2), anti-*Saccharomyces cerevisiae* antibodies (n=3) or antinuclear antibodies (n=2). The patients with a positive serological result for *M. pneumonia*e (55% female, mean age of 20 y) had IgM titers that ranged from 21 to > 27 UA/ml using the DiaSorin kit on the Liaison XL instrument.

Virological investigation

COVID-19 diagnosis at inclusion was performed by RT-PCR on nasopharyngeal swab using the cobas SARS-CoV-2 assay (Roche, Basel, Switzerland).

A total of 9 serological assays (Abbott, DiaSorin, Siemens, Bio-Rad, Wantai Total and IgM, bioMérieux IgG and IgM, Euroimmun IgA) were investigated according to the protocol recommended by each manufacturer (characteristics are summarized in Table 1). Positivity was established according to the threshold value recommended by each manufacturer.

A plaque reduction neutralization test (PRNT) was used for the detection and titration of neutralizing antibodies, as previously described (22). Briefly, a ten-fold dilution of each serum specimen in culture medium (Dulbecco's Modified Eagle Medium containing antibiotics and 2% foetal calf serum) was first heated for 30 min at 56°C to avoid complement-linked reduction of the viral activity. Serial two-fold dilutions (tested in duplicate) of the serum specimens in culture medium were mixed at equal volume with the live SARS-CoV2 virus. After gentle shaking and a contact of 30 min at room temperature in plastic microplates, 150 µL of the mix was transferred into 96-well microplates covered with Vero E6 cells. The plates were incubated at 37°C in a 5% CO_2 atmosphere. The reading was evaluated microscopically 5 to 6 days later when the cytopathic effect of the virus control reached 100 $TCID_{50}$/150 µL. Neutralization was recorded if more than 50% of the cells present in the well were preserved. The neutralizing titer was expressed as the inverse of the higher serum dilution that exhibited neutralizing activity; a threshold of 20 was used ($PRNT_{50}$ titer $\geq$ 20). All experiments were performed in a biosafety level 3 laboratory. The comparison of this VNT with a standardized assay using retroviruses pseudo-typed with the SARS-CoV-2 S viral surface protein found a high correlation and concordance (22).

Statistical analyses

For each test, the clinical sensitivity was estimated weekly after symptom onset considering SARS-CoV-2 RT-PCR results as the gold standard.

For VNT, the overall positive and negative percent agreements (OPA, PPA, NPA) were determined for each commercial serological assay as previously described (23). The correlation and concordance with the VNT were assessed using the Spearman and Cohen's Kappa coefficients, respectively. The concordance was classified as slight (Cohen's Kappa coefficient, [0-0.2]), fair [0.21-0.4], moderate [0.41-0.6], substantial [0.61-0.8], and almost perfect [0.81-1] according to Landis and Koch criteria (24). The Cohen's Kappa coefficient was not interpreted if the sensitivity was 100%. The estimation of the correlation coefficient was not performed due to an upper limit of signal to cut-off ratio for the Siemens and Bio-Rad assays. Clinical specificity was assessed with 69 pre-pandemic serum specimens collected in 2019. The estimates are given with their bilateral 95% confidence interval (CI) calculated using the Wilson method. The 95% CI for Cohen's Kappa coefficient was calculated using the bootstrap percentile method. The paired comparison of sensitivity between two assays was performed with the non-parametric McNemar test. The area under the ROC curve (AUC) was estimated to assess the overall performance of serological assays to detect the presence of neutralizing antibodies ($PRNT_{50} \geq 20$) or higher neutralizing antibody titers ($PRNT_{50} \geq 80$). Statistical analyses were carried out using SAS software, version 9.4 (Copyright (c) 2002-2003 by SAS Institute Inc., Cary, NC, USA.) and R software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered as statistically significant.

Results

Clinical sensitivity and specificity

During the first week after the onset of symptoms the sensitivity for the detection of SARS-CoV-2 antibodies ranged from 6.6% (DiaSorin, Liaison) to 25.0% (Euroimmun IgA). During the second week the sensitivity was >70% for three tests including Bio-Rad, Wantai Total Ab, and Euroimmun IgA assays (74.2%, 79.0% and 72.6%, respectively). The highest sensitivity was found at week 3 for Bio-Rad (96.6%), Wantai Total Ab (100%), Wantai IgM (94.9%), bioMérieux IgM (78.0%) and Euroimmun IgA (96.6%), at week 4 for Abbott (93.2%), and at week 6 for DiaSorin (93.2%), Siemens (98.3%) and bioMérieux IgG (94.9%). After this point, a decrease in sensitivity was noted for all assays except for the Wantai Total Ab which remained steady at 100% over the course of the disease (Table 1). The Wantai Total Ab assay had a significantly higher sensitivity before 14 days post-symptom onset with all other assays ($p<0.001$ for all comparisons), except with the Euroimmun IgA ($p=0.72$) and Bio-Rad ($p= 0.20$) assays. After 14 days post-symptom onset, the sensitivity was significantly different between Wantai Total Ab assay and all other assays ($p<0.001$ for Abbott, DiaSorin, Wantai IgM, bioMérieux IgM, Euroimmun IgA assays, $p=0.0015$ for bioMérieux IgG and Bio-Rad assays and $p=0.04$ for Siemens assay).

