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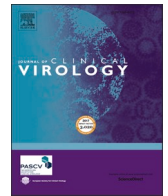
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Post-vaccination SARS-cov-2 infection in nursing home residents, Bordeaux, France

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ABSTRACT

Objective: To describe COVID-19 breakthrough infections in two nursing homes (NHs) sites of active COVID-19 clusters despite optimal vaccination coverage.

Methods: A cross-sectional study was conducted in two NHs of south-western France, following the investigation of COVID-19 clusters (February-March 2021). SARS-CoV-2-confirmed infection was defined by positive RT-PCR. Antibodies neutralization capacities were tested in a subgroup of fully-vaccinated and seropositive-residents.

Results: Of the 152 residents, 66% were female with median age 87 years (IQR: 80.0–90.2). Overall, 132 (87%) residents received 2 doses of vaccine, 14 (9%) one dose and 6 (4%) were unvaccinated. Forty-seven (31%) residents had confirmed infection (45 (98%) with variant 20I/501Y.V1). All 6 non-vaccinated residents, 4 /14 who had one dose and 37/132 that had two doses, were infected. Of the 39 residents reporting symptoms, 12 and 3 presented severe and critical disease, respectively. One resident with a confirmed infection died. Infected-residents had a median anti-S IgG titre of 19 116.0 (IQR: 3 028.0–39 681.8 AU/mL), 19 times higher than that of non-infected vaccinated persons (1,207.0; IQR: 494.0–2,782.0). In the subgroup of 19 residents tested for neutralizing antibodies, the neutralizing titre (50%) was strongly positively correlated with the anti-S IgG titre (correlation coefficient = 0.83), and 1.5 times higher for the infected than non-infected residents [5.9 (IQR: 5.3–6.9) vs. 3.6 (2.9–3.8)].

Conclusion: Institutionalized elderly persons who undergo breakthrough infection develop higher titres of anti-S IgGs, which are strongly correlated with the neutralizing capacity of the antibodies. These results advocate for additional vaccine doses in this population.

1. Introduction

Mass prophylactic vaccination is likely the only viable path to curb the COVID-19 pandemic caused by SARS-CoV-2 infection [1]. The

elicited specific antibody titres and neutralizing antibody concentrations are superior to those observed in COVID-19 human convalescent sera, across a wide age range. This humoral response is backed up by long-lasting cellular immunity [2]. Age is known to modulate COVID-19

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Table 1

Characteristics of nursing home residents for non-infected *versus* infected (Data are presented as n (%) unless otherwise indicated).

	Overall (N = 152)	Non-infected (n = 105)	Infected (n = 47)	p
Gender				0.266
Male	51 (33.6)	32 (30.5)	19 (40.4)	
Female	101 (66.4)	73 (69.5)	28 (59.6)	
Age, years				0.211
Median (IQR)	87.0 (80.0 to 90.2)	87.0 (80.0 to 91.0)	85.0 (80.0 to 89.0)	0.363
< 70	13 (8.6)	11 (10.5)	2 (4.3)	
70 – 79	23 (15.1)	14 (13.3)	9 (19.1)	
≥ 80	116 (76.3)	80 (76.2)	36 (76.6)	
KATZ autonomy score, median (IQR)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	0.86
Number of drugs, median (IQR)	8.0 (6.0 to 10.0)	8.0 (6.0 to 10.0)	8.0 (5.5 to 10.0)	0.688
CIRS-G score ≥ 3				0.141
<3	53 (34.9)	41 (39.0)	12 (25.5)	
≥ 3	99 (65.1)	64 (61.0)	35 (74.5)	
MMSE test score, median (IQR)	12.0 (0.0 to 17.2)	15.0 (5.0 to 20.0)	8.0 (0.0 to 14.5)	0.002
Vaccination against SARS-CoV2				0.001
Not vaccinated	6 (4.0)	0 (0.0)	6 (12.8)	
1 dose	14 (9.2)	10 (9.5)	4 (8.5)	
2 doses	132 (86.8)	95 (90.5)	37 (78.7)	
Detection of anti-S IgM antibodies [†]				<0.001
Negative	125 (82.8)	101 (96.2)	24 (52.2)	
Positive	26 (17.2)	4* (3.8)	22 (47.8)	
Detection of anti-N IgG antibodies [†]				<0.001
Negative	118 (78.1)	103 (98.1)	15 (32.6)	
Positive	33 (21.9)	2 (1.9)	31 (67.4)	
Anti-S IgG level, median (IQR), AU/ml	1 842.0 (695.0 to 7 300.0)	1 207.0 (494.0 to 2 782.0)	19 116.0 (3 028.0 to 39 681.8)	<0.001
Death				0.309
No	151 (99.3)	105 (100.0)	46 (97.9)	
Yes	1 (0.7)	0 (0.0)	1 (2.1)	

