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ORIGINAL ARTICLE

Humoral immune response after COVID-19 infection or BNT162b2 vaccine among older adults: evolution over time and protective thresholds

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Abstract The objectives of this study were to assess thedynamics of the SARS-CoV-2 anti-RBD-IgG response over time among older people after-COVID-19 infection or vaccination and its comparison with indicative levels of protection.Geriatric patients with SARS-CoV-2 serological test results were included anddivided into three groups. A vaccine group (n= 34), a group of natural COVID-19 infection (n = 32), and a group who contracted-COVID-19 less than 15 days after the first injection (n = 17). Eighty-three patients wereincluded; the median age with IQR was 87 (81–91) years. In the-vaccine group at 1 month since the first vaccination, the median titer of anti-RBD-IgGwas 620 (217–1874) BAU/ml with 87% of patients above the theoretical protective thresholdof 141 BAU/ml according to Dimeglio et al. (J Infec. 84(2):248–88, [7]). Seven months after the firstvaccination, this titer decreased to 30 (19–58) BAU/ml with9.5% of patients > 141 BAU/ml. In the natural COVID-19 infection group, at 1 monthsince the date of first symptom onset, the median titer was 798 (325–1320) BAU/ml with86.7% of patients > 141 BAU/ml and fell to 88 (37–385) with 42.9% of patients > 141BAU/ml at 2 months. The natural infection group was vaccinated 3 months after the infection.Five months after the vaccination cycle, the median titer was 2048 (471–4386) BAU/ml with83.3% of patients > 141 BAU/ml. This supports the clinical results describing the-decrease in vaccine protection over time and suggests

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that vaccination after infection canmaintain significantly higher antibody titer levels for a prolonged period of time.

Keywords SARS-CoV-2 · Serology · Anti-RBD IgG · Dynamics · Kinetics

Introduction

A better description of the kinetics of the anti-SARS-CoV-2 humoral response over time and its correlation with potential protection against COVID-19 among older people is necessary. Older people are often excluded from COVID-19 clinical studies even though they are the most likely to experience significant clinical harms from SARS-CoV-2. In a setting of immunosenescence, they may have lower levels of antibodies produced than those observed in young subjects [1, 2] including many vaccine responses that can be diminished and present more rapid waning of antibodies [3].

SARS-CoV-2 anti-RBD (receptor-binding domain of the spike protein) IgG are correlated with neutralizing antibodies [4–6] and are thought to be correlated with protection against COVID-19 [5, 7, 8].

The objectives of this study were to assess the dynamics of the SARS-CoV-2 anti-RBD IgG response over time among older people after COVID-19 infection and/or vaccination and its comparison with indicative levels of protection assumed by current data [5, 7].

Methods

We performed a monocentric, observational cohort study. The study was approved by the institutional ethics board of the University Hospital of Strasbourg. Consent was collected for all patients.

From November 2020 to October 2021, we included all geriatric hospital patients with available SARS-CoV-2 serological test results and a history of COVID-19 confirmed by RT-PCR or COVID vaccination. Exclusion criteria were the opposition to the use of the data for research purposes.

The following data was collected: demographic details (age, sex), clinical details (Charlson Comorbidity Index), a history of COVID-19 confirmed by RT-PCR, date of first symptom onset, COVID-19 vaccination, date of vaccinations, and SARS-CoV-2 serology test results.

Serum samples were tested using the Architect SARS-CoV-2 IgG II Quant assay (Abott), detecting IgG antibodies directed against the spike RBD of SARS-CoV-2. The results are expressed in binding antibody units/ml (BAU/ml), allowing interlaboratory comparison, as recommended by the WHO [9]. The sensitivity and specificity are 98.3% and 99.5% respectively [10].

Based on data from previous studies, we considered three indicative antibody titer thresholds thought at the time to be high enough to protect against SARS-CoV-2 infection: 141 BAU/ml for protection/vaccine efficacy > 89.3% as suggested in the study by Dimeglio et al. [7] and 165 BAU/ml and 506 BAU/ml, respectively, for a protection/vaccine efficacy of 70% and 80% according to Feng et al. [5]. They are only given as an indication, as a benchmark, to add a qualitative character to the antibody titer.