In addition, we evaluated the specificity using 69 pre-pandemic sera. No false positive result was found with the two Wantai assays, bioMérieux IgG, and Siemens assays. For the DiaSorin, Abbott, Bio-Rad and bioMérieux IgM assays, the specificity was higher than 95%. For the Euroimmun IgA assay, the specificity [95%CI] was 84.06%, [72.84-91.40] (Table 2).

Kinetics of neutralizing antibody titers

The neutralizing capacity of antibodies was determined at three time points for 57 patients (n=170 samples, Figure 1). No neutralizing antibodies were detected in 42.0% (21/50), 5.8%

(3/51), and 8.7% (6/69) of samples collected between, respectively, 1-14, 15-28, and more than 28 days after symptom onset. Of note, three out of 57 patients had no neutralizing antibodies throughout their follow-up.

For comparison, we also determined the titers of neutralizing antibodies in sera longitudinally collected from COVID-19 patients (n=44) admitted to an ICU (n=117 samples, Figure 1). Only one patient had no neutralizing antibodies throughout follow-up (until 45 days post symptoms). No neutralizing antibodies were detected in 42.3% (11/26), 2.3% (1/44), and 2.1% (1/47) of samples collected between, respectively, 1-14, 15-28, and more than 28 days after symptom onset.

For the samples with a detection of neutralizing antibody (n=140 and n=104 for patients with mild and severe COVID-19, respectively), the median [IQR] titer was 60 [40-100] vs 160 [80-320] between 1-14 days post symptom, reached 80 [60-120] vs 480 [240-640] between 15-28 days post symptom and decreased in samples collected after more than 28 days (median: 60 [40-120] vs 320 [120-640]).

Comparison of results between commercial kits and VNT

The Spearman coefficient [95%CI] assessing correlation between commercial kits and VNT varied from 0.43 [0.27-0.56] to 0.61 [0.49-0.71] (Figure 2, Table 3).

A slight and fair concordance with VNT ($PRNT_{50} \geq 20$) were noticed for the 2 IgM assays evaluated here (Kappa [95%CI]: 0.24 [0.14-0.36] for bioMérieux IgM and 0.40 [0.21-0.58] for the Wantai IgM assays). For the total Ab or IgG assays targeting the S protein, three had substantial concordance with VNT ($PRNT_{50} \geq 20$) (Kappa [95%CI]: 0.71[0.57-0.84] for bioMérieux, 0.70 [0.56-0.83] for DiaSorin, and 0.72 [0.55-0.85] for Siemens assays) while the concordance with the Wantai Total Ab assay was moderate (0.43 [0.23-0.63]; Table 3). The

OPA, assessing the observed concordance between commercial serological assay and VNT ($PRNT_{50} \geq 20$) confirmed that noticed with Cohen's kappa. In particular, the lowest OPA was reported for the 2 IgM assays and for the Wantai Total Ab assay. Moreover, the NPA with VNT ranged from 33.3% [21.1-48.3] for the Wantai Total Ab assay to 96.8% [86.8-99.3] for the DiaSorin and was < 90% for 7/9 assays. The PPA with VNT was > 90% for all tests except the DiaSorin and the two IgM based assays (Wantai and bioMérieux) (Table 3.

Finally, ROC curves were built to estimate the performance of each commercial serological assay for detecting the presence of neutralizing antibodies ($PRNT_{50} \geq 20$). The two IgM assays had the lowest AUC (0.80 for both). The AUC for the other assays found high performance to predict the presence of neutralizing antibodies reaching a value ≥ 0.96 for Siemens, Diasorin and bioMérieux IgG. The same methodology was applied for detecting higher neutralizing antibody titers ($PRNT_{50} \geq 80$); none of these commercial assays had sufficient performance (AUC<0.76).