IQR: interquartile range, CIRS-G: Cumulative Illness Rating Scale-Geriatric, MMSE: mini mental state examination.

[†]Serology results were not available for 1 resident.

*Of the 4 residents none-infected with detection of anti-S IgM antibodies, 2 were fully vaccinated and 2 received a sole dose of vaccine.

incidence and severity, and recent studies of vaccinated populations have described increasing COVID-19 cases among vaccinated elderly persons, including residents living in nursing homes (NHs) [3–5].

During the summer of 2021, more than 85% of NH residents in France received the complete two-dose mRNA vaccine schedule [6]. However, numerous case clusters were identified among vaccinated residents from March to July 2021, in more than 100 NHs in south-western France (Nouvelle Aquitaine region).

Our aim was to describe COVID-19 breakthrough infections in two NHs that became sites of active COVID-19 clusters despite optimal vaccination coverage. We examined the relationship between COVID-19 diagnosis, the level of anti-SARS-CoV-2 anti-S IgGs, and their neutralizing capacity in a subgroup of patients.

2. Methods

2.1. Study population and procedures

This cross-sectional study included all residents of two NHs affiliated with Bordeaux University Hospital, France. By early February 2021, the BNT162b2 mRNA vaccine (Pfizer) was administered to all residents.

Table 2

Characteristics of nursing home residents with confirmed SARS-cov-2 infection (Data are presented as n (%) unless otherwise indicated).

	N	n (%)
Symptoms and severity [§]	47	
No symptom	8	17.0
Mild/moderate	24	51.1
Severe	12	25.5
Critical	3	6.4
Temperature > 38° or < 36°	47	
No	22	46.8
Yes	25	53.2
Blood pressure < 100 mmHg	47	
No	25	53.2
Yes	22	46.8
Oxygen saturation <94%	47	
No	32	68.1
Yes	15	31.9
Diarrhea	47	
No	45	95.7
Yes	2	4.3
Resident falls	47	
No	46	97.9
Yes	1	2.1
Confusion	47	
No	46	97.9
Yes	1	2.1
Type of virus	46	
201/501.Y.V1	45	97.8
Wild-type (Wuhan strain)	1	2.2
Time between vaccination and infection [¶] , median (IQR), days	37	50.0 (43.0 to 60.0)

IQR: interquartile range.

[§]Symptoms were defined as mild/moderate, severe or critical according to NIH severity criteria.

[¶]Median time was estimated for residents with positive RT-PCR and complete 2 doses vaccine regimen.

Following identification of index cases on February 25 in one NH and March 17 in a second, all residents were tested for active SARS-CoV-2 infection using nasopharyngeal RT-PCR (Supplemental Methods T1) as part of the cluster investigation (March 17–April 15). Four weeks after cluster control, residents underwent sequential clinical evaluation and blood-sampling for serology testing to detect anti-SARS-CoV-2 antibodies elicited during either infection or vaccination (Supplemental Methods T1, Figure S1).

