

Immunogenicity after six months of BNT162b2 vaccination in frail or disabled nursing home residents: the COVID-A Study

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgs17620

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Running title: BNT162b2 vaccine and 6-month immunogenicity

Funding sources

This project received specific funding by the Instituto de Salud Carlos III, Ministerio de Economía y Competitividad, Spain. Ayuda cofinanciada por el Fondo Europeo de Desarrollo Regional FEDER. Una Manera de hacer Europa (Grant number COV20/00004). In addition, this work was supported by CIBERFES, Instituto de Salud Carlos III, Ministerio de Economía y Competitividad, España. Ayuda cofinanciada por el Fondo Europeo de Desarrollo Regional FEDER Una Manera de hacer Europa (Grant number CB16/10/00408).

Word, reference, and graphics count

Abstract: 292; Main text: 2,201; References: 24; Tables: 1; Figures: 2

Key points

- Older adults in long-term care facilities vaccinated with two doses of BNT162b2 SARS-CoV-2 vaccine lose 77.6% of antibody titers between one and six months after vaccination.
- Age, sex, comorbidities and cognitive status do not affect kinetics or extent of antibody decline.
- Pre-vaccination COVID-19 significantly reduces the decline in antibody titers and constitutes the only independent predictor of titer evolution.

Why does this paper matter?

Older adults in long-term care facilities lose SARS-CoV-2 antibodies during six months after the second BNT162b2 mRNA vaccine. A history of pre-vaccination COVID-19 was the only parameter that ameliorated the observed antibody decline. These data support the immunization with a third dose in this vulnerable, high-risk population.

Abstract

Background: There is incomplete information regarding evolution of antibody titers against SARS-CoV-2 after a two-dose strategy vaccination with BNT162b2, in older adults in long-term care facilities (LTCFs) with frailty, disability or cognitive impairment. We aimed to determine IgG antibody titer loss in old adults in LTCFs.

Methods: Multicenter longitudinal cohort study including 127 residents (90 females, 37 males) with a mean age of 82.7 years (range 65-99) with different frailty and disability profiles in two LTCFs in Albacete, Spain. Residents received 2 doses of BNT162b2 as per label, and antibody levels were determined 1 and 6 months after the second dose. Age, sex, previous history of COVID-19, comorbidity (Charlson index), performance in activities of daily living (Barthel index), frailty (FRAIL instrument), and cognitive status were assessed.

Results: The mean antibody titers 1 and 6 months after the second vaccine dose were 32,145 AU/mL (SD 41,206) and 6,182 AU/mL (SD 13,316) respectively. Across all participants, the median antibody titer loss measured 77.6% (IQR 23.8%). Notably, the decline of titers in individuals with pre-vaccination COVID-19 infection was significantly lower than in those without history of SARS-CoV-2 infection (72.2% vs 85.3%; $p<.001$). The median titer decrease per follow-up day was 0.47% (IQR 0.14%) and only pre-vaccination COVID-19 was associated with lower rate of antibody decline at 6 months (HR 0.17; 95% CI 0.07-0.41; $p<.001$). Frailty, disability, older age, cognitive impairment, or comorbidity were not associated with the extent of antibody loss.

Conclusions: Older adults in LTCFs experience a rapid loss of antibodies between over the first six months after the second dose of BNT162b2 vaccine. Only pre-vaccination COVID-19 is associated with a slower rate of antibodies decrease. Our data support immunization with a third dose in this vulnerable, high-risk population.

Key words: BNT162b2 vaccine; COVID-19; Immunogenicity; Frailty; Disability; Older adults

KEYWORDS:

BNT162b2 vaccine, COVID-19, disability, frailty, immunogenicity, nursing homes, antibody titers

INTRODUCTION

Older adults constitute the most prevalent target-group of SARS-CoV-2 vaccination in most industrialized countries.^{1,2} The coronavirus disease (COVID-19) pandemic has had a great impact on mortality in nursing homes and long-term care facilities (LTCF),^{3,4} and residents have been prioritized for early vaccination with mRNA COVID-19 vaccines, as they belong to the most vulnerable groups in society.⁵ The use of mRNA vaccines in residents of nursing homes in Spain is 71% effective against symptomatic and asymptomatic SARS-CoV-2 infection, prevents 88% of hospitalizations and reduces COVID-19 mortality by 97%.⁶

An antibody test to detect IgG titers provides a simple and rapid surveillance tool for potentially monitoring effectiveness of vaccines over time⁷ and this surrogate marker is considered by many particularly useful in the pandemic context to obtain early estimates of vaccine effectiveness. We have previously described that the BNT162b2 mRNA COVID-19 vaccine is safe and robustly immunogenic in older adults, independent of frailty, cognitive impairment, comorbidities or disability profiles.⁸ However, little is known about the stability of antibody levels in these high-risk individuals.