Discussion

In a longitudinal study of 76 HCW with RT-PCR-confirmed COVID-19, we found that the Wantai Total Ab assay had the best clinical sensitivity over the course of the disease. In particular, the sensitivity reached and remained at 100% as soon as week 3 post symptom onset. This finding observed in patients with mild COVID-19 is consistent with previous reports of excellent sensitivity of this test, notably in severe patients (3,14). Importantly, the sensitivity of the commercial tests can be higher in patients with severe COVID-19 in line with a stronger humoral immune response. In particular, we found lower neutralizing antibody titers in mild patients than in ICU patients in the present study. These findings are consistent with previous studies (25–28) and raise questions about protective immunity after an infection although the immune response is not exclusively driven by the neutralizing antibody response. The immunological correlates of protection as well as the durability of natural immunity are still unknown, but patients with mild symptoms who had a low neutralizing antibody titer may be insufficiently protected to prevent a reinfection. The occurrence of reinfections in humans has been explored during a SARS-CoV-2 outbreak with a high attack rate (85.2%), which showed that individuals with preexisting neutralizing antibodies were not infected (10). Further studies are needed to investigate the correlation between neutralizing antibody titers and the risk of reinfections in mild COVID-19 patients. In addition, following the FDA recommendation regarding the required titer for convalescent plasma donors (titer ≥ 160), the data presented here show that only a few patients with mild COVID-19 could be eligible. Thus, the ability of a commercial test to assess the neutralizing antibody response needs to be determined. With this aim, a prior study compared three commercial assays (Roche Total Ab, Abbott IgG, both tests targeting the N protein, and Euroimmun IgG assays targeting the S protein) to VNT on 66 specimens (17), and found that the NPA was >90% for all assays only at a low neutralizing titer of 20 while the NPA dramatically decreased when higher neutralizing titers were used, making

them imperfect proxies for neutralization. For instance, the NPA for neutralizing titers was <60% for all 3 the assays at a cutoff of 128. This study also suggested an increase in the manufacturer cutoff in order to improve the NPA, which can be very useful in a vaccination setting or for plasma donor screening (17).

Although the study design above (17) was different, notably regarding the disease severity of the patients enrolled, these findings are highly consistent with those of our present study that found the lowest NPA for the Wantai Total Ab assay (33%) and a NPA below 90% for all tests except for bioMérieux IgG and DiaSorin. Importantly we also found with an AUC analysis that all the commercial tested performed poorly at a neutralizing antibody titer of 80.

Furthermore, the concordance between VNT and the Wantai Total Ab assay was only moderate while the concordance was substantial with bioMérieux IgG, DiaSorin, Siemens, Abbott, Euroimmun IgA and Bio-Rad. The low NPA and moderate concordance noticed for the Wantai Total Ab might be partially explained by the ability of this test to detect RBD-specific antibodies at the very early phase of infection, irrespective of their neutralizing properties in line with the delay required for antibody maturation (29). The first study comparing VNT with commercialized tests (14) found that the Wantai Total Ab assay had the best characteristics to detect functional antibodies in different stages and severity of disease. However, the median interval between the onset of symptoms and sample collection was 43 days for the samples obtained from patients with mild symptoms (n=71 samples). Thus, the antibodies could be detected with both the Wantai Total Ab and the VNT assay at this time, explaining the high PPA values observed (14). In our study as well as other reports (15,16,17), a high PPA with VNT was also found for most of the commercial serological assays. Nevertheless, for determining the presence of neutralizing antibodies in serum specimen with commercial assays, the NPA should be maximized to avoid misinterpretation.

Furthermore, as previously reported (29,30,31), not all RBD-binding antibodies have neutralizing properties, which is consistent with our findings that the RBD-based assays do not have perfect concordance with VNT. Conversely, antibodies targeting a region other than the S protein may have functional activity (19,32–34). In the present study, the Abbott and Bio-Rad assays directed against the N protein presented a substantial concordance with VNT. N-directed and RBD-neutralizing antibodies can be produced concomitantly over the course of the disease, which can also explain this finding.

In addition to the different targeted antigens, the heterogeneity in assay performance found here could be related to various factors including the detected isotypes. Moreover, antibody concentrations may also be very different according to the time since symptom onset and according to clinical severity of the disease (25). In our study, serum samples were collected longitudinally from disease diagnosis, enabling us to explore the early phase of the antibody response in a cohort of HCW, which constitutes one of the main strengths of the present study.

The present study does, however, have certain limitations. For instance, clinical specificity was not extensively studied; yet, the Euroimmun IgA assay seemed to have the worst specificity, which is consistent with previous studies reporting a lack of specificity for this assay (4,5,14). In addition, the performance of other notable commercial assays such as Euroimmun IgG or Roche Ig Total were not assessed. Second, not all the samples were systematically tested by VNT, in-line with the labor-intensive nature of this method. Finally, the size of the tested population remains small, contributing to wide CI, which limits the interpretation and extrapolation of the results.

