

# Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination

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Summary:

This study compared antibody responses in two age groups (<60/ >80 years) after first and second BNT162b2 COVID-19 vaccination. While the majority in both groups developed SARS-CoV-2 spike-specific antibodies, IgG and neutralization titers were significantly lower in the elderly group.

## Abstract

### Background:

The SARS-CoV-2 pandemic has led to the development of various vaccines. Real-life data on immune responses elicited in the most vulnerable group of vaccinees over 80 years old is still underrepresented despite the prioritization of the elderly in vaccination campaigns.

### Methods:

We conducted a cohort study with two age groups, young vaccinees below the age of 60 and elderly vaccinees over the age of 80, to compare their antibody responses to the first and second dose of the BNT162b2 COVID-19 vaccination.

### Results:

While the majority of participants in both groups produced specific IgG antibody titers against SARS-CoV-2 spike protein, titers were significantly lower in elderly participants. Although the increment of antibody levels after the second immunization was higher in elderly participants, the absolute mean titer of this group remained lower than the <60 group. After the second vaccination, 31.3 % of the elderly had no detectable neutralizing antibodies in contrast to the younger group, in which only 2.2% had no detectable neutralizing antibodies.

### Conclusion:

Our data showed differences between the antibody responses raised after the first and second BNT162b2 vaccination, in particular lower frequencies of neutralizing antibodies in the elderly group. This suggests that this population needs to be closely monitored and may require earlier revaccination or/and an increased vaccine dose to ensure stronger long lasting immunity and protection against infection.

## Introduction

In December 2019, authorities in China's Wuhan province reported a lung disease of unknown cause. Back in January 2020, the sequence of a novel coronavirus was published and identified as the causative agent of this disease [1]. In March of the same year, the World Health Organization (WHO) declared the spread of this virus a public health emergency of international concern. With limited drug treatment options available, research on prophylactic immunization, especially for high-risk groups, became a priority [2].

Hence, rapid vaccine development became a global effort, which led to the emergency approval of 13 COVID-vaccines as of now [3-6], with many others in different advanced stages of development. The types of vaccines that are currently in use or under investigation in various clinical stages include non-replicating viral vector vaccines, formulations based on replicating viral vectors or virus like particles as well as inactivated vaccines and vaccines based on protein subunits (reviewed in [7]). A novel development in vaccine formulation that also received emergency approval, are mRNA based vaccines. These are also main vaccine types currently used in the western world, in particular the two mRNA technology vaccines Comirnaty (BNT162b2) by Biontech/Pfizer and mRNA-1273 by Moderna.

The Biontech/Pfizer and Moderna vaccines were not only the first approved COVID-vaccines, they are also the first approved drugs to employ the novel mRNA technology. While mRNA has long been discussed as a potent alternative to conventional vaccine formulations [8], the hurdle of low RNA stability and inefficient delivery had to be overcome to make full use of this technology. In recent years, the use of modified nucleosides, in particular modified uridine, the removal of double-stranded RNA by HPLC, codon optimization and the delivery via lipid-nanoparticles were developed. These advances helped to decrease innate sensing of the synthetic mRNA and thus, paved the way to efficient use of RNA vaccines. Currently approved vaccines also employ these methods [9, 10]. However, this new class of vaccines also carries certain disadvantages just as other drug formulations. This includes the stability of mRNA during transport and storage as well as still limited cellular uptake compared to other systems such viral vectors [11].

Early studies on mRNA vaccines from Biontech/Pfizer [5] and Moderna [12] showed high efficacy and safety of the formulations. With mass vaccinations being carried out using these vaccines, more promising reports on the effectiveness of the vaccines after completing the full vaccination schedule (prime and boost dose) were published [13-15]. The current vaccination strategy for the Biontech/Pfizer Comirnaty (BNT162b2) is a two-step "prime and boost" procedure in which the first vaccination is followed by a second vaccination with the same dose at least 21 days later [5]. Studies suggest that effectiveness of the vaccine is lower in individuals who received only the first dose compared to individuals who received the full vaccination regimen [16, 17].