Pfizer has recognized a decrease in BNT162b2 efficacy, decreasing from 95% to 91% six months after the second dose of the two-dose regimen,⁹ but data stratified by functional status, frailty, cognitive status, or comorbidity is not available. In a preprint, a significant increase in the risk of COVID-19 was described particularly among patients older than 60, who had received their last vaccine dose >146 days ago, suggesting progressive loss of vaccination induced antibody levels.¹⁰

The use of booster shots is an area of ongoing debate, further fueled by the emergence of more contagious strains¹². However, most research on immunogenicity of BNT162b2 has been conducted in younger individuals with limited follow-up for only a few weeks.¹¹ To support decision-making specifically for older adults, and, consequently, to prevent outbreaks in LTCFs, we thus studied development of antibody levels to BNT162b2 in older adults.

METHODS

The COVID-A study is a longitudinal cohort study that included 953 residents from five LTCFs in Albacete. Inclusion criteria for the COVID-A study were living in one of the five LTCFs in Albacete, Spain, since the beginning of the pandemic, an age of 65 years or older, and permission and availability to participate in the study.⁵ Data regarding sociodemographics, performance in activities of daily living, cognitive status, and clinical variables were collected before vaccination. The first vaccine dose was administered between December 30, 2020, and January 31, 2021, and second dose between January 20 and February 19, 2021 (mean days 21; SD 0.8) to all individuals included here. Vaccines were administered on-site at the LTCFs using standard protocols.

In 134 residents of two LTCFs, we measured antibody levels between days 7 and 43 days after the second dose of the BNT162b2 mRNA COVID-19 vaccine (Pfizer, New York, United States, and BioNTech, Mainz, Germany). The mean antibody titers in residents with and without previous COVID-19 infection were 49,878 AU/ml and 15,274 AU/ml, respectively (mean difference 34,604; 95% confidence interval [CI]: 27,699–41,509). As reported previously, those with pre-vaccination COVID-19 had an increased antibody level after the vaccine ($B = 31.33$; 95% CI: 22.72–39.95; $p < .001$).⁸ Frailty, disability, older age, sex, cognitive impairment, or comorbidities were not associated with different antibody titers. The confirmation of pre-vaccination COVID-19 was made by PCR at the time. Before vaccination, from the 332 residents of the LTCFs included, 72 died of COVID-19 (21.7%).

Both LTCFs were closed to external visits and all rapid screening tests that were administered for every resident and all staff to determine new infections were negative throughout the entire study period. While problems with assays or occult infections cannot be formally excluded, these results lead us to believe that none of the residents were infected during the study follow-up period.

A second antibody measurement was conducted in 127 patients between June 15th and September 2nd, 2021. Between the first and second antibody detection, 7 residents were lost for follow-up due to mortality (2 heart failure, 2 non-COVID-19 respiratory infections) or technical laboratory problems (3 residents). Median days from second dose to second antibody determination were 183 (IQR 16; range 131–220 days), and median days between first and second antibody determination were 157 (IQR 28; range 105–204 days).

IgG antibody levels against the viral spike protein in serum or plasma were measured using the SARS-CoV-2 IgG QUANT (Abbott) antibody test kit. Levels <50 AU/mL were considered as negative. As the upper limit of quantification of the assay is 40,000 AU/mL, we used dilutions to increase the upper limit to 80,000 AU/mL.