Three groups are presented. A vaccine group ($n=34$) that received two BNT162b2/Comirnaty injections 21 days apart, a group of natural COVID-19 infection ($n=32$), and a third group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection ($n=17$).

The comparison of the quantitative variables uses the Student's test or the Mann–Whitney-Wilcoxon test. The comparison of qualitative variables uses the $\chi 2$ test or the Fisher's exact test.

Results

Eighty-three patients were included, including 59 women (71%). The median age and Charlson Comorbidity Index with interquartile range (IQR) were 87 (81–91) years and 7 (5–8.5). The median age for women was 88 (82–92) and for men 85 (77–90) ($p=0.06$). The median Charlson Comorbidity Index for women was 7 (5–8) and for men 7 (5–9) ($p=0.95$). Age, sex, and comorbidities were overall balanced between the three groups (Table 1).

Table 1 Age, sex, and Charlson Comorbidity Index

	Vaccine group = 2 BNT162b2/Comirnaty injections 21 days apart	Natural COVID group	Group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection	Total	
Number of participants	34	32	17	83	
Age—year					
Median	87	87.5	87	87	$p = 0.74$ Kruskal–Wallis test
Interquartile range	80.5–88.5	82.75–91	79–92	81–91	
Sex—number (%)					
Women	24 (70.6%)	24 (75.0%)	11 (64.7%)	59 (71.1%)	$p = 0.75$ Chi-squared test
Men	10 (29.4%)	8 (25.0%)	6 (35.3%)	24 (28.9%)	
Charlson Comorbidity Index					
Median	7	7	7	7	p = 0.62 Kruskal–Wallis test
Interquartile range	5–9	5–8	7–8	5–8.5	

Serological assessment and antibody titers

The results in the different groups as a function of time are shown in Fig. 1 and Table 2.

In the vaccine group at 1 month since the first vaccination, 38 (33.5–40.5) days since first vaccination, all the patients had already received their second vaccine on day 21 since first vaccination; the median titer of anti-spike RBD IgG with IQR was 620 (217–1874) BAU/ml with 87% of patients above the threshold of 141 BAU/ml. At 2 months since the first vaccination, the median titer of anti-RBD IgG was 526 (182–945) BAU/ml with 75% of patients above the threshold of 141 BAU/ml. Seven months after the first vaccination the median titer of anti-RBD IgG was 30 (19–58) BAU/ml with 9.5% of patients above the threshold of 141 BAU/ml.