In Germany and many other countries worldwide, COVID-vaccinations at the beginning of 2021 were offered in a prioritization procedure. First, individuals who are at particularly high risk for severe courses of COVID-19 disease or who are professionally in close contact with such vulnerable people were vaccinated. These two prioritized groups included senior residents of nursing homes aged  $\geq 80$  years, and their caregivers typically aged  $\leq 65$  years. This is of particular importance since SARS-CoV-2 and its associated disease COVID-19, can result in a remarkable variable severity of clinical symptoms, from asymptomatic infection to severe COVID-19 with lung manifestation and acute respiratory distress syndrome in up to 14% of patients [18]. Here, the elderly population is primarily at risk for severe disease, as adults over 65 years of age accounted for approximately 80% of hospitalizations [19, 20]. Additionally, prolonged disease, delayed viral clearance, and a higher fatality rate is also reported to be age-related [21].

Although vaccination is key to prevent infections, vaccine responses are often found to be lower in elderly adults. In numerous studies, the markedly reduced vaccine success in older adults has been attributed to adaptive immunosenescence. Reduced vaccination success in elderly adults is especially known for hepatitis B, pneumococcal, and influenza vaccinations [22, 23]. Although hallmarks of immunosenescence depend on multifaceted factors and vary greatly between individuals, they are considered to be related to i) the decreased ability to respond to new antigens associated with a reduced peripheral plasmablast response; (ii) decreased capacity of memory T cells and (iii) a low level of persistent chronic inflammation. This leads to declining immune efficiency and fidelity, resulting in

increased susceptibility to infectious diseases and decreased response to vaccinations [23-26].

With the experience from previous vaccinations, the question arose whether there are also differences in the immune response between younger and older people after immunization against SARS-CoV-2. We therefore started a daily practice study in a nursing home immediately after the start of the official vaccination campaign in Germany at the end of December 2020. In order to accommodate two distinctly different populations in this study, we compared the induction of immune responses between young and older vaccinees (< 60 years and > 80 years, respectively) who received their first and second vaccination on the same day. For this purpose, IgG titers against SARS-CoV-2 spike S1 and neutralization titers were determined after both the first and the second vaccination since antibody titers and in particular, neutralization titers, together with T-cell responses are the main arms of the adaptive immune response and hence, levels of protection are suggested to be potentially estimated based on neutralizing antibody titers [27]. Finally, the self-reported side effects corresponding to the sum of symptoms after vaccination were examined for a potential correlation between the severity of the symptoms and antibody response.

## **Methods**

### **Study population**

The ethics committee of the Medical Faculty at the Heinrich-Heine University Düsseldorf, Germany (study no. 2021-1287), approved the study. Participants were volunteers from the SBK nursing home in Cologne, Germany. Characteristics of the study population are summarized in Table 1. Informed consent was obtained from all volunteers (N = 179) before sampling.

### **Medical questionnaires**

In order to assess the subjective perception of post-vaccination reactions, medical questionnaires including the following categories were scored according to the sum of reported reactions: i) elevated temperature and fever, ii) chills, iii) pain at the injection site, iv) head/limb pain, v) fatigue/tiredness, vi) nausea/dizziness, vii) other complaints (unscored).

### **Sample processing:**

All blood samples were collected on January 15<sup>th</sup>, 2021 (first collection, 17—19 days after first immunization) and February 5<sup>th</sup>, 2021 (second collection, 17 days after second immunization) and stored at 4 °C. Samples were subjected to the respective assays within 72h after each collection. For cross validation, a subset of samples from the first blood collection were run during analysis of samples from the second blood collection. Positive and negative samples, which were previously tested, were included in all assay.

### **Commercially available Anti-SARS-CoV-2 tests systems**

Samples were tested for Anti-SARS-CoV-2 antibodies using two commercially available test systems: Euroimmun Anti-SARS-CoV-2-QuantiVac-ELISA measuring IgG levels against SARS-CoV-2 spike S1 subunit and Abbott Architect SARS-CoV-2 IgG recognizing SARS-CoV-2 nucleocapsid (N) antibodies.