As baseline functional variables we assessed disability in basic activities of daily living measured with the Barthel Index,¹³ and frailty status determined with the FRAIL instrument.¹⁴ The Barthel Index was subdivided into four categories: no disability (90–100 points), low disability (60–85 points), moderate disability (40–55 points), and severe disability (<40 points). Frailty was considered when the FRAIL instrument score was equal or superior to three positive criteria. Chronic diseases or comorbidities were retrieved from the medical records, and comorbidity was determined with the Charlson Comorbidity Index.¹⁵ High comorbidity was defined as a Charlson Comorbidity Index score of 3 or higher. The cognitive status of the residents was assessed using the Global Deterioration Scale (GDS) from Reisberg with scores 1–3, 4–5 and 6–7 indicating no dementia, mild-to-moderate dementia and severe dementia, respectively.¹⁶ The diagnosis of COVID-19 infection before vaccination was based on positive SARS-CoV-2 PCR, positive serology, and/or antigen rapid test retrieved from the medical records.

Data are presented as medians $\pm$ interquartile range (IQR) because continuous variables did not meet normal distribution criteria, or number of participants (%) in categorical variables. Differences were analyzed with χ^2 tests, Mann-Whitney *U*-tests or Kruskal-Wallis tests as indicated. Linear regression models were constructed to analyze the adjusted variables associated

with antibody titers. Our research was conducted in accordance with the Helsinki Declaration for human medical research and approved by the local Ethics Review Committee, record 2021-55. All participants, or their legal guardians, provided written informed consent before their inclusion in the study.

RESULTS

Compared to the residents included in the present immunogenicity substudy, the 72 residents who died before vaccination due to COVID-19 were older (age ≥ 80 years 84.7% vs 63.0%), more frequently male (52.8% vs 29.1%), had higher disability (Barthel index 0-35 61.1% vs 47.2%), frailty (FRAIL ≥ 3 66.7% vs 42.5%), and comorbidity scores (Charlson index ≥ 3 41.7% vs 29.9%), and showed a higher cognitive decline (GDS 6-7 51.4% vs 44.1%). In addition, between the first and second antibody detection, 7 residents were lost for follow-up. The reasons for this lost for follow-up were mortality (4 residents: 2 heart failure, 2 non-COVID-19 respiratory infections), and technical laboratory problems (3 residents). We could not find significant differences between those lost for follow-up and included participants in baseline characteristics, although the former were slightly older (89.0 vs 83.0 years).

Median antibody titers of participants, both one month and six months after the second vaccine dose are presented in table 1. Only the Barthel Index was associated with lower decrease in antibodies between 1- and 6-months follow-up, and previous COVID-19 infection with antibody titers 1- and 6-months after complete vaccination.

The median decrease in antibody levels was 77.6% (IQR 23.8%) for the complete sample, being lower in residents having passed COVID-19 previously. The median titer decrease per follow-up day was 0.47% (IQR 0.14%) for the complete sample. The only resident without antibody titers in the first measurement, associated to a lymphoproliferative disorder, neither showed antibodies after 6 months. Only two residents (1.6%) improved antibody titers from 1 to 6 months follow-up, three more (2.3%) had stable values, seven (5.5%) lost less than 50% of previous

titers, 27 (21.3%) lost between 50% and <70%, 59 (46.5%) between 70% and <90% (Figure 1). A total of 26 (20.5%) residents lost between 90% and 99%, and in two cases (1.6%) no antibodies were detected (Figure 1). None of the participants tested positive for COVID-19 between 1- and 6-month follow-up, and no new malignant pathology or immunodeficiency that might explain the loss of antibody titers was diagnosed during the study period. Participants with an antibody loss $\geq 90\%$ frequently presented at least one impaired immune system-related chronic condition, including eleven residents with diabetes (39.3%), eight with chronic kidney disease (28.6%), six with hypothyroidism (21.4%) and four with different immunodeficiencies (psoriasis 1, lymphoproliferative disorder 1, rheumatoid arthritis 1, enolism 1; 14.3%).

Figure 2 presents the density of antibody loss adjusted by the functional, cognitive, comorbidity and sociodemographic characteristics of the sample. Multivariate analysis using Cox proportional hazard models showed that only pre-vaccination COVID-19 was an independent preventive predictor of immunogenicity loss by >90% (HR 0.17; 95% CI 0.07-0.41; $p<.001$), or >70% after 6 months (HR 0.59; 95% CI 0.38-0.94; $p=.025$). By contrast, frailty, disability, older age, cognitive impairment, or comorbidities were not associated with a differential loss of SARS-CoV-2 antibodies.