The results presented here confirm that the Wantai Total Ab assay showed the higher sensitivity for detecting SARS-CoV-2 antibodies after exposure. For the screening of neutralizing antibodies in serum specimens, an optimized cut-off maximizing the NPA needs to be established, as previously suggested for the Wantai Total Ab assay (14). However, the

data presented here suggest that other tests targeting the S protein as Siemens, DiaSorin or bioMérieux IgG might be more useful for this indication.

These tests or others cannot substitute for a VNT for assessing functional antibody response; neutralizing assays remain the gold standard and easy-to-use tests, such as those based on pseudoviruses (5,22,35), should be developed and standardized. Furthermore, the recent development of surrogate virus neutralization tests based on antibody-mediated blockage of the interaction between ACE-2 receptor and the RBD is very promising as they were designed in an ELISA format, enabling high-throughput testing (30,36,37).

In conclusion, our study provides original data concerning the performance of widely-used serological tests, which could help diagnostic laboratories in the choice of a particular assay according to the intended use.

COVID-SER study group

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All authors were involved in the analysis and interpretation of data as well as drafting the manuscript or revising it critically for important intellectual content. A. Bal, B. Pozzetto, V. Pitiot, F. Gueyffier, J.-B. Fassier, and S. Trouillet-Assant made substantial contributions to the conception and design of the study and designed the experiments. B. Pozzetto performed VNT. M.-A. Trabaud and V. Escuret performed the serological assay experiments. N. Guibert, A. Paul, C. D'Aubarede-Frieh, A. Massardier-Pilonchery, A. Boibieux, and J.-B. Fassier were involved in patient care, V. Pitiot performed the data collection, S. Trouillet-Assant, A. Boibieux, M.-A. Trabaud, and B. Pozzetto performed the data analysis. M. Rabilloud and C. Langlois-Jacques performed the statistical analysis. A. Boibieux and S. Trouillet-Assant wrote the paper, B. Lina, B. Pozzetto, J.-B. Fassier, A. Paul, V. Escuret, and M.-A. Trabaud revised the manuscript content. All authors read and approved the final manuscript.

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Manufacturer (platform)	**Abbott (Architect)**	**DiaSorin (Liaison®)**	**Siemens (Atellica®)**	**Bio-Rad**	**Wantai**		**bioMérieux (Vidas®)**		**Euroimmun**
name	SARS-CoV-2 IgG	SARS-CoV-2 S1/S2 IgG	SARS-CoV-2 Total	Platelia SARS-CoV-2 Total Ab	SARS-CoV-2 Total Ab	SARS-CoV-2 IgM	SARS-CoV-2 IgG	SARS-CoV-2 IgM	SARS-CoV-2 IgA
type	CMIA	CLIA	CLIA	ELISA	ELISA	ELISA	ELFA	ELFA	ELISA
	N	S1+S2	RBD	N	RBD	RBD	RBD	RBD	S1
ensitivity vs SARS-CoV-2 RT-PCR [95%CI]									
after symptom onset (n)									
	9.84 [5.17-17.91]	6.56 [2.98-13.83]	6.56 [2.98-13.83]	18.03 [11.35-27.43]	22.95 [15.36-32.84]	13.11 [7.55-21.81]	8.20 [4.05-15.90]	11.48 [6.34-19.88]	25.00 [17.02-35.14]
(63)	59.68 [49.23-69.31]	32.26 [23.41-42.59]	41.94 [32.18-52.37]	74.19 [64.18-82.19]	79.03 [69.41-86.23]	64.52 [54.11-73.71]	39.68 [30.17-50.04]	49.21 [39.09-59.38]	72.58 [62.47-80.81]
(59)	91.53 [83.60-95.81]	83.05 [73.61-89.59]	89.83 [81.52-94.65]	96.61 [90.26-98.87]	100.00 [95.62-100.00]	94.92 [87.94-97.95]	86.44 [77.50-92.19]	77.97 [67.97-85.50]	96.61 [90.26-98.87]
(59)	93.22 [85.73-96.92]	86.44 [77.50-92.19]	93.22 [85.73-96.92]	94.92 [87.94-97.95]	100.00 [95.62-100.00]	89.83 [81.52-94.65]	93.22 [85.73-96.92]	69.49 [58.96-78.32]	91.53 [83.60-95.81]
(65)	86.15 [77.66-91.76]	92.31 [85.03-96.21]	93.85 [86.98-97.21]	92.19 [84.81-96.15]	100.00 [96.00-100.00]	84.62 [75.89-90.58]	90.77 [83.13-95.15]	52.31 [42.23-62.20]	84.62 [75.89-90.58]
(59)	89.83 [81.52-94.65]	93.22 [85.73-96.92]	98.31 [92.75-99.62]	91.53 [83.60-95.81]	100.00 [95.62-100.00]	88.14 [79.49-93.44]	94.92 [87.94-97.95]	45.76 [35.51-56.38]	88.14 [79.49-93.44]
(73)	89.04 [81.58-93.71]	89.04 [81.58-93.71]	95.89 [90.15-98.35]	88.89 [81.34-93.62]	100.00 [96.38-100.00]	81.94 [73.38-88.20]	87.67 [79.97-92.68]	43.84 [34.67-53.44]	79.45 [70.69-86.11]