A subgroup of fully-vaccinated, seropositive residents was selected according to RT-PCR status and clinical phenotype [mild/moderate and severe disease as defined by the National Institutes of Health (NIH) [7]] to evaluate antibody neutralization capacity (in-house syncytia inhibition assay, Supplemental Methods T1). Data collection was declared to the Bordeaux University Hospital data protection committee, and analysis was carried out according to the Declaration of Helsinki.

2.2. Statistical analysis

Categorical and continuous variables are reported as percentages (compared using Fisher's exact test) and median (interquartile range) (compared using Wilcoxon-Mann-Whitney test), respectively. Recent SARS-CoV-2-confirmed infection was defined by a positive RT-PCR test. Boxplots display the median titre and interquartile ranges for anti-S IgG antibody titres and neutralizing 50% titres on a logarithm-10 scale. All tests were two-sided. Bonferroni-adjusted P-values were estimated for stratified comparisons, and P-values < 0.05 were considered significant in unadjusted comparisons. Analyses were performed using R (version 3.5.2) (packages: tidyverse, finalfit, ggpubr).

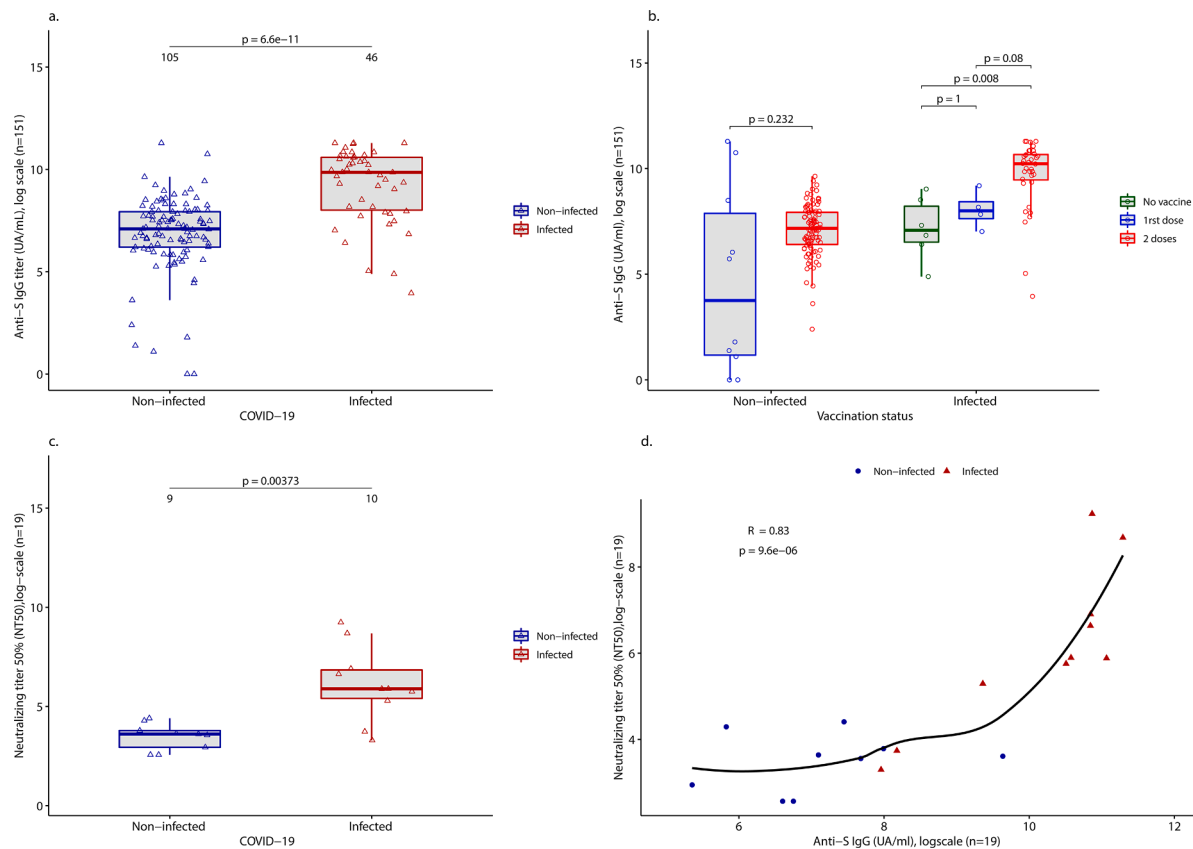


Fig. 1. Distribution of anti-S IgG antibody titre and neutralizing antibody (Nab) titre with 50% inhibition. A total of 151 NH residents had available anti-S IgG titre, and 19 had available neutralizing antibodies (Nab) titre. An aberrant neutralizing test result for 1 non-infected patient was not included. (a) Anti-S IgG antibody titre in 151 NH residents according to the RT-PCR test results; (b) anti-S IgG antibody titre in 151 nursing home residents according to the RT-PCR test result, stratified by vaccine status; (c) Nab titre with 50% inhibition in 19 selected NH residents according to the RT-PCR test result; (d) correlation between Nab titre with 50% inhibition (NT50) and anti-S IgG titre in 19 selected NH residents tested for Nab titre. Figures (a)–(c) display boxplots showing the distribution of anti-S IgG antibody titre and Nab titre with 50% inhibition in selected residents. Boxes with central horizontal lines indicate the median of the titre on a log-10 scale; the boxes' lower limit is the 25th percentile and the upper limit is the 75th percentile. The vertical lines indicate 1.5 times the interquartile range. Two-tailed P-values were determined using the Wilcoxon-Mann-Whitney test, with Bonferroni correction for stratified analyses. In (d), the r and P-values are from two-tailed Spearman's correlation.

