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Short communication

SARS-CoV-2 outbreak in a nursing home after vaccination with BNT162b2: A role for the quantification of circulating antibodies

Jordi Càmara [a,b,*], Aida González-Díaz [a,b], Irene Barrabeig [c,d], Miguel Fernández-Huerta [a], Laura Calatayud [a,b], Jordi Niubó [a], Sara Martí [a,b], Mª Ángeles Domínguez [a,e,f], Carmen Ardanuy [a,b,f]

[a] Microbiology Department, Hospital Universitari Bellvitge, University of Barcelona-IDIBELL, L'Hospitalet de Llobregat, Spain
[b] CIBER de Enfermedades Respiratorias (CIBERes), ISCIII, Madrid, Spain
[c] Epidemiological Surveillance and Response to Public Health Emergencies Unit in Barcelona South. Agency of Public Health of Catalonia, Generalitat of Catalonia, Spain
[d] CIBER de Epidemiología y Salud Pública (CIBEResp), ISCIII, Madrid, Spain
[e] CIBER de Enfermedades Infecciosas (CIBERinfec), ISCIII, Madrid, Spain
[f] Departament of Pathology and Experimental Therapeutics, University of Barcelona, Barcelona, Spain

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ABSTRACT

We describe an outbreak of SARS-CoV-2 (B.1.351) in a nursing home. At the outbreak onset 96% of residents and 76% of HCW had received two doses of BNT162b2. Twenty-eight residents (28/53) and six HCW (6/33) were infected. Infected residents had lower levels of anti-S antibodies compared to those who were not infected (157 vs 552 U/mL). Among 50 residents with available serological status, nineteen (19/25) with serum concentration < 300 U/mL and seven (7/25) with concentration > 300 U/mL acquired SARS-CoV-2 (RR 2.7 [95 %CI 1.4–5.3]). The quantification of circulating antibodies could be useful in detecting people with an impaired immune response who are at high risk of acquiring and spreading SARS-CoV-2.

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1. Introduction

The introduction of COVID-19 vaccines has changed the landscape of the pandemic. COVID-19 vaccines have been shown to be effective in preventing disease caused by SARS-CoV-2 [1] which has led to a reduction in the incidence rate of severe disease in countries with high vaccination rates [2]. Nevertheless, the emergence of SARS-CoV-2 lineages partially resistant to neutralization by vaccine-induced immunity is of concern [3].

In Catalonia, the vaccination program for residents and healthcare workers (HCW) of nursing homes began in December 2020. A weekly screening program using nucleic acid amplification tests (NAATs) was established to prevent SARS-CoV2 dissemination until a 70% vaccination rate was reached. Since then, residents and HCW were only tested if they had symptoms compatible with COVID-19 or had close contact with infected individuals.

In this work we report an outbreak due to the variant of concern (VOC) B.1.351 (Beta) among nursing home residents who were fully vaccinated with BNT162b2 mRNA COVID-19 vaccine.

2. Methods

Detection of SARS-CoV-2 in upper respiratory samples was performed by NAATs, either RT-PCR targeting E, RdRP/S and N regions (Allplex™ SARS-CoV-2, Seegene) or transcription mediated amplification (TMA), targeting N region (Procleix SARS-CoV-2, Grifols). Anti-SARS-CoV-2 antibody detection in serum was performed through electrochemiluminescence immunoassays (Elecsys®; Roche Diagnostics). Anti-nucleocapsid (N) total antibodies were detected by Elecsys® Anti-SARS-CoV-2 assay (qualitative; signal sample/cut-off > 1.0 positive and < 1.0 negative). Anti-spike (S) total antibodies detection was performed by Elecsys® Anti-SARS-CoV-2 S (quantitative; measuring range: 0.40–2500 U/mL; positive ≥ 0.80 U/mL). Differences in the level of anti-S antibodies between infected and non-infected residents were assessed through Mann-Whitney *U* test. All positive samples were subjected to whole genome sequencing (Illumina MiSeq). Sequences were uploaded to GISAID. A SNP-based phylogenetic tree was con-

* Corresponding author at: Microbiology Department, Hospital Universitari Bellvitge, University of Barcelona-IDIBELL, C/ Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Spain.
E-mail address: jcamara@bellvitgehospital.cat (J. Càmara).

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structed by RaxML-NG [4] using GTR + F + I + G4 model and visualized with iTOL (itol.embl.de/itol.cgi). Demographic data (age, sex, symptoms and date of vaccination) were collected from electronic resources.