Table 1. Clinical sensitivity of 9 SARS-CoV-2 commercial serological assays. Positivity was established according to threshold value recommended by each manufacturer. Ab, antibodies; Ig, immunoglobulin; ELISA. enzyme-linked immunosorbent assay; CMIA, chemiluminescence microparticule immune assay; CLIA, chemiluminescence immune assay; ELFA, enzyme-linked fluorescent assay, n, number of samples; CI, confidence interval; RBD, Receptor Binding Domain; S1, spike protein subunit 1.

Manufacturer (platform)	Abbott (Architect)	DiaSorin (Liaison®)	Siemens (Atellica®)	Bio-Rad	Wantai		bioMérieux (Vidas®)		Euroimmun
name	SARS-CoV-2 IgG	SARS-CoV-2 S1/S2 IgG	SARS-CoV-2 Total Ab	Platelia SARS-CoV-2 Total Ab	SARS-CoV-2 Total Ab	SARS-CoV-2 IgM	SARS-CoV-2 IgG	SARS-CoV-2 IgM	SARS-CoV-2 IgA
type	CMIA	CLIA	CLIA	ELISA	ELISA	ELISA	ELFA	ELFA	ELISA
	N	S1+S2	RBD	N	RBD	RBD	RBD	RBD	S1
donors (n=30)	0/30	0/30	0/30	0/30	0/30	0/30	0/30	0/30	3/30
positive for antinuclear antibodies (n=10)	1/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	3/10
positive for rhumatoid factors (n=10)	0/10	0/10	0/10	0/10	0/10	0/10	0/10	3/10	2/10
suffered from inflammatory bowel disease(n=10)	0/10	1/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10
positiive for *M. pneunomiae* IgM (n=9)	0/9	0/9	0/9	1/9	0/9	0/9	0/9	0/9	2/9
Specificity [CI 95%]	98.55 [91.11-99.92]	98.55 [91.11-99.92]	100.00 [93.43-100.00]	98.55 [91.11-99.92]	100.00 [93.43-100.00]	100.00 [93.43-100.00]	100.00 [93.43-100.00]	95.65 [86.99-98.87]	84.06 [72.84-91.40]

Table 2. Clinical specificity of 9 SARS-CoV-2 commercial serological assays. Ab, antibodies; Ig, immunoglobulin; ELISA. enzyme-linked immunosorbent assay; CMIA, chemiluminescence microparticule immune assay; CLIA, chemiluminescence immune assay; ELFA, enzyme-linked fluorescent assay, n, number of samples; CI, confidence interval; RBD, Receptor Binding Domain; S1, spike protein subunit 1

