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Letter to the Editor

Amplitudes and kinetic of antibodies after second and third doses of BNT162b2 vaccine in nonagenarians and centenarians with and without prior SARS-CoV-2 infection

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To the Editor,

We have read with great interest the recent article by Alice Pierobon showing that vaccine effectiveness against COVID-19 during an outbreak in a nursing home (NH) correlates with anti-Spike IgG [1]. In this study, anti-Spike IgG below 50 binding antibody units (BAU)/mL 28 weeks after two vaccine doses resulted in a higher risk of SARS coronavirus 2 (SARS-CoV-2) infection and severe form of the disease.

A high enough level of immunity is necessary to keep spread low in NHs whereby persons share common spaces. However, in older adults, immunosenescence and inflammaging, a dysregulated and chronic inflammation, may impair the ability of the immune system to respond to vaccination [2]. Spike antibodies were undetectable in about 40% of the SARS-CoV-2 naive residents after one dose, and about one-third of residents have low levels of antibodies after two doses [3]. NH residents naturally immunized before vaccination appeared protected from infection, but those who were vaccinated without history of prior SARS-CoV-2 infection were frequently infected and at risk for severe disease [4]. A third dose of vaccine was proposed, in priority to NH residents in September 2021 in France. Even after this booster dose, impairment in the humoral vaccine response at extreme of age may compromise the possibility of a herd immunity in NHs. We assessed the immune response and the proportion of poor vaccine responders after prime and booster vaccination in nonagenarians and centenarians NH residents.

In this study performed between March and October 2021, we compare the response to BNT162b2 vaccine in NH residents depending on their age, 95 years or older vs. less than 95 years of age, and their history of prior SARS-CoV-2 infection. Residents living in 14 NHs having faced a COVID-19 outbreak in 2020 were invited to participate in the study. The study was approved by the Montpellier University Hospital institutional review board (IRB-MTP_2020_06_202000534 and IRB-MTP _2021_04_202000534).

The humoral response against SARS-CoV-2 receptor-binding domain (RBD) was tested six weeks after the second BNT162b2 dose, before the third dose (six months after the second dose), and six weeks after the third dose. The primary outcomes were the level of RBD-IgG (SARS-CoV-2 IgG II Quant assay, Abbott Diagnostics; Abbott Park, IL, USA) and proportion of poor responders to vaccination (<264 BAU/mL) [5] after second and third BNT162b2 dose. Nucleoprotein-IgG levels were quantitated in residents with prior SARS-CoV-2 infection using the SARS-CoV-2 IgG assay (Alinity i, Abbott Diagnostics).

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Table 1
Levels of RBD-IgG and nucleoprotein-IgG in and NH residents

		N	Six weeks post 2nd dose, median (IQR)	p[a]	Six months post 2nd dose, median (IQR)	p[a]	Relative difference median (IQR)[b]	Six weeks post 3rd dose, median (IQR)	p[a]	Relative difference, median (IQR)[c]
Prior SARS-CoV-2 infection										
RBD-IgG	Total	111	4312.4 (1850.1–7700.9)		742.8 (339.1–1541.5)		81.3 (70.9–88.3)	3384.0 (1666.65–6260.8)		327.1 (151.7–881.1)
	Female	89	4312.4 (2408.5–8051.9)	0.279	780.6 (375.3–1669.5)	0.235	81.5 (70.4–88.2)	3751.2 (1807.5–6163.4)	0.313	311.7 (151.9–960.9)
	Male	22	4012.4 (1545.4–5559.2)		560.5 (221.0–1021.4)		81.1 (74.3–89.2)	2725.8 (1550.4–6683.9)		432.8 (236.2–972.1)
	≤95	85	4462.5 (2090.5–8051.9)	0.502	613.3 (335.4–1742.3)	0.684	81.8 (72.7–89.3)	3266.4 (1742.3–6683.9)	0.629	310.5 (151.9–960.9)
	>96	26	3869.7 (1850.1–7486.4)		943.3 (432.7–1498.1)		76.9 (69.4–85.8)	4196.4 (1666.7–5794.7)		406.2 (99.2–595.9)
N-IgG, S/CO	Total	111	1.57 (0.53–3.07)		0.63 (0.25–1.56)			0.56 (0.21–1.38)		
	Female	89	1.77 (0.50–3.39)	0.229	0.65 (0.25–1.56)	0.176		0.58 (0.22–1.32)	0.496	
	Male	22	1.11 (0.63–2.20)		0.40 (0.20–1.23)			0.41 (0.20–1.38)		
	≤95	85	1.32 (0.45–2.73)	**0.005**[d]	0.53 (0.20–1.30)	**0.024**[d]		0.49 (0.21–1.17)	0.112	
	>96	26	2.71 (1.23–4.84)		1.37 (0.49–2.30)			0.90 (0.36–2.04)		
Naive of SARS-CoV-2 infection										
RBD-IgG, BAU/mL	Total	296	348.1 (119.4–752.6)		35.2 (15.5–70.4)		89.0 (81.2–93.1)	1926.8 (875.1–3866.7)		5658.7 (2556.2–10356.7)
	Female	218	319.7 (117.9–764.8)	0.544	36.7 (15.9–82.8)	0.445	89.0 (80.6–92.5)	1911.9 (870.9–3934.7)	0.751	5415.3 (2453.9–9761.3)
	Male	78	428.8 (142.4–746.2)		31.5 (15.5–61.5)		90.1 (85.0–94.9)	1975.2 (903.4–3818.5)		6016.7 (3150.6–11318.1)
	≤95	249	391.1 (190.4–800.9)	**<0.001**[d]	38.2 (17.9–75.8)	**<0.001**[d]	89.5 (82.2–93.3)	2064.4 (1016.3–3873.8)	**<0.001**[d]	5716.4 (2401.9–9728.9)
	>96	47	116.2 (36.1–348.9)		16.2 (4.3–38.5)		87.6 (76.4–91.4)	990.9 (212.4–3364.1)		4805.0 (2401.9–9728.9)