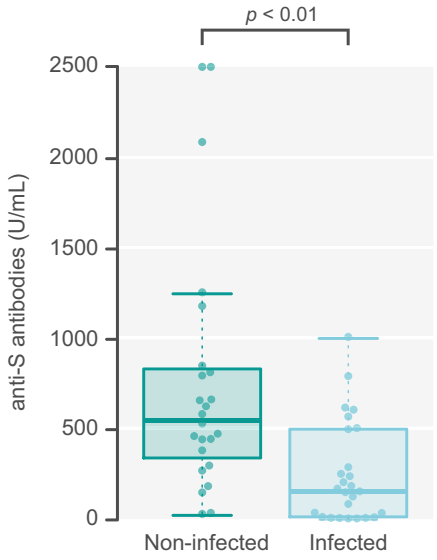
The Clinical Research Ethics Committee of Hospital Universitari de Bellvitge approved this work (PR191/21) and waived the requirement of written informed consent as this was a retrospective and non-interventional study with samples obtained as part of the clinical routine. Patient's data were always anonymized and protected according to national normatives.

3. Results

The index case was a HCW who presented mild symptomatology and a positive RT-PCR in April 19th 2021. Five days later, a resident with symptoms compatible with COVID-19 had a positive RT-PCR. At the time, 96% of residents (51/53, the remaining two residents had one dose) and 76% of HCW (25/33, two had received one dose and six were unvaccinated) had received two doses of BNT162b2. Infection control measures were implemented immediately, including isolation of all residents and screening of residents and HCW through RT-PCR. Twenty-six residents (26/53) and six HCW (6/33) were detected by RT-PCR. The median RT-PCR cycle-threshold (Ct, N gene) for residents was 21.7 (range 16.7–39.7). Of them, sixteen presented mild symptoms and ten remained asymptomatic (Supplementary material, Table 1). One resident was diagnosed with pneumonia and had positive urinary pneumococcal antigen detection suggesting pneumococcal pneumonia. Also, one resident required hospitalization due to the severity of underlying conditions. All residents evolved favourably and no mortality was observed at 30 days. Two additional residents (positive TMA and negative RT-PCR) were subsequently detected. Both displayed seroconversion of total anti-N antibodies which confirmed the SARS-CoV-2 infection

At the outbreak onset, the serological status of 26 infected and 24 non-infected residents was available. The median number of days since the second vaccine dose was 88 in both groups. Infected residents were older and more frequently women (Fig. 1). The median anti-S antibodies concentration of the infected residents was significantly lower than that of the non-infected (157 vs 552 U/mL, $p < 0.001$). In order to estimate a cut-off that could efficiently identify those residents with higher risk of SARS-CoV-2 acquisition, we performed a Receiver-Operating Characteristic (ROC) analysis (Supplementary material, Table 2). By setting a cut-off of 293 U/mL, 74% of non-infected residents could be correctly identified, although this cut-off would fail to identify 29% of infected residents. It should be noted that this analysis was limited to the low numbers in our series and would require further studies with a larger population. Nevertheless, when analysing the proportion of infected residents by different cut-offs of anti-S antibodies, the risk of SARS-CoV-2 acquisition was always higher for those residents with serum anti-S antibodies below the cut-off (Supplementary material, Table 3). For instance, by selecting a cut-off of 300 U/mL, 19 of 25 residents with a serum concentration < 300 U/mL and 7 of 25 residents with concentration > 300 U/mL acquired SARS-CoV-2 (RR 2.7 [95 %CI 1.4–5.3]). Total anti-N antibodies, evidence of a previous infection, were detected in two residents (one infected and one non-infected). Two weeks later, 23 of 25 infected residents showed a significant booster effect, with anti-S antibodies mostly above the detection range of the technique (>2,500 U/mL). Two infected residents, who had no evidence of anti-S antibodies in the first analysis, showed a low anti-S response (156 and 159 U/mL).

WGS analysis identified variant B.1.351 in all but one of the positive samples. All viruses harboured mutations in the Spike protein



Residents, n	24	26
Age, years	84.5 (77-91)	86.5 (81-94)
Female, %	58.3	73.1
Time since second dose, days	88 (75-88)	88 (88-88)
N gene, Ct	-	21.7 (19.7-25.9)
anti-S antibodies, U/mL	552 (335-827)	157 (9-494)

Fig. 1. Concentration of anti-Spike protein antibodies of infected and non-infected residents. Data are shown as median and interquartile range. The time since the second dose refers to the days between the date of the anti-S antibodies test and the date of the second dose.

related to lower antibody neutralizing activity or increased transmissibility, such as K417N, E484K, N501Y or D614G. Surprisingly, the B.1.1.7 (Alpha) variant was identified in one case, the only infected resident who had positive anti-N antibodies at onset. In order to confirm this result, we performed an RT-PCR targeting E484K, N501Y and ΔH69-ΔV70 changes (Allplex™ SARS-CoV-2 Variants I, Seegene), which yielded positive for all amino acid changes. In-depth analysis of WGS reads showed mixed sequences in the available positions that discriminate between B.1.1.7 and B.1.351, supporting the coexistence of both variants (Alpha/Beta, 3/1 reads proportion). Phylogenetic analysis was performed for all B.1.351 viruses collected in Catalonia until June 2021 (Fig. 2). Those viruses collected from patients in the nursing home clustered together confirming their epidemiological relationship. The same cluster included viruses collected from patients non-related to the outbreak suggesting that this clone was circulating in the community at the outbreak onset.