Manufacturer (platform)	**Abbott (Architect)**	**DiaSorin (Liaison®)**	**Siemens (Atellica®)**	**Bio-Rad**	**Wantai**		**bioMérieux (Vidas®)**		**Euroimmun**
Assay name	SARS-CoV-2 IgG	SARS-CoV-2 S1/S2 IgG	SARS-CoV-2 Total	Platelia SARS-CoV-2 Total Ab	SARS-CoV-2 Total Ab	SARS-CoV-2 IgM	SARS-CoV-2 IgG	SARS-CoV-2 IgM	SARS-CoV-2 IgA
Assay type	CMIA	CLIA	CLIA	ELISA	ELISA	ELISA	ELFA	ELFA	ELISA
Antigen	N	S1+S2	RBD	N	RBD	RBD	RBD	RBD	S1
Overall, Negative and Positive Percent Agreement with VNT									
OPA [95%CI]	88.9 [84.3-92.3]	89.5 [85.0-92.7]	91.2 [87.0-94.2]	89.4 [84.9-92.7]	87.7 [82.9-91.2]	81.2 [75.8-85.6]	90.1 [85.7-93.3]	62.2 [56.0-68.1]	88.3 [83.7-91.8]
NPA [95%CI]	74.2 [59.7-84.8]	96.8 [86.8-99.3]	80.7 [66.7-89.7]	61.3 [46.6-74.2]	33.3 [21.1-48.3]	56.7 [41.9-70.4]	90.3 [78.1-96.1]	83.9 [70.4-91.9]	67.7 [53.0-79.6]
PPA [95%CI]	92.1 [87.6-95.1]	87.9 [82.6-91.7]	93.6 [89.3-96.2]	95.7 [91.9-97.8]	99.3 [96.9-99.9]	86.4 [81.0-90.5]	90.1 [85.1-93.5]	57.4 [50.5-64.1]	92.9 [88.4-95.7]
OPA [95%CI] <14dps	85.4 [75.2-91.9]	68.8 [57.0-78.5]	83.3 [72.8-90.4]	85.4 [75.2-91.9]	75.0 [63.6-83.8]	81.3 [70.4-88.8]	69.4 [57.8-79.0]	75.5 [64.3-84.1]	81.3 [70.4-88.8]
OPA [95%CI] >14dps	90.0 [84.6-93.7]	97.5 [93.9-99.0]	94.2 [89.6-96.8]	91.6 [86.4-94.9]	92.4 [87.4-95.6]	83.2 [76.8-88.1]	98.3 [95.1-99.5]	58.3 [50.8-65.5]	90.8 [85.6-94.3]
Concordance with VNT - Cohen's Kappa coefficient [95%CI]									
Overall (n=170)	0.64 [0.49-0.79]	0.70 [0.56-0.83]	0.72 [0.55-0.85]	0.62 [0.44-0.76]	0.43 [0.23-0.63]	0.40 [0.21-0.58]	0.71 [0.57-0.84]	0.24 [0.14-0.36]	0.61 [0.43-0.76]
<14 dps	0.70 [0.45-0.88]	0.41 [0.19-0.60]	0.68 [0.45-0.84]	0.69 [0.45-0.86]	0.46 [0.21-0.67]	0.61 [0.35-0.79]	0.41 [0.29-0.76]	0.52 [0.27-0.72]	0.60 [0.35-0.79]
>14 dps	0.40 [-0.06-0.72]	0.86 [0.65-1]	0.51 [0-0.89]	0.45 [-0.05-0.79]	NA	0.08 [-0.09-0.35]	0.90 [0.71-1.00]	0.18 [0.02-0.25]	0.55 [0.06-0.81]
Correlation between Ab level and neutralizing Ab titer									
Spearman coefficient [95%CI]	0.47 [0.33-0.60]	0.53 [0.39-0.65]	NA	NA	0.56 [0.43-0.66]	0.54 [0.40-0.65]	0.61 [0.49-0.71]	0.50 [0.32-0.65]	0.43 [0.27-0.56]
Receiver operating characteristic (ROC) curves for serological assays at two neutralizing Ab titer - AUC [95%CI]									
$PRNT_{50} \geq 20$	0.94 [0.89-0.98]	0.96 [0.94-0.99]	0.96 [0.94-0.99]	0.85 [0.77-0.94]	0.93 [0.88-0.98]	0.80 [0.71-0.88]	0.97 [0.94-0.99]	0.80 [0.72-0.88]	0.91 [0.85-0.97]
$PRNT_{50} \geq 80$	0.65 [0.57-0.73]	0.74 [0.66-0.81]	0.73 [0.66-0.81]	0.65 [0.58-0.72]	0.75 [0.68-0.82]	0.68 [0.60-0.76]	0.75 [0.68-0.82]	0.67 [0.58-0.75]	0.64 [0.55-0.72]

Table 3. Association of SARS-CoV-2 commercial serological and a virus neutralization test. Ab, antibodies; Ig, immunoglobulin; ELISA, enzyme-linked immunosorbent assay; CMIA, chemiluminescence microparticule immune assay; CLIA, chemiluminescence immune assay; ELFA, enzyme-linked fluorescent assay; n, number of samples; CI, confidence interval; dps, days post onset of symptoms, test; VNT, virus neutralization test; OPA, overall percent agreement; NPA, negative percent agreement, PPA positive percent agreement.

Figure Legends

Fig. 1. Kinetics of neutralizing antibody titers in patients with mild and severe COVID-19 according to the post-symptom interval. Green points represent mild COVID-19 patients, red points represent severe COVID-19 patients admitted to ICU, and blue points represent patients without neutralizing antibodies throughout follow-up. Dotted lines correspond to the limit of quantification of neutralizing antibodies. Fit Loess curve represents local polynomial regression performed using the Loess method. CI at 95% is indicated (grey area).

