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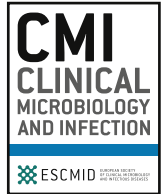
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Letter to the Editor

Six-month antibody response to SARS-CoV-2 in healthcare workers assessed by virus neutralization and commercial assays

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To the Editor,

Since the SARS-CoV-2 emergence in December 2019, one of the major concerns has been the duration of immune protection after a first episode. This question is of paramount importance for healthcare workers (HCWs), who are a highly exposed population and among the first targets of vaccination programmes. To date, the

persistence of SARS-CoV-2 antibodies in HCWs 6 months after disease onset (ADO) has not been studied with both a virus neutralisation test and commercial assays.

HCWs who experienced COVID-19 during the early phase of the pandemic were included in a prospective study conducted at the University Hospital of Lyon, France [1]. Serum samples collected 6 months ADO were tested using three commercial assays: the Wantai Ab assay, which detects total antibodies against the receptor binding domain (RBD) of the S protein, the bioMérieux Vidas assay, which detects IgG to the RBD, and the Abbott Architect assay, which detects IgG to the N protein. The neutralizing antibody (NAb) titre was determined by a virus neutralization assay (VNA) using live virus as previously described [2].

A total of 296 HCWs were included; the median (interquartile range, IQR) age was 41 (32–51) years and 17.2% (51/296) were male. The median duration between symptom onset and inclusion was 186 (180–196) days. Of note, 8/296 HCWs (2.7%) were asymptomatic and the onset of disease was established on the basis of the median date of the RT-PCR positive result of the ward cluster. All participants were tested positive for SARS-CoV-2 serology at least 2 weeks ADO. The SARS-CoV-2 infection was also documented by RT-PCR test in 170 patients.

The positivity rate at 6 months ADO was 100% with the Wantai assay, 84.8% with the Vidas assay and 55.4% with the Architect assay. Only 51% of HCWs were positive for the presence of NABs. Positive NAB titres ranged from 20 to 240. Only 27/296 (9.1%) had a

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NAb ≥ 80 (Fig. 1A, please see supplementary information for raw data). No difference in positivity rates with any assay was observed between patients with a SARS-CoV-2 infection documented by RT-PCR and the rest of the cohort.

Of the 296 HCWs, six (2.0%) developed a clinical form requiring hospitalization; all were positive with the three serological assays and for the presence of NAb with a median titre of 40 (range 30–160). By contrast, in asymptomatic HCWs, 8/8, 5/8 and 4/8 were

positive with Wantai, Vidas and Architect assays, respectively, and only 3/8 exhibited NAbs with low titres (range 30–60).

The area under the ROC curve (AUC) was estimated for assessing the performance of serological assays for two NAb titres (PRNT₅₀ ≥ 20 or PRNT₅₀ ≥ 80 ; (Fig. 1C, E, G). The highest AUCs were found with the Vidas assay: 0.85 (95% CI 0.81–0.89) and 0.95 (0.92–0.97), respectively. The Wantai and Abbott assays had AUCs of, respectively, 0.73 (0.68–0.79) and 0.70 (0.64–0.76) for