DISCUSSION

The main conclusion of our study is that older adults in LTCFs lose SARS-CoV-2 antibody titers after a two-regimen BNT162b2 mRNA SARS-CoV-2 vaccination strategy by a median of 77.6% between month 1 and month 6 after the second dose, irrespective of disability, frailty, cognition status, comorbidity, age, or sex. The only factor that significantly impacted the decline in antibody levels was pre-vaccination SARS-CoV-2 infection. We were not able to explain effects on antibody changes of SARS-CoV-2 infection after the second vaccine dose because in our sample none of the residents was infected during that period of time.

Recent research has detected that BNT162b2, despite a gradual decline in vaccine efficacy, leads to high safety and efficacy across all age strata (40.7% > 55 years old; range 16-89 years), at 6-months follow-up.¹⁷ In addition, several publications have analyzed the kinetics of SARS-CoV-2 antibodies after BNT162b2 vaccination. In recent work from Chile, the SARS-CoV-2 IgG positivity among BNT162b2 vaccine recipients four weeks after the first dose was 79.4%, increasing to 96.5% three weeks after the second dose, and remaining above 92% until the end of the study (16 weeks after second dose).¹⁸ However, only 5.1% of the cohort were older than 60 years, and no information about adults older than 70 years was provided. However, the authors reported that lower seropositivity was observed among participants aged 60 years and older, when compared to those aged 18 to 39 years (-0.677; 95% CI -0.857 to -0.497). Another study showed that in older adults, mainly in those over eighty years old, serum neutralization and levels of binding IgG or IgA were lower for different variants of concern (wild type, alpha, beta and gamma) than in younger adults after the first dose with BNT162b2 vaccine, increasing across all ages after the second dose.¹⁹ A UK study of 605 participants demonstrated significantly declining S-antibody levels for both ChAdOx1 and BNT162b2 vaccines. Levels for BNT162b2 were reduced by about two-fold between 21–41 days and 70 days or more after the second dose, and this reduction was maintained after stratification for age, sex, and clinical vulnerability, although with higher reductions in older adults.²⁰ However, only three of the participants were older than 80 years. Finally, another study in 122 participants with a median age of 34 years old (IQR 27-45) and without a diagnosis of pre-vaccination COVID-19, spike protein receptor-binding domain (S-RBD) IgG levels decreased from 24,534 AU/mL (IQR 13,985-36,616) one week after the second dose, to 5,226 AU/mL (IQR 3,097-6,924) at 12 weeks, and to 1,383 AU/mL (IQR 893-2,463) after 6 months.²¹ These data align overall well with the findings in our cohort. However, in our study, participants without pre-vaccination COVID-19 decreased from 7,447 AU/mL to 693 AU/mL, thus showing overall lower levels than in the young population described.

Data from Van Praet et al²² has described dynamics of antibody loss in 100 older adults in institutions from two Belgian long-term care facilities who were vaccinated with two doses of the BNT162b2. In COVID-free residents, antibodies after 4- and 24-week follow-up were 1,621 AU/mL and 218 AU/mL respectively (87% loss), and in those with pre-vaccination COVID-19, figures were 29,819 AU/mL and 5,593 AU/mL respectively (81.2% loss). While antibody levels are slightly higher, these findings qualitatively confirm the observed trends of declining humoral responses in older adults in institutions, mainly in those without prior COVID-19. Another study in Valencia, Spain, showed that nursing home residents with postvaccination antibodies, also displayed detectable responses at follow-up, although overall, levels were significantly lower after 6 months [median of 2,249 IU/ml at baseline vs. median 307 IU/ml at follow-up, 86.4% loss].²³ However, while a lack of association between IgG levels and age has been reported²⁴, no studies have analyzed differences in antibody decline depending on frailty, disability, comorbidity, age, or cognitive impairment. Our study is the first to do so.

Persistence of several antigen-specific antibodies against SARS-CoV-2, including the S-RBD has been found up to 6 months following mild COVID-19, in healthcare workers.²⁵ Their study showed that almost all patients retained neutralizing antibodies at 6 months post infection. In our study, participants with a history of COVID-19 also retained higher antibody titers compared to those without prior disease. However, in this group, we also observed a decrease in antibody titers. This may support a third immunization dose in the most vulnerable populations such as the group we describe, especially for those without previous COVID-19.