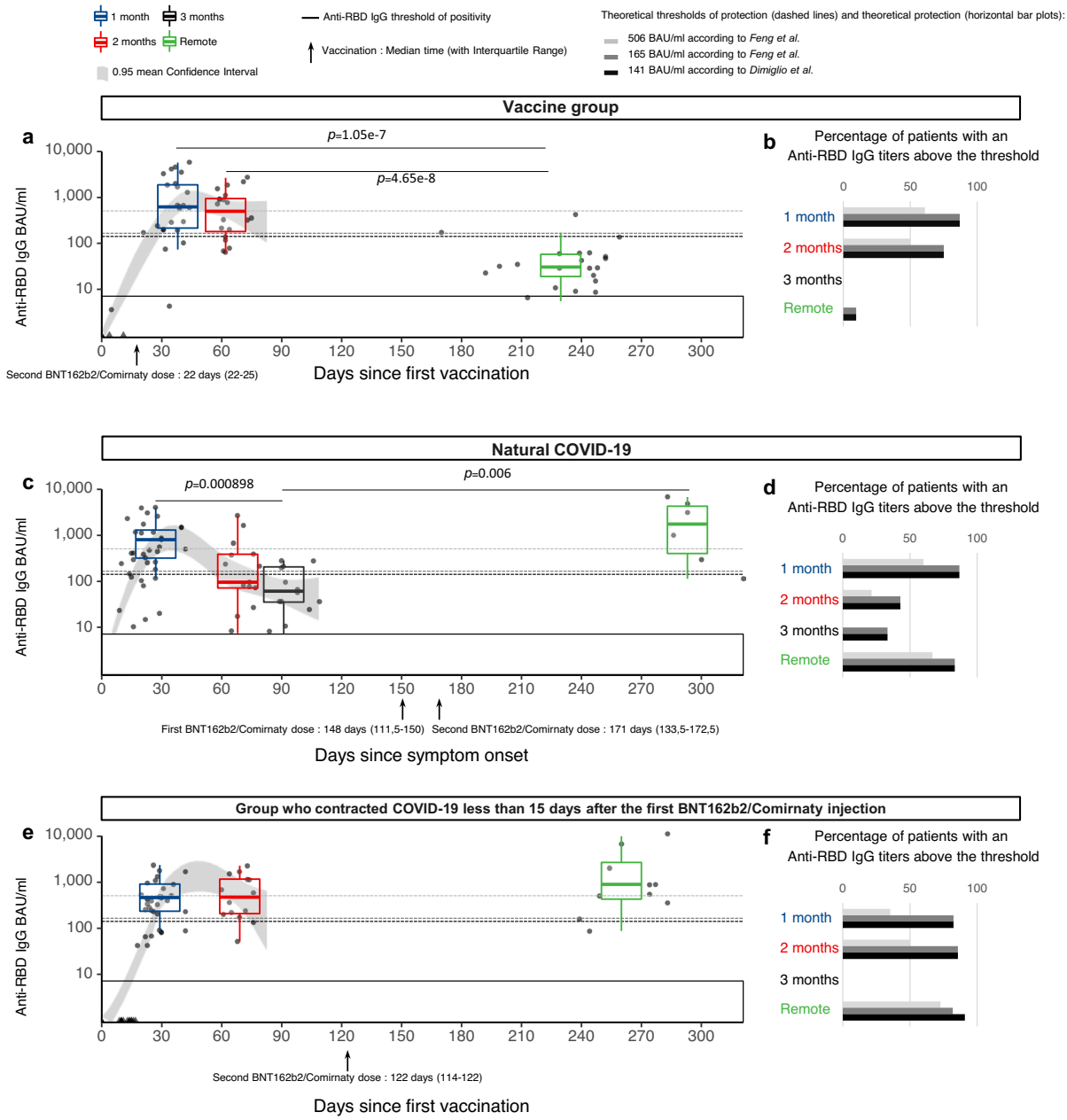
In the natural COVID-19 infection group, at 1 month since the date of first symptom onset, the median titer of anti-RBD IgG was 798 (325–1320) BAU/ml with 86.7% of patients above the threshold of 141 BAU/ml and fell to 88 (37–385) with 42.9% of patients above the threshold of 141 BAU/ml at 2 months. At 3 months, the median titer of anti-RBD IgG was 56 (29–203) BAU/ml with 33.3% of patients above the threshold of 141 BAU/ml. The natural infection group was vaccinated 3 months after the infection. Six months after the first vaccination, that is to say, 5 months after the second vaccination, the median titer of anti-RBD IgG was then 2048 (471–4386) BAU/ml with 83.3% of patients above the threshold of 141 BAU/ml.

In the group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection, at 1 month from the first injection, the median titer of anti-RBD IgG was 463 (234–914) BAU/ml with 82.4% of patients above the threshold of 141 BAU/ml. At 2 months, the median titer of anti-RBD IgG was 484 (208–1167) BAU/ml with 85.7% of patients above the threshold of 141 BAU/ml.

They received their second dose at 3 months, and 4.5 months after the second dose the median titer of anti-RBD IgG was 898 (437–2824) BAU/ml with 90.9% of patients above the threshold of 141 BAU/ml.

Anti-RBD IgG titers according to age, sex, and comorbidities

In Table 3, anti-RBD IgG titers are given according to age, sex, and comorbidities. Due to the small numbers in subgroups, these data should



only be considered as descriptive and not supporting inferential statistical approaches.

Considering all three groups together at 1 and 2 months, age ($p = 0.04$ and 0.03) and a Charlson Comorbidity Index (CCI) score ≥ 7 ($p = 0.02$ and 0.03) were associated with a lower antibody titer.