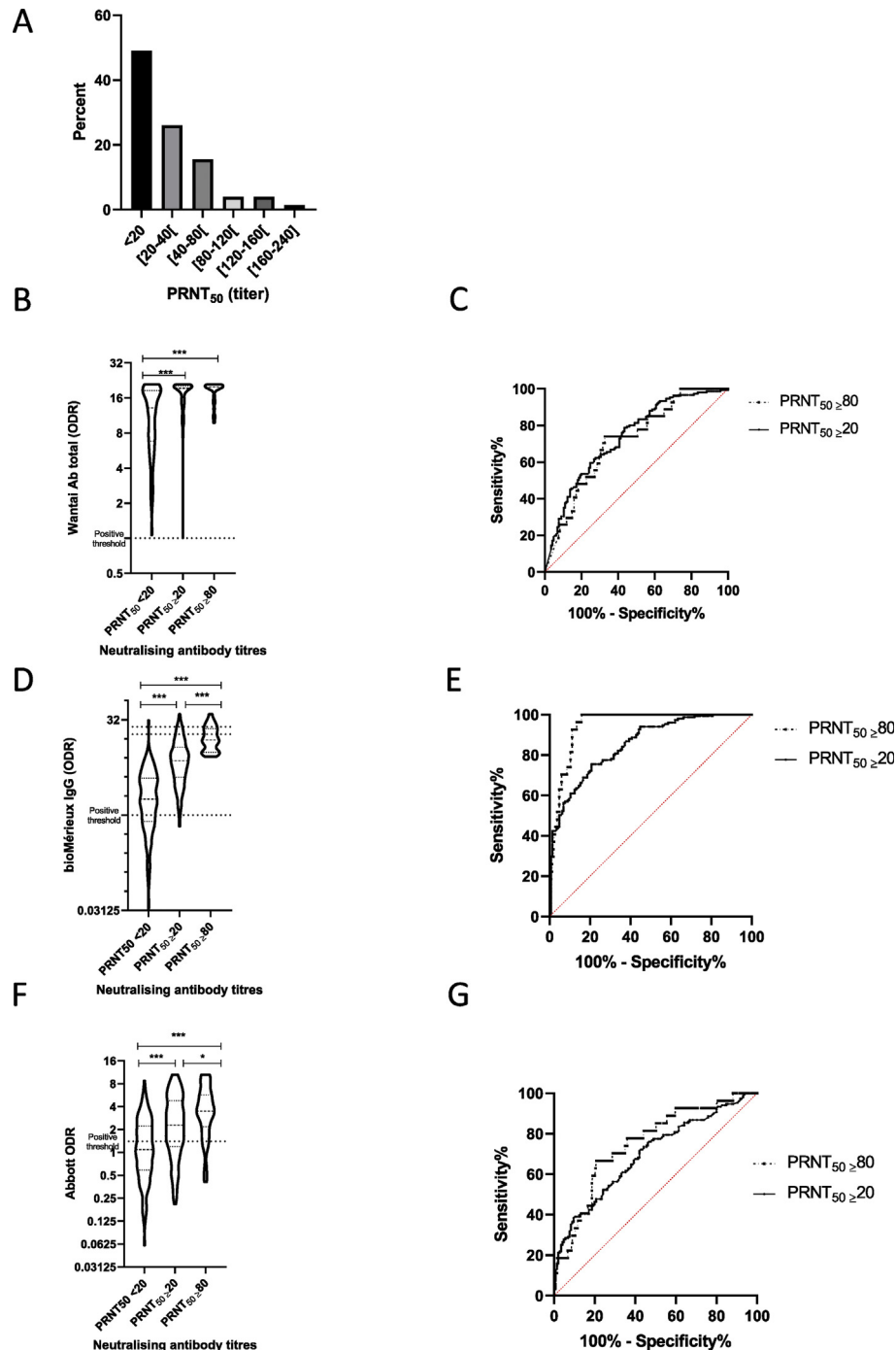


Fig. 1. (A) Distribution of neutralisation antibody titres in convalescent subjects ($n = 296$) 6 months after SARS-CoV-2 infection. (B, D, F) Violin plots describing ODR according to neutralising antibody titres. Dotted lines described positive threshold recommended by each manufacturer. Comparisons was performed using the Kruskal Wallis test followed by Dunn's test. *** $p < 0.001$, * $p < 0.05$. (C, E, G) ROC curves were built to estimate the performance of Wantai (C), bioMérieux (E) and Abbott (G) assays for detecting the presence of neutralising antibodies (PRNT₅₀ ≥ 20 , continuous line) and high neutralizing antibody titre (PRNT₅₀ ≥ 80 , dotted line). ODR, optical density ratio; PRNT, plaque reduction neutralization titres.

PRNT₅₀ \geq 20, and 0.71 (0.62–0.81), 0.75 (0.66–0.85) for PRNT₅₀ \geq 80. These results suggest that an optimized ratio with some commercial serological assay could be found to maximize the positive predictive value enabling to select individuals with a NAb titres \geq 80. For instance, with the Vidas assay, the median (IQR) ratio for samples with PRNT₅₀ \geq 80 was 15.4 (9.7–22.7) vs. 5.9 (3.3–9.2) for samples with a titre between 20 and 80 and 1.8 (0.8–3.8) for samples without NAb (Fig. 1F). Among the 27 samples with NAb titre \geq 80, all had a Vidas ratio above 8 compared with 31.5% and 3.5% of the samples with a titre between 20 and 80 or without NAb, respectively.

The findings of the present study indicate that, 6 months after infection, NABs were no longer detected in about half of HCWs who presented mainly mild COVID-19. Overall, the detection of SARS-CoV-2 Abs with commercial tests was higher despite important heterogeneity between the assays evaluated herein. In a previous study [3], about 40% of asymptomatic subjects became negative for IgG to the N protein within 3–6 months, which is consistent with that presented herein for the Architect assay. This suggests that assays detecting only antibodies against the N protein must not be used in long-term seroprevalence surveys. By contrast, the Wantai assay could be very useful for epidemiological purposes as 100% of the HCWs were still positive at 6 months ADO. Although VNA should remain the reference standard to assess the protective antibody response, the data presented herein suggest that some commercial assays could be useful for first-line screening of long-term presence of NABs as previously reported within 4 months ADO [2,4].

Despite these observations of the decrease in NABs in patients with mild COVID-19, it is important to note that they do not preclude the protective role of an anamnestic antibody response in previously exposed subjects, nor that of the long-term cellular immunity [5].

Transparency declaration

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Ethics

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](https://clinicaltrials.gov) (NCT04341142).

COVID-SER study group

Adnot Jérôme, Alfaiate Dulce, Bal Antonin, Bergeret Alain, Boibieux André, Bonnet Florent, Bourgeois Gaëlle, Brunel-Dalmas Florence, Caire Eurydice, Charbotel Barbara, Chiarello Pierre, Cotte Laurent, d'Aubarede Constance, Durupt François, Escuret Vanessa, Fascia Pascal, Fassier Jean-Baptiste, Fontaine Juliette, Gaillot-Durand Lucie, Gaynard Alexandre, Gillet Myriam, Godinot Matthieu, Gueyffier François, Guibert Nicolas, Josset Laurence, Lahousse Matthieu, Lina Bruno, Lozano Hélène, Makhoulfi Djamilia, Massardier-Pilonchéry Amélie, Milon Marie-Paule, Moll Frédéric, Morfin Florence, Narbey David, Nazare Julie-Anne, Oria Fatima, Paul Adèle, Perry Marielle, Pitiot Virginie, Prudent Mélanie, Rabilloud Muriel, Samperiz Audrey, Schlienger Isabelle, Simon Chantal, Trabaud Mary-Anne, Trouillet-Assant Sophie, Valette Martine.

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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.2021.01.003>.

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