Advanced age, frailty, disability and comorbidity have all been associated with immunosenescence and inflammaging, both conditions associated with an increased severity of COVID-19 in older populations.²⁶ Immunosenescence has deleterious impacts on both innate and adaptive immunity. An intact immune response is paralleled by a rapid response of innate phagocytes, natural killer cells and chemical defense mechanisms after virus invasion, producing supportive inflammation. Phagocytosis involves specialized macrophages presenting antigens to

naïve T-cells, producing an adaptive response, consisting of T-cell mediated cellular (CD4⁺ helper and CD8⁺ cytotoxic) and humoral B-cell antibody defense. Finally, regulatory T-cells complete the picture of the immune response, promoting the development of memory cells, and guiding the transition from a pro-inflammatory state into healing and repair..²⁷ The findings of our study may also suggest that B-cell antibody production is not significantly impaired in frail older adults, and that other defects related to immunosenescence such as the innate response or regulatory T-cell activity, may be the main cause of the increased disease severity in this population. Supporting this hypothesis is the recent finding that there is an impaired functional T-cell response to SARS-CoV-2 in older adults following BNT162b2 vaccination.²⁸

Notably, our data do not allow us to conclude about the level of protection against SARS-CoV-2 in older adults in institutions. Although antibody production protects against SARS-CoV-2 infection and reduces disease severity in older populations,^{29,30} immunity is multifactorial, and IgA-mediated mucosal immunity, other CD4⁺ and CD8⁺ T-cell responses, and innate immunity also constitute important factors^{31,32} as demonstrated by the observation that vaccinated individuals without detectable antibody levels or with a time-associated decline in neutralizing antibodies nevertheless appear to have some clinical protection.³³ This protection may be related to vaccine-associated increases in the level of highly specific memory B cells, that migrate in response to inflammation and secrete IgA at mucosal sites.³³ In addition, BNT162b2 induces high levels of interferon- γ T-cell responses in both young and old adults,³⁴ although the production of interferon- γ and interleukin-2 by SARS-CoV-2 spike-specific T-cells is lower in older adults when compared to younger populations.¹⁹

Our study has several limitations. First, from the nearly 1,000 residents living in the 5 facilities, our study only recruited 15%. Although our sample was composed of residents with different frailty, disability, and cognitive impairment profiles, this low recruitment rate might raise concerns regarding additional confounders and incentivizes further investigations, ideally in a multicenter setting to increase generalizability. Second, LTCF patients antibody levels had not been

evaluated prior to vaccination, raising the possibility that pre-vaccination levels might impact the measured titers. Third, while the follow-up period for the antibody measurement after full vaccination is short (7 to 43 days). However, a meta-analysis has shown an average effectiveness of full vaccination against SARS-CoV-2 infection of 95% shortly (≥ 7 days) after completion.³⁵ Lastly, SARS-CoV-2 infection resulted in a high mortality rate (21.7%) before vaccination, and so the group that survived may not be representative of the range of responsiveness to vaccination of the complete population. It is possible that the poorest responders to infection would have also exhibited a more rapid decline in antibody levels following vaccination. However, the sample included in our study accounted for the complete range of age, frailty, disability, comorbidity and cognitive impairment in older residents, without relevant differences in the 6-month antibody level decrease.

The clinical implications of waning antibody levels post vaccination are not yet clear, and although there was a decline in antibody levels in the analyzed population, these values cannot be directly translated into the extent of reduced protection against SARS-CoV-2 infection. The main strength of our study is the fact that none of the participants presented COVID-19 during the follow-up period, and both institutions included were COVID-free during the study period. This situation avoids the bias of reinfection in antibodies titration.

CONCLUSIONS AND IMPLICATIONS

In conclusion, older adults in long-term care institutions experience a decline in SARS-CoV-2 antibodies between one and six months after the second dose of BNT162b2 mRNA vaccine. Only pre-vaccination COVID-19 was significantly associated with a lower rate of antibody decrease. As such, our data lend support to recommendations for immunization with a third dose in this vulnerable, high-risk population.