3. Results

3.1. Characteristics of NH residents

Overall, 152 residents were included: 66% were female, and 76% were aged ≥ 80 years (median age = 87 years) (IQR: 80.0–90.2 years) (Table 1, Figure S2). Vaccination was achieved with two doses in 132 (87%) residents and one dose in 14 (9%); 6 (4%) were unvaccinated. At the time of the study, 47 (31%) residents had RT-PCR-confirmed SARS-CoV-2 infection. Anti-S IgM antibodies were detected in 26 (17%) residents; including 4 with a negative RT-PCR test (2 fully-vaccinated and 2 received one dose). Infected residents were mostly female (40%) and aged ≥ 80 years (77%). All 6 non-vaccinated residents, 4 of the 14 who had one dose, and 37 of the 132 that had two doses were infected. Only one resident died; he had a positive RT-PCR test.

3.2. Clinical features of residents with confirmed COVID-19

Of the 47 infected residents with a positive test, 8 (17%) had no symptom, 39 (83%) reported at least one symptom consistent with COVID-19, and 12 and 3 fulfilled the criteria for severe and critical disease, respectively (Table 2). The most common symptoms were temperature variation [> 38 °C or < 36 °C; $n = 25$ (53%)] and blood pressure decrease [< 100 mmHg; $n = 22$ (47%)] (Table 2). As a severe disease criterion, severe respiratory symptoms (oxygen saturation $<$

94%) affected 15 (32%) residents. The viral strains were characterized as variant 20I/501Y.V1 in 45 (98%) residents and wild-type virus (Wuhan strain) in 1 (2%) resident (1 missing data). Median time between complete vaccination and infection was 50 days (IQR: 43.0–60.0)

3.3. Serology and neutralizing antibody testing

Residents with breakthrough infection had a median anti-S IgG titre of 19 116.0 (IQR: 3 028.0–39 681.8 UA/mL), which is 19 times higher than that of non-infected vaccinated persons (1207.0; IQR: 494.0–2782.0 UA/mL) (Fig. 1a, Table 1). The median anti-S IgG titre was significantly higher in infected residents with two vaccine doses (Fig. 1b).