Abbreviations: N, nucleoprotein; RBD, receptor binding domain.
[a] Wilcoxon Mann-Whitney two-sided tests.
[b] Difference between six months post 2nd dose and six weeks post 2nd dose.
[c] Difference between six weeks post 3rd dose and six months post 2nd dose.
[d] p-value statistically significative difference.

A total of 412 NH residents were tested at the 3 time points. Five residents infected after the prime vaccination were excluded. Among residents included, 307/407 were women (75.4%), 100/407 were men (24.6%) with a median age of89 (84–94 years). Of residents, 111/407 (27.3%) had SARS-CoV-2 infection before prime vaccination, of whom 26/111 (23.4%) were over 95 years old (Table 1). Of the SARS-CoV-2 naive residents, 47/296 were over 95 years old (15.9%).

RBD-IgG vaccine response after the second dose was lower in SARS-CoV-2 naive residents aged of over 95 years than in younger residents ($p < 0.001$) (Table 1, Supplemental material, Fig. S1a). In the older group, a majority of the residents had a poor vaccine response (<264 BAU/mL) after the second dose (34/47; 72.3%), whereas a minority of younger residents were poor responders (89/249; 35.7%). Six months after the second dose, the nadir of RBD-IgG level was also lower in residents aged over 95 years, as compared to younger NH residents ($p = 0.00011$). Median RBD-IgG level was below 1000 BAU/mL after the third dose in the older group of residents, whereas the third dose elicited RBD-IgG levels around 2000 BAU/mL in younger residents ($p = 0.0007$). About a quarter of residents over 95 years remained poor responders after the third dose of vaccine 27.7% (13/47) vs. 7.2% (18/249) of those younger.

In residents with prior SARS-CoV-2 infection, RBD-IgG levels six weeks after second and third BNT162b2 vaccine doses were similar in residents aged over 95 years and younger residents (Table 1, Supplementary material, Fig. S1b). Likewise, the nadir of RBD-IgG six months was similar in the two groups ($p = 0.7$). Levels of nucleocapsid-IgG was higher in residents aged over 95 years six weeks and six months after the second dose when compared to younger counterparts ($p = 0.005$ and $p = 0.02$, respectively). This result suggests that residents in the older groups had had more sever forms of COVID-19 than younger NH residents.

One limitation of our study is the absence of a control group of mild age. However, our results indicate that an immunization resulting from both an infection and a vaccination triggers a robust humoral response in NH residents over 95 years. By contrast, vaccination alone induces a relatively low antibody response after three vaccine doses in naïve residents over 95 years. Poor vaccine responders may be especially susceptible to infection and may play a significant role in SARS-CoV-2 transmission, compromising herd immunity in NHs. Special precautions may be recommended to protect this vulnerable population.

Transparency declaration

The authors declare that there are no conflict of interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

AP has performed experiments and statistical analysis. LG and MCP performed statistical analysis. SH, AMM, PP, PVP, JB, and HB have discussed the results and wrote the manuscript. ET has conceived the study, discussed the results, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.05.025.

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