Case fatality rate at 1 month

In the group with natural COVID-19 patients, we had a case fatality rate at 1 month of 10% among 40 COVID-19 patients (four patients had died within a month and four patients were not included because their serologies were not available).

◂**Fig. 1** Kinetics of anti-SARS-CoV-2 RBD IgG and theoretical protection against COVID-19 among older adults. Panel **a**: Evolution of humoral response (anti-RBD IgG BAU/ml) over time in the vaccine group. Panel **c**: Evolution of humoral response (anti-RBD IgG BAU/ml) over time in the natural COVID-19 infection group. Panel **e**: Evolution of humoral response (anti-RBD IgG BAU/ml) over time in the group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection. Time axis reflects days since symptom onset (natural COVID) or after BNT162b2 vaccine first injection (vaccine group and group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection). Arrows under the x axis represent the BNT162b2/Comirnaty injections with its time in days (and its interquartile range) since symptom onset for natural COVID-19 or since first vaccination for the vaccine group and the group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection. Boxplots display anti-RBD IgG BAU/ml distribution at 1, 2, and 3 months or during the post-period (first quartile, median, third quartile, and whiskers represent 1.5 times the interquartile range from the first and third quartiles). The confidence interval of the mean (0.95 level) was estimated for each group using the LOESS method to describe the dynamics of the humoral response during the first months. Significant differences between periods were estimated within each group using pairwise non-parametric Kruskal–Wallis tests. Only significant Holm-adjusted p values ($p < 0.05$) are indicated. Horizontal dashed lines represent the theoretical threshold of protection against COVID-19 as suggested by Dimeglio et al. (141 BAU/ml for protection/vaccine efficacy > 89.3%) and by Feng et al. (165 BAU/ml and 506 BAU/ml for protection/vaccine efficacy of 70% and 80%). Panels **b**, **d**, and **f**: percentage of patients with theoretical protection against COVID-19 = percentage of patients with anti-RBD IgG titers above a protective threshold for each group: **b** vaccine group, **d** natural COVID-19, **f** group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection, periods and different theoretical thresholds as defined in panel **a**

In the group who contracted COVID-19 less than 15 days after the first vaccination, the case fatality rate was 5.7% at one month.

In the vaccine group, no patients died within 1 month of vaccination.

Discussion

Seven months after the first vaccination in COVID-naive patients, the RBD antibody titer decreases with a median of 30 BAU/ml and only 9.5% of patients above the theoretical protective threshold of 141 BAU/ml. A drop by a factor of 20 compared to the peak values. In COVID-19 patients, a median titer of 56 BAU/ml is observed at 3 months with 33.3% of patients above the threshold of 141 BAU/ml. However, COVID-19 patients vaccinated at a distance from their infections and patients who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection who then received their second vaccine 3 months after infection present 5 months post-completion of the vaccination schedule, antibody levels higher than peak levels observed at 1 month in those exposed to natural infection or standard vaccination alone.

On the humoral level, this supports the clinical results describing the decrease in vaccine protection over time [11] and suggests that vaccination after infection can maintain significantly higher antibody titer levels for a prolonged period of time.

In our geriatric cohort, we described lower anti-RBD IgG titers in patients with older age and higher Charlson Comorbidity Index score.

With three hospital clusters of COVID-19 patients from November 2020 to February 2021, we had a case fatality rate at 1 month of 10% among 40 COVID-19 patients. Note that this case fatality rate was 28.9% among the clusters that we faced in March 2020 [12]. All the COVID-19 confirmed cases enrolled in this study were diagnosed before the local active circulation of the variants of concern (VOC) alpha/beta/gamma/delta/omicron, which was confirmed by sequencing 20 COVID-19 patients from the study.

In the vaccine group, no patients died within 1 month of vaccination. In the group who contracted COVID-19 less than 15 days after the first vaccination, the case fatality rate was 5.7% at 1 month.

These preliminary data are reassuring on the tolerance of receiving a COVID-19 vaccine around an infection not yet documented at the time of the vaccine and starting within 15 days after the first dose.