4. Discussion

COVID-19 vaccines have been a breakthrough in the fight against SARS-CoV-2. Nevertheless, the possible reduction in their efficacy in preventing disease caused by SARS-CoV-2 variants with amino acid changes in the Spike protein is of concern. Here we describe the spread of the B.1.351 variant among a cohort of vaccinated elderly.

Since early 2021, the VOC B.1.1.7 (Alpha) progressively replaced the local variant B.1.77, representing around 95% of new infections in April 2021. The prevalence of other VOCs was low and mainly related to imported cases. Among 10,111 viral sequences in the

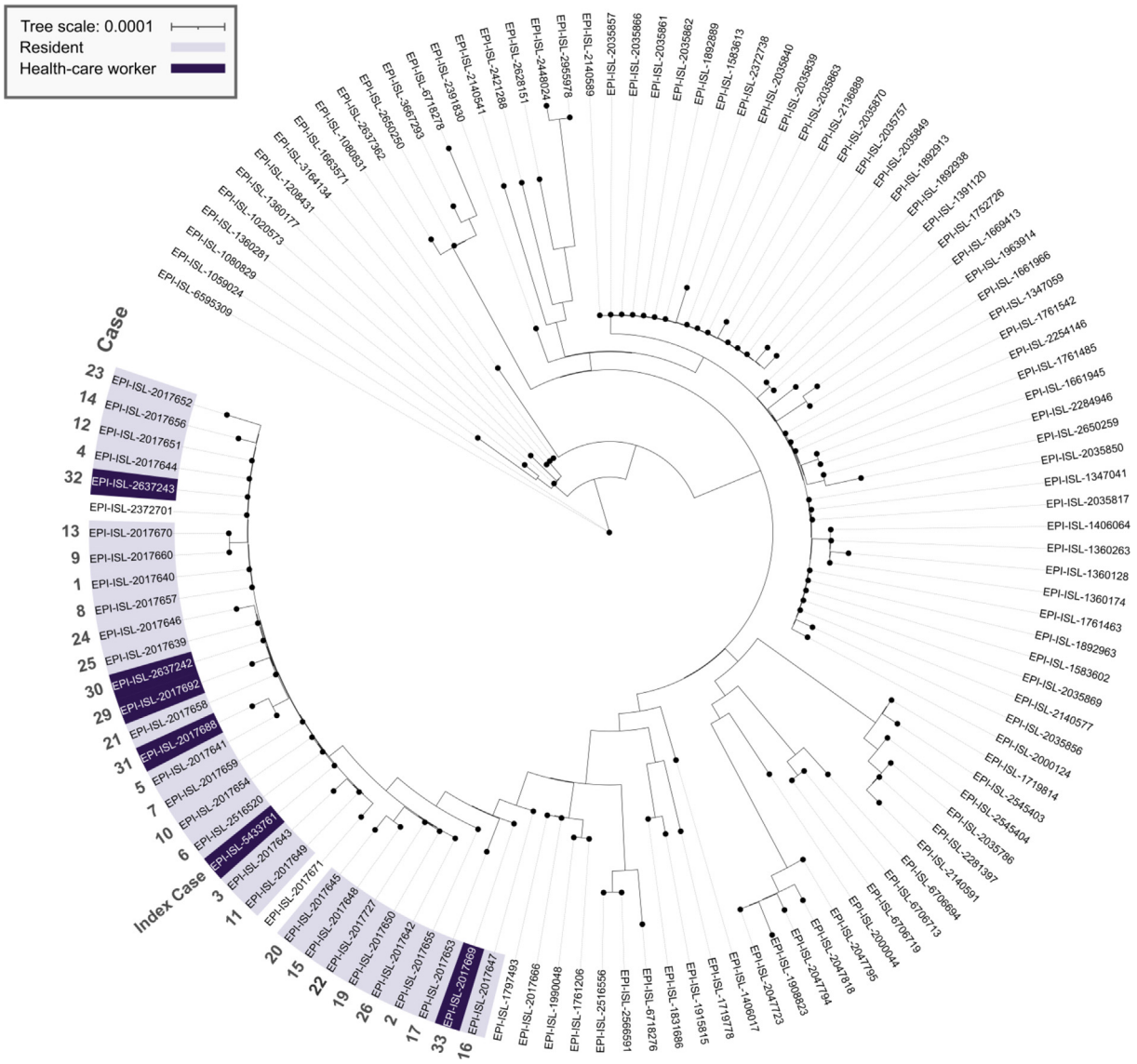


Fig. 2. Phylogenetic tree of SARS-CoV-2 viruses (B.1.351 lineage) collected in Catalonia until June 2021. Sequences collected in the nursing home are highlighted in blue (dark blue, health-care workers; light blue, residents). GISAID accession numbers are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