FINANCIAL DISCLOSURE

This project received specific funding by the Instituto de Salud Carlos III, Ministerio de Economía y Competitividad, Spain, Ayuda cofinanciada por el Fondo Europeo de Desarrollo Regional FEDER Una Manera de hacer Europa (Grant number COV20/00004). In addition, this work was supported by CIBERFES, Instituto de Salud Carlos III, Ministerio de Economía y Competitividad, España, Ayuda cofinanciada por el Fondo Europeo de Desarrollo Regional FEDER Una Manera de hacer Europa (Grant number CB16/10/00408).

ACKNOWLEDGMENTS

The authors sincerely thank the Complejo Hospitalario Universitario de Albacete (CHUA), Diputación de Albacete, Nuñez de Balboa and San Vicente de Paul's nursing homes for their invaluable assistance.

CONFLICT OF INTEREST

JS declares his conflicts at <https://www.nature.com/onc/editors>

All other authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

- Sergio Salmerón Ríos: Design of the work, data interpretation, drafting of the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

- Marta Mas Romero, Elisa Belén Cortés Zamora, María Teresa Tabernero Sahuquillo, Inmaculada García Nogueras, Juan de Dios Estrella Cazalla, Antonio Murillo Romero: Data acquisition, drafting of the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Luis Romero Rizos, Pedro Manuel Sánchez-Jurado: Data analysis and interpretation, critically revision for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Pedro Abizanda, Justin Stebbing, Volker Lauschke: Design of the work, data analysis and interpretation, drafting of the work, critically revision for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- All authors had a role in writing the final manuscript and approved the final version.

SPONSOR'S ROLE

None/

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Figure Legends

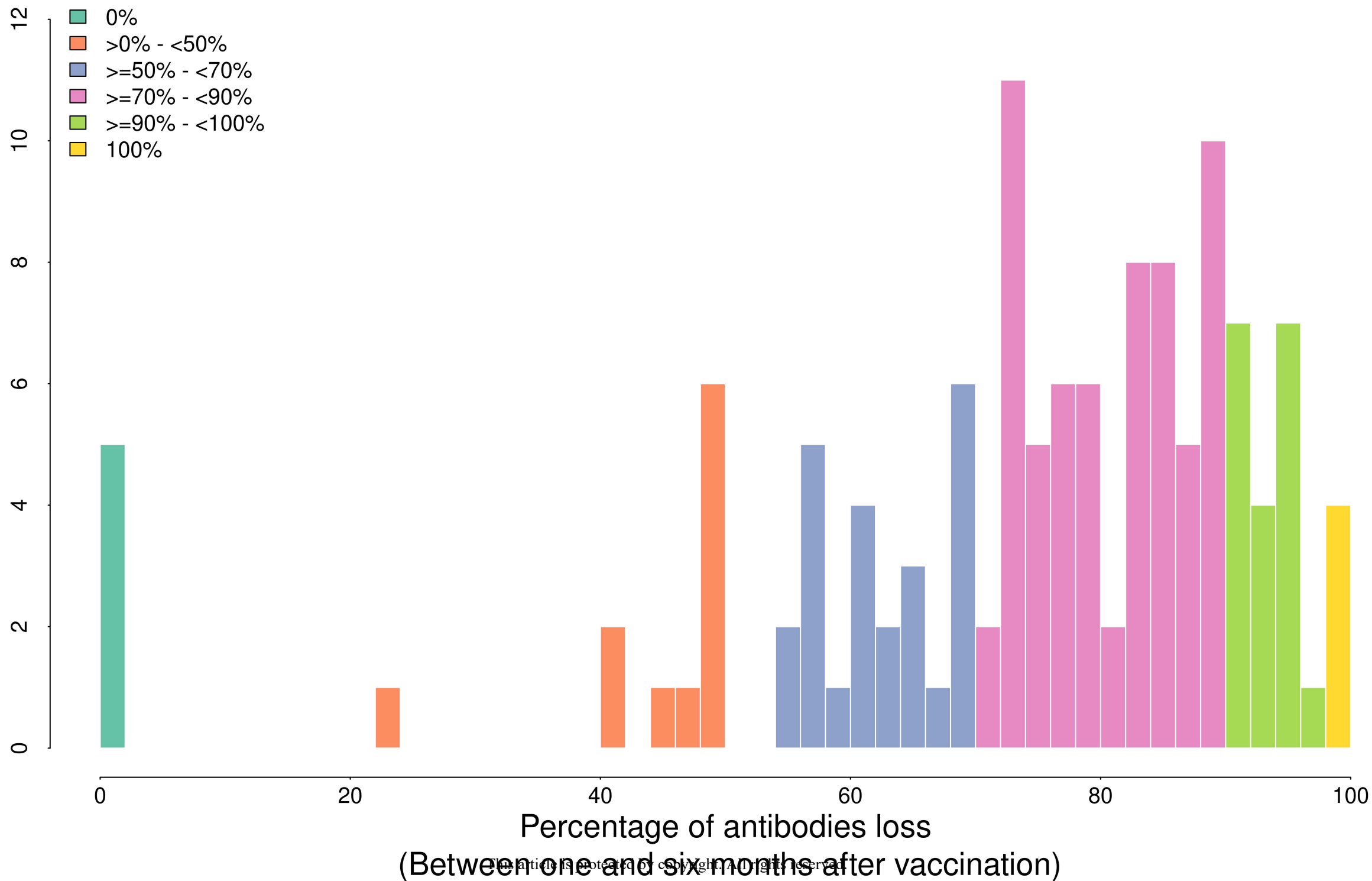
Figure 1. Percentage of antibodies loss between one and six months after vaccination