Age and humoral response after COVID-19 or vaccination

Regarding the humoral immune response after COVID-19 vaccines

Concerning the initial response and its peak, a significant negative correlation between the age of vaccinated individuals and anti-RBD IgG response is now

Table 2 Antibody titers and theoretical protection against COVID-19 among older adults

	Serology at 1 month	Serology at 2 months	Serology at 3 months		Remote serology
Vaccine group = 2 BNT162b2/Comirnaty injections 21 days apart					
N = 34	*N* = 23	*N* = 20	*N* = 0		*N* = 21
Days since first vaccination	38 (33.5–40.5)	62 (60.75–64)			218 (199–224)
Anti-RBD IgG BAU/ml	**620 (217–1874)**	**526 (182–945)**			**30 (19–58)**
Theoretical protection = percentage of patients with anti-RBD IgG titers above the following threshold					
Cut-off anti-RBP total = 141 BAU/ml for protection against SARS-CoV 2 > 89.3% according to Dimeglio et al	**87.0**	**75.0**			**9.5**
Cut-off anti-RBD IgG = 165 BAU/ml for vaccine efficacy of 70% according to Feng et al	**87.0**	**75.0**			**9.5**
Cut-off anti-RBD IgG = 506 BAU/ml for vaccine efficacy of 80% according to Feng et al	**60.9**	**50.0**			**0**
Natural COVID group				2 BNT162b2/ Comirnaty injections 21 days apart	
N = 32	*N* = 15	*N* = 14	*N* = 15		*N* = 6
Days since first symptom onset (DSO)	27 (26.5–29)	68 (65–74)	91 (90–98)		293 (288–298)
Days since the second vaccination following COVID infection					144 (115–182)
Anti-RBD IgG BAU/ml	**798 (325–1320)**	**88 (37–385)**	**56 (29–203)**		**2048 (471–4386)**
Theoretical protection = percentage of patients with anti-RBD IgG titers above the threshold					
Cut-off anti-RBP total = 141 BAU/ml for protection against SARS-CoV 2 > 89.3% according to Dimeglio et al	**86.7**	**42.9**	**33.3**		**83.3**
Cut-off anti-RBD IgG = 165 BAU/ml for vaccine efficacy of 70% according to Feng et al	**86.7**	**42.9**	**33.3**		**83.3**
Cut-off anti-RBD IgG = 506 BAU/ml for vaccine efficacy of 80% according to Feng et al	**60**	**21.4**	**0**		**66.7**

Table 2 (continued)

	Serology at 1 month	Serology at 2 months	Serology at 3 months		Remote serology
Group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection				Second BNT162b2/ Comirnaty injection	
N = 17	*N* = 17	*N* = 14	*N* = 0		*N* = 11
Days since first vaccination	29 (28–30)	69 (64–73)			260 (251.5–275,5)
Days since the second vaccination					138 (131–160)
Anti-RBD IgG BAU/ml	**463 (234–914)**	**484 (208–1167)**			**898 (437–2824)**
Theoretical protection = percentage of patients with anti-RBD IgG titers above the threshold					
Cut-off anti-RBP total = 141 BAU/ml for protection against SARS-CoV 2 > 89.3% according to Dimeglio et al	**82.4**	**85.7**			**90.9**
Cut-off anti-RBD IgG = 165 BAU/ml for vaccine efficacy of 70% according to Feng et al	**82.4**	**85.7**			**81.8**
Cut-off anti-RBD IgG = 506 BAU/ml for vaccine efficacy of 80% according to Feng et al	**35.3**	**50**			**72.7**

The data are medians (with interquartile range) for the study of anti-RBD IgG titers and for the temporal expression of the parameter studied. The data are effectives for description of sample size. The data are percentages for the expression of theoretical protection of patients with antibody titer above the suggested threshold

described in a fairly consensual way [13–16]. This correlation could be particularly strong in the initial phase, namely before and just after the second dose. Thus, showing a slower and less intense response [13].

Concerning The Plateau/Waning phase, the age of vaccinated individuals continues to have a significant negative correlation with anti-RBD IgG response up to 6 months after the second dose [13, 17]. In addition to diminished post-vaccine responses, older individuals could present a more rapid waning of antibodies after the vaccinations [18].