Serum from nine RT-PCR-negative and ten RT-PCR-positive fully vaccinated NH residents was further analysed to determine the neutralization status (Fig. 1c). Six of the RT-PCR-positive persons had mild/moderate symptoms, two had severe symptoms, and two had critical symptoms. The neutralizing titre (50%) was strongly positively correlated with the anti-S IgG titre (correlation coefficient = 0.83) (Fig. 1d). The median neutralizing titre (50%) was 1.5 times higher for the infected than non-infected residents [5.9 (IQR: 5.3–6.9) vs. 3.6 (2.9–3.8)] (Fig. 1c).

4. Discussion

Up to 30% of the investigated elderly vaccinated persons were infected with SARS-CoV-2, one-third of whom had a severe clinical presentation. This finding is in line with recent studies reporting a measurable increase in COVID-19 cases among vaccinated elderly adults [3,4], although, interim trials did not identify age as a contributing factor to overall vaccine efficacy [1]. Conversely, our observations are consistent with data showing that initial neutralizing antibody titres in response to vaccination were negatively associated with age [8].

In our study, fully vaccinated individuals with breakthrough infection had significantly higher anti-S IgG titres, suggesting that complete vaccination did not achieve full humoral immunity. We observed a strong positive correlation between anti-S IgG titre and neutralization capacity. While this correlation did not depend on whether individuals had a breakthrough infection or not, anti-S IgG titres were generally much higher in the infected group. It may therefore be possible to estimate individual patient protection with simple S-serology. The threshold level of this protection needs to be more precisely ascertained to generate a suitable surrogate marker, as long as cellular immunity cannot be routinely investigated.

Our neutralization test was based on the vaccine strain S protein, and not on emerging variants of concern (VOCs) [9, 10]. Several SARS-CoV-2 VOCs have been reported to be less well-neutralized by vaccine-induced antibodies. The infected elderly persons in the present study were vaccinated against the wild-type SARS-CoV-2 virus and exposed, in most instances, to the Alpha VOC (UK strain, lineage B.1.1.7, 201/501Y.V1), which did not harbor immune escape mutations such as 484 K, 484Q or 452R.

The effects of reduced neutralizing antibody titres due to both age and VOCs should be considered when designing policies around booster vaccinations, especially for individuals aged > 80 years living in NHs. These persons constitute a highly COVID-19-vulnerable group; the disease can have a highly detrimental impact on social and psychological status. Clearly, the latter consequences should be avoided, especially the dramatic effects of self-isolation. An acceptable degree of protective measures should be temporarily implemented while deploying vaccines according to an optimized schedule [11].

The main limitation of this study was the small sample size; the P-values should be interpreted with caution. We also cannot rule out the possibility of unrecognized infection prior to vaccination.

Our results indicate that, among vaccinated institutionalized elderly persons with breakthrough infection develop higher titres of anti-S IgGs, and there is a strong correlation of anti-S IgGs with antibody-neutralizing capacity. These results advocate for an additional vaccine dose in this population.

5. Patient and public involvement

Neither patients nor the public were involved in the design, conduct, or reporting of this study. This study does not contain patient identifiable data and addressed a national research priority question in the urgent context of vanning efficacy of vaccines against SARS-cov-2 virus.

6. Access to data

The data may be available on request to the guarantor (NS)

7. Contributors

Study conception and design: NS, MD, ML, M-EL, EO, WH, MN, MB
Collection and verification of data: HW, CT, PT, LB, M-EL, NS, ML, MN, MB, ET, PD

Cleaning and analysis of data: EO, ML, NS, MD

Drafting of the manuscript: NS, MD, M-EL, EO, ML, HW, CT, VG

All authors were involved in interpretation of the results and

critically reviewed the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

8. Funding

None

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jcv.2022.105134](https://doi.org/10.1016/j.jcv.2022.105134).

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