Figure 2. Percentage of antibodies loss between one and 6 months after vaccination by patient characteristics

Table 1. 1-month and 6-month antibody titers after second dose BNT162b2 mRNA COVID-19 vaccine in institutionalized older adults.

	Number of participants N (%)	Antibody titers		% antibody titers loss between 1 month and 6 months
		1-month post second vaccine dose	6-months post second vaccine dose	
Complete sample	127	32,145 (41,206)	6,182 (13,316)	77.6 (23.8)
Age				
< 80 years	47 (37.0)	27,872 (27,495)	3,723 (10,240)	80.7 (21.0)
≥ 80 years	80 (63.0)	37,608 (52,451)	8,274 (14,130)	76.0 (25.0)
Sex (n, %)				
Female	90 (70.9)	32,130 (41,496)	6,295 (10,241)	79.4 (18.4)
Male	37 (29.1)	33,319 (48,868)	4,895 (26,152)	72.1 (32.5)
Barthel index				
90-100	16 (12.6)	9,761 (48,999)	1,137 (10,359)*	80.7 (40.9)
60-85	29 (22.8)	40,000 (42,826)	8,274 (21,629)*	73.8 (31.0)
40-55	22 (17.3)	34,705 (43,373)	7,590 (17,372)*	76.9 (28.0)
0-35	60 (47.2)	31,889 (45,575)	5,849 (10,157)*	78.8 (19.9)
FRAIL				
Frail (≥ 3)	54 (42.5)	32,030 (40,728)	5,578 (12,529)	78.8 (21.5)
Non frail (<3)	73 (57.5)	35,478 (41,419)	8,224 (19,135)	76.6 (24.3)
GDS				
1-3	47 (37.0)	33,114 (27,495)	5,578 (26,805)	74.7 (34.5)
4-5	24 (18.9)	40,766 (38,666)	7,530 (10,883)	81.5 (17.2)
6-7	56 (44.1)	31,889 (46,104)	6,067 (10,762)	79.3 (20.1)
Charlson Index				
Low comorbidity (<3)	89 (70.1)	28,123 (34,931)*	5,253 (10,529)	79.4 (19.5)
High comorbidity (≥ 3)	38 (29.9)	40,000 (57,828)*	8,885 (25,863)	73.6 (28.8)
Pre-vaccination COVID				
No	54 (42.5)	7,447 (17,585)‡	643 (3,152)‡	85.3 (15.9)‡
Yes	73 (57.5)	40,000 (34,580)‡	11,076 (19,495)‡	72.2 (23.4)‡

All values are medians (IQR). GDS: Global Deterioration Scale from Reisberg. * $p<0.05$. ‡ $p<0.001$. Comparisons using Mann-Whitney *U*-test and Kruskal-Wallis test when necessary.



Percentage of antibodies loss (between one and six months after vaccination)