Naaber et al. [13] and Collier et al. [19] described in a non-geriatric population that the decline of the anti-RBD IgG levels was present in all participants, and at 6 months, they were then only at 7% and 3.5% of their peak levels, detected at 1 week after the second dose.

These results were obtained among younger patients. Nevertheless, we note that they correspond to what we observed in our study among older adults with remote anti-RBD IgG levels at 30 BAU/ml (7 months after the first dose), i.e., 5% of the 620 BAU/ml peak at 1 month.

Table 3 Antibody titers according to age, sex, and comorbidities

	Serology at 1 month	Serology at 2 months	Serology at 3 months		Remote serology
Vaccine group = 2 BNT162b2/Comirnaty injections 21 days apart					
$N=34$	$N=23$	$N=20$	$N=0$		$N=21$
Anti-RBD IgG BAU/ml	620 (217–1874)	526 (182–945)			30 (19–58)
Age < 87, > 87, p	1152 (202–3069), 579 (282–657), $p=0.64$	812 (235–1580), 317 (155–832), $p=0.35$			51 (31–116), 28 (12–48), $p=0.11$
Age in year, Spearman's test p value	$p=0.44$	**$p=0.06$**			**$p=0.06$**
Sex: female, male, p	620 (197–1652), 1869 (251–3891), $p=0.61$	348 (136–874), 2137 (1168–2406), $p=0.18$			30 (16–48), 44 (23–116), $p=0.38$
Charlson Comorbidity Index < 7, ≥ 7, p	1652 (237–3445), 572 (218–1104), $p=0.31$	898 (553–1972), 314 (136–866), $p=0.07$			36 (28–88), 27 (10–50), $p=0.14$
Charlson Comorbidity Index, Spearman's test p value	$p=0.24$	**$p=0.05$**			$p=0.14$
Natural COVID group				2 BNT162b2/Comirnaty injections 21 days apart	
$N=32$	$N=15$	$N=14$	$N=15$		$N=6$
Anti-RBD IgG BAU/ml	798 (325–1320)	88 (37–385)	56 (29–203)		2048 (471–4386)
Age < 87, > 87, p	798 (387–1483), 708 (309–1146), $p=0.95$	236 (76–389), 26 (7–95), $p=0.19$	66 (36–210), 30 (11–155), $p=0.22$		**4814 (3958–5808), 296 (205–645), $p=0.02$**
Age in year, Spearman's test p value	$p=0.73$	$p=0.10$	$p=0.39$		**$p=0.02$**
Sex: female, male, p	622 (243–1207), 1156 (857–1863), $p=0.29$	233 (77–603), 49 (21–113), $p=0.19$	66 (36–205), 29 (19–79), $p=0.28$		2048 (774–4027), 2555 (1425–3684), $p=0.94$
Charlson Comorbidity Index < 7, ≥ 7, p	**1320 (1125–1667), 446 (181–798), $p=0.04$**	81 (76–1621), 95 (26–371), p = 0,52	66 (46–145), 35 (19–211), $p=0.46$		3898 (2446–5350), 1699 (250–3530), $p=0.50$
Charlson Comorbidity Index, Spearman's test p value	**$p=0.06$**	p = 0,27	$p=0.61$		$p=0.17$

Table 3 (continued)