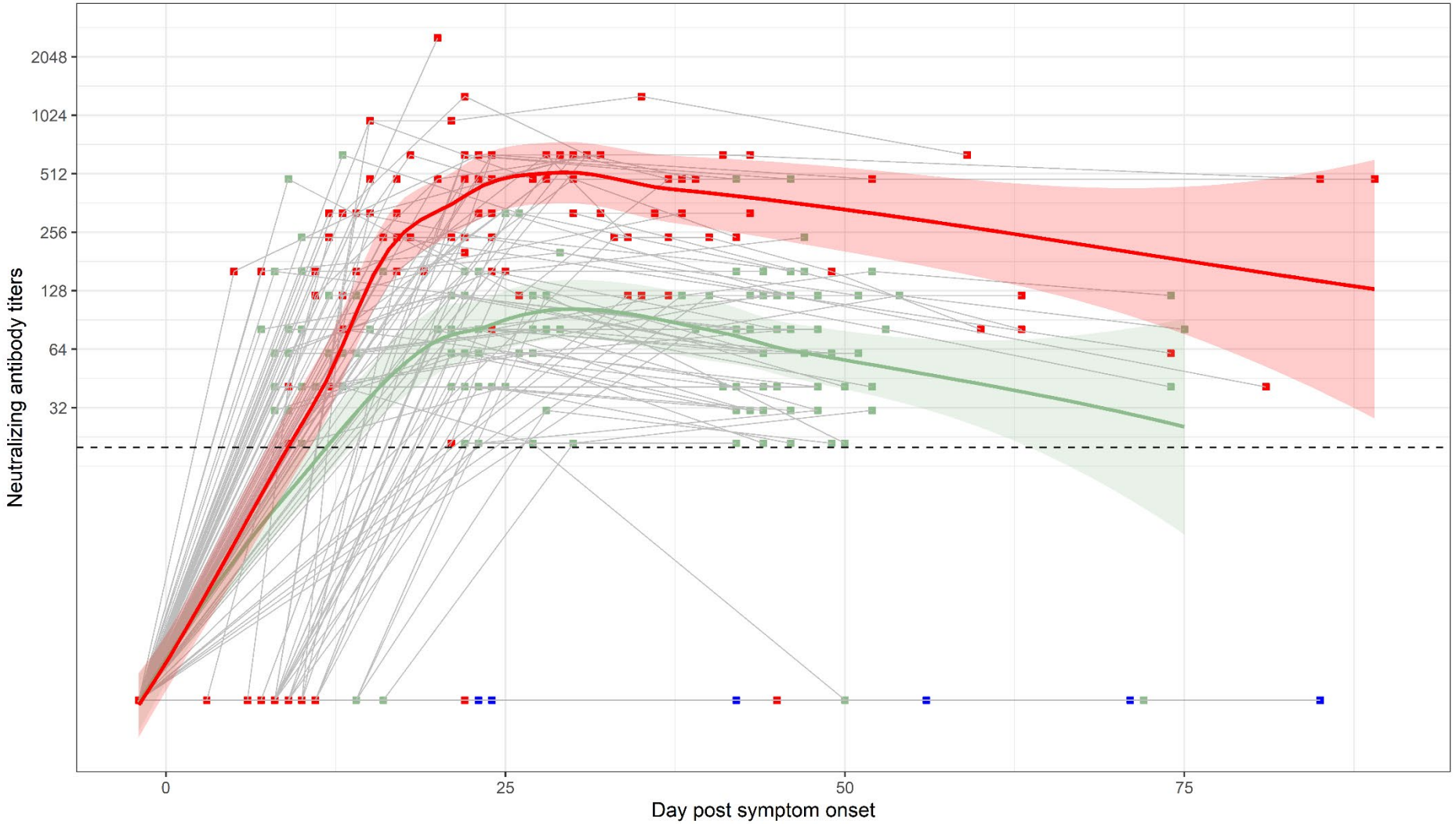
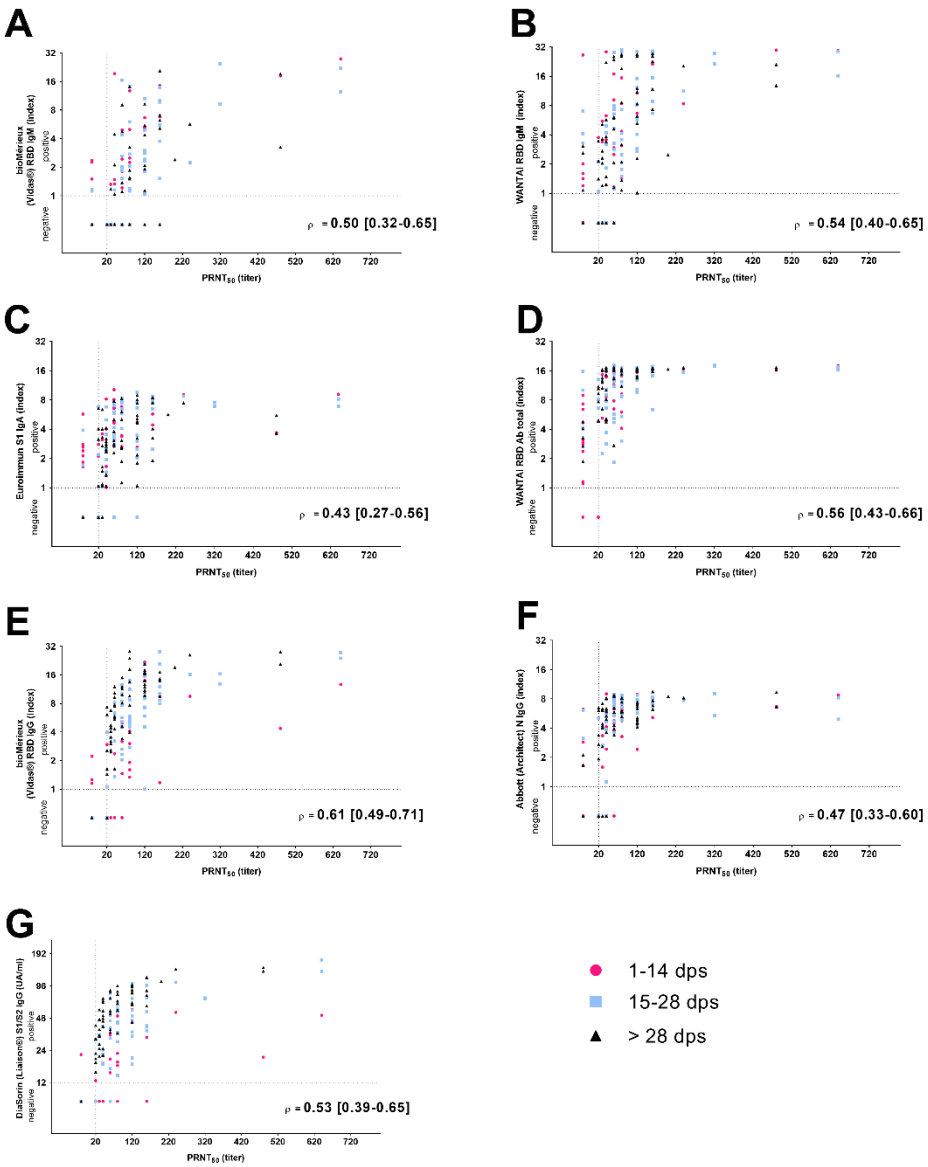