GISAID database (https://www.gisaid.org/, last accessed 3rd November 2021) from samples collected in Catalonia from January to June 2021, 119 (1.2%) belonged to variant B.1.351. The fact that the outbreak was caused by a low-prevalent lineage does not seem to be accidental. First reported in South Africa in October 2020, the B.1.351 lineage has shown to be poorly cross-neutralized by antibodies generated after infection due to variants circulating during the first wave [5,6]. This was associated with the occurrence of amino acid changes in the receptor-binding domain (RBD) of the Spike protein [3]. There are few data on SARS-CoV-2 infections in nursing homes following the start of vaccination programs. In the US, an outbreak among vaccinated individuals in a nursing facility was caused by an infrequent R.1 lineage harbouring the E484K change [7]. In France, another nursing home outbreak caused by the B.1.351 lineage showed a significant impact on the occurrence of disease in both vaccinated and unvaccinated residents [8]. The fact that these outbreaks were caused by viruses harbouring RBD changes evidences the role of these modifications in the SARS-CoV-2 spread among immunized people. In this sense, we evidenced the presence of B.1.1.7 variant in the nursing home at the same time that B.1.351 variant expanded, which was not the case with B.1.1.7. In our study, residents were asymptomatic or had mild symptoms, which is consistent with previous outbreaks that showed lower rates of severe disease for the vaccinated cohorts. This highlights the extreme importance of vaccinating people at risk of developing COVID-19. Nevertheless, as vaccination rate has increased, so has the frequency and diversity of viruses harbouring RBD changes for which vaccines show reduced activity, requiring close surveillance.

Most infected residents were vaccinated with two doses of BNT162b2 and had anti-S antibodies at the time of infection. Interestingly, infected residents had lower levels of anti-S antibodies than non-infected residents. It appears that the presence of a certain level of circulating antibodies may be a factor that helped preventing SARS-CoV-2 acquisition. The role of circulating antibody quantification in estimating the immune response against SARS-CoV-2 is unclear. SARS-CoV-2 antibodies decline over time after COVID-19 infection [9] but the dynamics of this reduction are different depending on the severity of the disease. For instance,

asymptomatic individuals may have a weak immune response with early negativization of IgG and neutralizing antibody levels [10]. However, immune cellular response could last longer and thus confer protection despite low levels of circulating antibodies [9]. Regarding the humoral response after BNT162b2, substantial reduction of the neutralization activity was reported for the B.1.351 variant [11]. However, cellular immunity after BNT162-2 has also been reported to be effective against both B.1.1.7 and B.1.351 variants [12]. It is remarkable that the study population was one of the first vaccinated cohorts and corresponds to elderly individuals with probably impaired immunity. This could mean weaker response after vaccination and faster negativization of circulating antibodies [13]. Then, this population may be more susceptible to SARS-CoV-2 acquisition, especially if a variant partially resistant to serum neutralization is involved. As most individuals belonged to the same vaccination cohort, the lower anti-S levels is likely related to individual factors, which may also affect the capacity to generate an effective immune response. As we were unable to assess cellular immunity, which is crucial for preventing SARS-CoV-2 acquisition and disease, the data presented in this study cannot determine the role that individual factors or the virus lineage have played in its dissemination. Despite the apparent decline in antibody immunity, protection against serious disease was still evident in our cohort, reinforcing the benefits of vaccinating vulnerable populations.

5. Conclusions

Besides highlighting the extreme importance of vaccinating people at risk of developing COVID-19, the data from this study show that the quantification of circulating antibodies could be useful in detecting people with an impaired immune response who are at high risk of acquiring and spreading SARS-CoV-2. This information is of great interest in selecting high-risk populations and in prioritizing vaccination efforts.

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Author's contributions

JC, IB, and CA conceived and designed the study. JC, IB, MFH, LC and JN contributed to data collection. JC, AGD, IB, MFH and SM contributed to data analyses and interpretation. The work was supervised by MAD and CA. JC wrote the first draft of the manuscript. All authors revised and approved the final manuscript.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.03.026.

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