	Serology at 1 month	Serology at 2 months	Serology at 3 months	Remote serology
Group who contracted COVID-19 less than 15 days after the first BNT162b2/Comirnaty injection			Second BNT162b2/ Comirnaty injection	
$N=17$	$N=17$	$N=14$	$N=0$	$N=11$
Anti-RBD IgG BAU/ml	463 (234–914)	484 (208–1167)		898 (437–2824)
Age < 87, > 87, p	618 (404–1170), 331 (91–489), $p=0.11$	698 (224–1171), 369 (203–1153), $p=0.90$		734 (441–1583), 898 (437–4428), $p=0.79$
Age in year, Spearman's test p value	***p* = 0.05**	$p=0.80$		p = 0,35, $p=0.74$
Sex: female, male, p	406 (221–492, 828 (484–1242), $p=0.30$	369(200–1356), 598 (401–885), $p=1.00$		511 (261–1477), 2250 (813–4405), $p=0.32$
Charlson Comorbidity Index < 7, ≥ 7, p	618 (470–1150), 406 (208–914), $p=0.25$	934 (816–1053), 306 (196–1255), $p=0.44$		909 (734–2256), 705 (312–3237), $p=0.63$
Charlson Comorbidity Index, Spearman's test p value	$p=0.09$	$p=0.23$		$p=0.96$
Total				
$N=83$	$N=55$	$N=48$	$N=15$	$N=38$
Anti-RBD IgG BAU/ml	564 (236–1417)	334 (110–945)	56 (29–203)	100 (29–813)
Age < 87, > 87, p	742 (265–1874), 523 (205–965), $p=0.25$	380 (121–1268), 278 (110–747), $p=0.29$	66 (36–210), 30 (11–155), $p=0.22$	413 (61–3102), 58 (27–363), $p=0.09$
Age in year, Spearman's test p value	***p* = 0.04**	***p* = 0.03**	$p=0.39$	$p=0.57$
Sex: female, male, p	491 (205–1149), 914 (346–2472), $p=0.19$	359 (120–892), 220 (103–1027), $p=0.74$	66 (36–205), 29 (19–79), $p=0.28$	59 (29–474), 355 (53–1474), $p=0.24$
Charlson Comorbidity Index < 7, ≥ 7, p	**1156 (446–2157), 454 (196–873), *p* = 0.01**	**828 (148–1761), 239 (120–697), *p* = 0.07**	66 (46–145), 35 (19–211), $p=0.46$	170 (30–909), 87 (27–511), $p=0.50$
Charlson Comorbidity Index, Spearman's test p value	***p* = 0.02**	***p* = 0.03**	$p=0.61$	$p=0.30$

The data are medians (with interquartile range) for the study of anti-RBD IgG titers. The data are effectives for description of sample size. Statistical differences between groups were assessed using non-parametric Mann–Whitney-Wilcoxon test due to non-normal distribution except for the comparisons between remote serology titers and age > < 87 and sex which were performed using parametric Student's test due to normal distribution assumption. The correlation between quantitative variables was assessed using Spearman's rank correlations

Regarding the humoral immune response after COVID-19

Unlike the humoral immune response after COVID-19 vaccines, the relationship between age and antibody levels following natural COVID-19 infection is markedly more complex. In this systematic review of Post et al. [6], evidence on correlates of antibody response and age after COVID-19 were conflicting or inconclusive.

Some authors have described that antibody titers may gradually increase in adulthood with a peak in antibody levels seen between the ages of 60 and 80 [20].

Since COVID-19 severity is positively associated with SARS-CoV-2 anti-RBD IgG titers [21]. This much more frequent severity among older adults [16, 21] and immunosenescence could be two forces with opposite effects partly explaining the complex relationship between age and anti-RBD IgG titers after COVID-19 infection.

Vaccination after COVID-19 and COVID-19 after vaccination

Bates et al. [16] reported on a study of patients with a median age between 38 and 50 years old that SARS-CoV-2 infection before or after vaccination gives a significantly larger boost to the SARS-CoV-2 anti-RBD IgG titer and neutralizing antibody response compared to two doses of vaccine alone, whether infection occurs before or after vaccination.

Interestingly, while age negatively correlated with antibody response after vaccination alone, no correlation with age was found in breakthrough (vaccination then infection) or hybrid immune groups (infection then vaccination) [14, 16].

In their study among older nursing home residents, Dyer et al. [17], using another anti-RBD serological test and expressing their data in U/ml, observed 6 months after the vaccine in vaccinates with a history of COVID-19, antibody levels 10 times higher than the peak observed at 5 weeks from the second vaccination in naïve patients with COVID.

We also observed such a boost in our study. The humoral response was actually much stronger and seemed to last longer. Bates et al. [16] reported the absence of difference observed in antibody titers according to the chronology of vaccination and infection or infection and vaccination. This is encouraging for vaccinated patients who, contracting the virus, have lower mortality and then more durable and robust protection over time.