2048
1024
512
256
128
64
32
Neutralizing antibody titers
0
25
50
75
Day post symptom onset

Fig. 2. Correlation between SARS-CoV-2 neutralizing antibody titers and antibodies level determined by SARS-CoV-2 commercial serological assays. Magenta dots indicate sample collected ≤14 days post onset of symptoms (dps), blue dots indicate samples collected from 14-28 dps, black dots indicate specimen collected more than 28 dps. Spearman correlation coefficients and 95% confidence interval are indicated. For all correlations the p-values of the Spearman test were < 0.001.


A
bioMérieux (Vidas®) RBD IgM (index)
negative
positive
ρ = 0.50 [0.32-0.65]
PRNT50 (titer)
B
WANTAI RBD IgM (index)
negative
positive
ρ = 0.54 [0.40-0.65]
PRNT50 (titer)
C
Euroimmun S1 IgA (index)
negative
positive
ρ = 0.43 [0.27-0.56]
PRNT50 (titer)
D
WANTAI RBD Ab total (index)
negative
positive
ρ = 0.56 [0.43-0.66]
PRNT50 (titer)
E
bioMérieux (Vidas®) RBD IgG (index)
negative
positive
ρ = 0.61 [0.49-0.71]
PRNT50 (titer)
F
Abbott (Architect) N IgG (index)
negative
positive
ρ = 0.47 [0.33-0.60]
PRNT50 (titer)
G
DiaSorin (Liaison®) S1/S2 IgG (UA/ml)
negative
positive
ρ = 0.53 [0.39-0.65]
PRNT50 (titer)
1-14 dps
15-28 dps
> 28 dps