Dynamics of Neutralizing Antibody Responses Following Natural SARS-CoV-2 Infection and Correlation with Commercial Serologic Tests. A reappraisal and Indirect Comparison With Vaccinated Subjects

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Dynamics of Neutralizing Antibody Responses Following Natural SARS-CoV-2 Infection and Correlation with Commercial Serologic Tests.
A reappraisal and Indirect Comparison With Vaccinated Subjects

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INTRODUCTION

Following COVID-19 infection or vaccination, numerous antibodies are produced targeting different epitopes of the virus or the spike protein. Nevertheless, not all these antibodies are able to efficiently neutralize the virus since they can bind an epitope which is not essential for the virus entry into the cell. Therefore, the detection of neutralizing antibodies (NAbs) is of particular importance because these are the antibodies that can prevent the binding of the RBD of the S protein to the angiotensin-converting enzyme 2 (ACE2) receptor present at the surface of human cells, preventing the entry of the virus into the host cells.

METHOD

Study Population:

- 62 RT-PCR confirmed COVID-19 patients for 114 samples from day 1 to day 296 after symptoms onset.

In this cohort, we assessed:

- Six commercial binding assays:
  - **Roche nucleocapsid** (NCP) total antibody assay
  - **Roche RBD total antibody** assay
  - **DiaSorin S1/S2 IgG** assay
  - **Ortho S1 IgG** assay
  - **Ortho S1 total antibody** assay
  - **Phadia S1 IgG** assay
- Two neutralizing techniques:
  - **Surrogate virus neutralization test** (sVNT)
  - **Pseudo virus neutralization test** (pVNT)

RESULTS

Figure 1

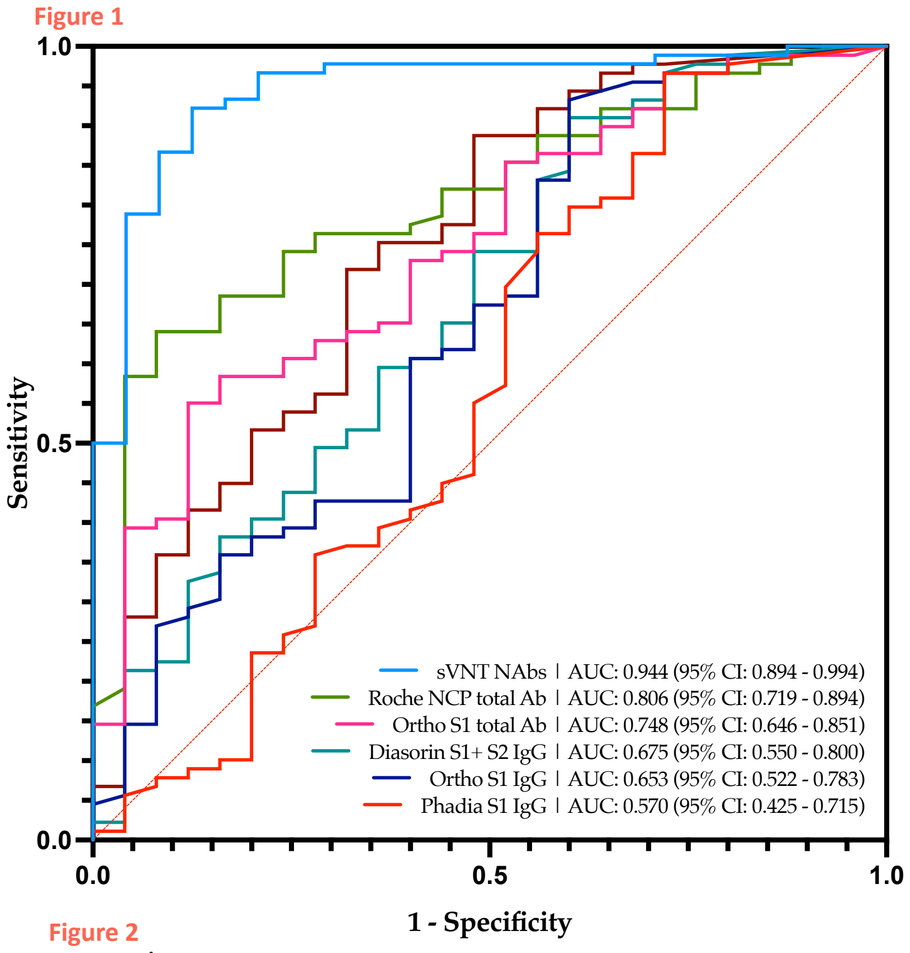
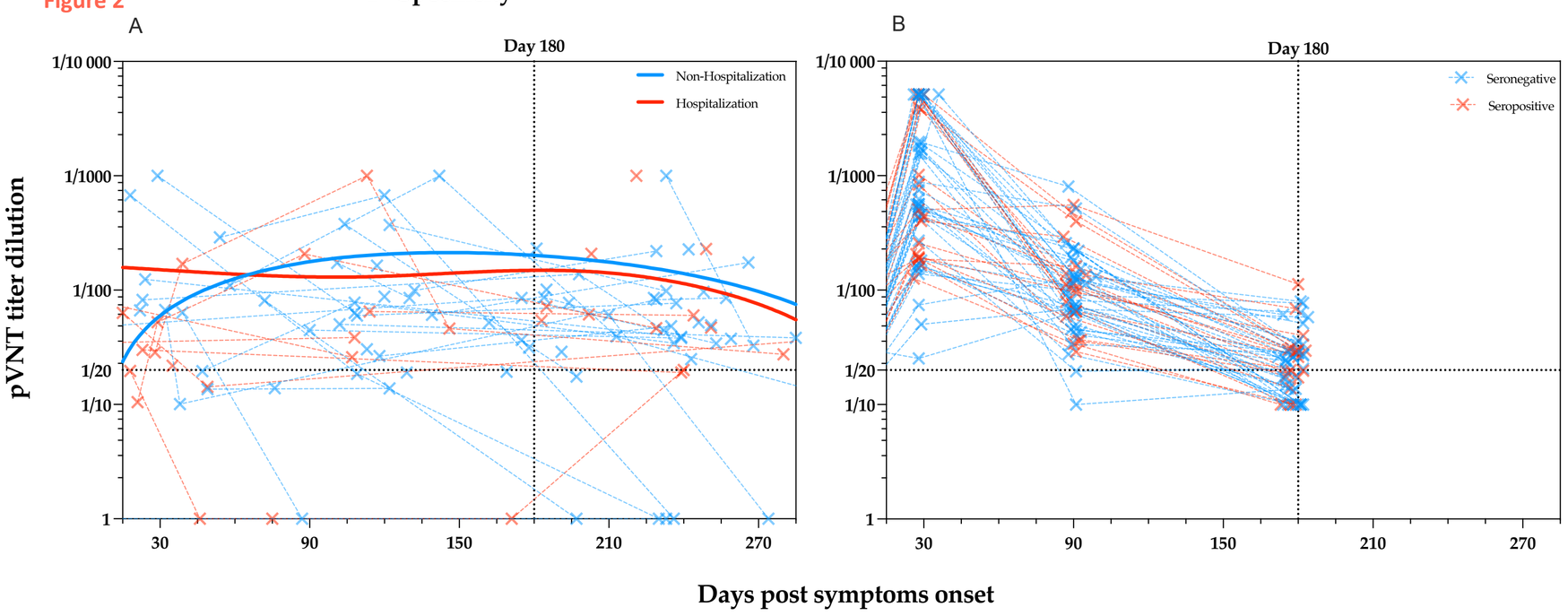