Considerations about sex and COVID-19 and COVID-19 vaccine

This cohort includes 71% women. This is the usual sex ratio in our Geriatrics departments. Due to small numbers, and a group of women older than men, the descriptions in subgroups are purely observational.

But since sex may influence inter-individual variability on SARS-CoV-2 response with a role of sex chromosomes and sex hormones [22, 23] this ratio could have consequences on the description of the immune response made in this study.

Women have an overall tendency to have higher antibody responses to many vaccines, but with counterexamples like diphtheria, meningococcal, pneumococcal vaccine, and tetanus vaccination and faster waning of antibodies following hepatitis and PPV23 vaccination [3].

The impact of sex on the immune response in the context of SARS-CoV-2 is not so clear.

Evidence on correlates of antibody response and sex after COVID-19 can be conflicting or inconclusive [6, 24]. But it has been suggested that when men displayed higher antibody levels shortly after infection, they present a possible faster decay of the anti-RDB IgG than in women after COVID-19 so that the difference is no longer visible at 3–6 months [24, 25].

Regarding anti-SARS-CoV-2 vaccination, some studies showed significantly higher anti-SARS-CoV-2-RBD IgG antibody levels after the BNT162b2 vaccine in women than men [15, 26]; others found no significant association of antibody concentration with sex [27].

So at this stage, the answer is not clear cut. Even if there were a difference, it might not be relevant on an individual scale and therefore may not have any consequence on a vaccination decision according to the expected humoral response.

We did not observe higher antibody titers in women. Our data do not allow analysis in subgroups; however, we observed in all subgroups whose median anti-RBD IgG titer was above the threshold of 141–165 BAU/ml, higher titers in men than women, without any significant difference. The numbers are

low and there are confounding factors with, among other things, older women in this cohort and the presence of more serious forms in men in general [28].

Protective thresholds, anti-RBD IgG, neutralizing antibody assays, and variants of concern (VOC)

Protective thresholds of IgG antibodies directed against the spike RBD of SARS-CoV-2 are highly speculative.

Also even if the BAUs and the thresholds were to become clearer at a certain time, these thresholds would change over time as the variants evolve and the humoral avidity could decrease in addition to the indisputable humoral decrease. They are just given as an indication, as landmarks. However, they make it possible to present the dynamics of anti-RBD IgG titer in a more informative way than giving an isolated and incomparable antibody titer or worst, to present only its qualitative character: positive/negative. This is all the more interesting as the range of values for these serologies is very wide.

Neutralizing antibody assays are the gold standard for evaluating the in vitro efficacy of the humoral response, with infectious SARS-CoV-2 neutralization assays at best, then pseudovirus-based neutralization tests and possibly antibody-binding assays with RDB–ACE2 competitive assays [8].

Evaluation of the in vitro efficacy of humoral responses was not the objective of this study. The objectives of this study were to assess the dynamics of the SARS-CoV-2 anti-RBD IgG response over time among older people after COVID-19 infection or vaccination and its comparison with indicative/speculative levels of protection assumed by data at the time of the study.

The reasoning is based on the correlation between SARS-CoV-2 anti-RBD IgG titers and neutralizing antibody assay titers [14, 17, 29–31] and the correlation between SARS-CoV-2 anti-RBD IgG titers and the occurrence of infection [5, 7].

It is important to note that Feng et al. [5] estimated the anti-RBD IgG protection threshold in settings in which the VOC Alpha was dominant; the study by Dimeglio et al. [7] was performed before the local appearance of VOC Delta. These speculative protective thresholds predate the circulation of VOC Delta and Omicron.

Since a reduction in neutralization titers has been observed with VOC Beta, Gamma, Delta [8], and now even more strongly with Omicron [32], if new studies with these VOCs still confirm a correlation between anti-RBD IgG titers and neutralization titers, the speculative protection thresholds could have significantly increased.

Therefore, we may now expect a lower proportion of patients above the "protective thresholds" acquired via vaccination still based on the Wuhan strain.

Author contribution All authors made substantial contributions to this article.

Declarations

Competing interests The authors declare no competing interests.

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