Table 1

Serological assay	Roche RBD total antibody assay	Roche NCP total antibody assay	DiaSorin S1/S2 IgG assay	Ortho S1 IgG assay	Ortho S1 total antibody assay	Phadia S1 IgG assay	sVNT
Cut-off definition	Manufacturer: 0.8 U/mL	Manufacturer: 1.0 COI	Manufacturer: 15.0 U/mL	Manufacturer: 1.0 S/V	Manufacturer: 1.0 S/V	Manufacturer: 0.7 U/mL	Manufacturer: 10.0 U/mL
	Adapted: 5.9 U/mL	*Adapted: 37.7 COI*	*Adapted: 11.4 U/mL*	*Adapted: 0.3 S/V*	*Adapted: 165.0 S/V*	*Adapted: 2.5 U/mL*	*Adapted: 16.6 U/mL*
Sensitivity (95% CI)	97.8% (92.2%-99.7%)	97.8% (92.2%-99.7%)	87.6% (79.0% - 93.7%)	90.0% (81.9-95.3%)	98.9% (94.0%-100.0%)	97.1% (92.1% - 99.7%)	97.8% (92.3% - 99.7%)
	88.8% (80.3% - 94.5%)	*61.8% (50.9% - 71.9%)*	*91.0% (83.1% - 96.0%)*	*93.3% (85.9% - 97.5%)*	*53.9% (43.0% - 64.6%)*	*96.6% (90.5% - 99.3%)*	*97.7% (92.1% - 99.7%)*
Specificity (95% CI)	33.3% (15.6-55.3%)	12.5% (2.7%-32.4%)	44.0% (24.4% - 65.1%)	41.7% (22.1%-63.4%)	16.7% (4.7%-37.4%)	16.0% (4.5% - 36.1%)	65.2% (42.7% - 83.6%)
	52.0% (31.3% - 72.2%)	*84.0% (63.9% - 95.5%)*	*40.0% (21.1% - 61.3%)*	*40.0% (21.1% - 61.3%)*	*84.0% (63.9% - 95.5%)*	*28.0% (12.1% - 49.4%)*	*92.0% (74.0% - 99.0%)*

Using the cut-off provided by the manufacturers, the sensitivity did not statistically differ between the different serological assays investigated in this study (**Table 1, Figure 1**). The specificity was below 50.0% for all assays meaning that these assays generate many false positive results for the detection of NAbs. In general, serological assays targeting **total antibodies** generate **less false negative results**. This means that also **measuring both IgA and IgM permit to better evaluate the neutralizing capacity of the serum than just targeting IgG.** The sVNT test showed **the best correlation** with the pVNT technique.

Figure 2



Concerning COVID-19 patients, from day 14 to day 291, more than **75% of the samples were positive for NAbs** (n=87/110, 79.1%). Six months post symptoms onset, the majority of the samples (n=44/52, 84.6%) were still positive for NAbs. (Figure 2 A)

This is in sharp contrast with the results we obtained 6 months post-vaccination in our cohort of healthcare workers which have received the two dose regimens of BNT162b2. In this cohort **43% (n=25/58) of the participants no longer exhibit NAbs activity 180 days after the administration of the first dose of BNT162b2.**

Those who were seropositive at baseline seemed to lose their neutralizing capacity (n=7/18, 39%). (Figure 2 B)

CONCLUSION

The correlation between the pVNT results and the sVNT results is better than the other tests but the data remains very heterogeneous. Results obtained with the infected and the vaccinated cohort suggest that there is a relationship between the development of NAbs and the time of exposure to the virus. Patients with prolonged exposure to SARS-CoV-2 had a higher NAbs titer than patients who cleared the virus earlier. **These results deserve further investigations to better understand the difference in the dynamic of antibody production after COVID-19 disease and vaccination.**

CONTACT INFORMATION

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