Euroimmun ELISA was performed on the Euroimmun Analyzer I-2P according to the manufacturer's instructions. The assay encompasses a 6-point calibration curve and issues the IgG antibody concentration as standardized units (BAU/ml = Binding Antibody Units). Results  $< 25.6$  BAU/ml were considered as negative,  $\geq 25.6$  BAU/ml  $\leq 35.2$  BAU/ml as indeterminate, and  $> 35.2$  BAU/ml as positive. The lower detection limit for undiluted samples was  $< 3.2$  BAU/ml, the upper detection limit was  $> 384$  BAU/ml. For samples over the detection limit, 1:10 or 1:100 dilutions were performed in IgG sample buffer according to the manufacturer's instruction. The SARS-CoV-2 IgG chemiluminescent microparticle immunoassay (CMIA) from Abbott was performed on an ARCHITECT i2000 SR after the second blood collection. The relation of chemiluminescent RLU and the calibrator is given as the calculated index (S/C). An index (S/C)  $< 1.4$  as was considered negative,  $\geq 1.4$  was considered positive.

## **In-house SARS-CoV-2 neutralization test**

A serial dilution endpoint neutralization test [28] with the infectious SARS-CoV-2 isolate (EPI\_ISL\_425126) was performed in a BSL-3 facility to determine the SARS-CoV-2 neutralization capacity of the serum samples after the first and second vaccination. Serial dilutions of heat-inactivated (56°C, 30 minutes) serum samples were pre-incubated in cell-free plates with 100 TCID<sub>50</sub> units of SARS-CoV-2 for 1 hour at 37° C. After pre-incubation, 100µl of cell suspension containing 7×10<sup>4</sup>/ml Vero cells (ATTC-CCL-81) were added. Plates were incubated at 37°C, 5% CO<sub>2</sub> for 4 days before microscopic inspection for virus-induced cytopathic effect (CPE). The neutralization titer was determined as the highest serum dilution without CPE. Tests were performed as independent duplicates for each sample. Positive, negative, virus only, and cell growth controls were run during each assay.

## **Statistical analysis**

The data were analyzed using SPSS Statistics 25 (IBM<sup>®</sup>) and GraphPad Prism 9.0.00 (GraphPad Software, San Diego, CA, USA). Categorical data were studied using Fisher's exact test or Pearson's chi-square test, depending on the sample size. Quantitative data were analyzed by the non-parametric Mann-Whitney U test for two groups of paired and unpaired samples. Simple linear regression was performed using GraphPad Prism version 9.0.0 (the coefficient of determination R<sup>2</sup> and p-values are given in the figures).

## **Results**

### **Participant characteristics**

In total, blood samples from 176 volunteers, young and elderly vaccinees (<60 / >80 years of age) were analysed for vaccine-induced SARS-CoV-2 spike specific IgG titers and SARS-CoV-2 neutralizing antibodies after a prime and boost vaccination campaign using BNT162b2 (Comirnaty Biontech/Pfizer) to screen for age-related differences in their immune response. Therefore, samples were collected at two time points, 17—19 days after the first vaccination and 17 days after the second vaccination. To be able to distinguish the immune response of the vaccinees from



those who had already undergone a previous SARS-CoV-2 infection we also determined infection-induced SARS-CoV-2 nucleocapsid specific antibodies using the SARS-CoV-2 IgG chemiluminescent microparticle immunoassay (CMIA). Three vaccinees were tested positive and therefore were excluded from the dataset. While group sizes were comparable (93 participants <60 years of age versus 83 participants >80 years of age), there was an overrepresentation of female participants compared with males (124 female to 52 male) (Table 1).

### **Vaccination-induced SARS-CoV-2 spike specific IgG levels differ between young and elderly vaccinees after the first and second vaccination**

The first sample collection was carried out 17—19 days after the volunteers received their first vaccination in late December 2020. At this time point, quantitative SARS-CoV-2 spike S1 specific IgG levels between the two groups differed significantly ( $p < 0.0001$ ). For the younger group of vaccinees, IgG titers ranged between 0—3840.0 BAU/ml with a mean of 313.3 BAU/ml after the first vaccination. Only 4.4 % of the participants had titers below the cut-off, and 2.3% were indeterminate (Figure 1A). The mean titer for the group > 80 years of age was 41.2 BAU/ml with titers ranging from 0—484.7 BAU/ml. In this group, 65.9% showed titers below the cut-off (>35.6), and 9.4% were indeterminate.

The second sample collection was carried out 17 days after the volunteers received their second vaccination, at a time point when full protection is suggested (>7 days according to [5]). Nevertheless, there was still a significant difference in IgG levels between the two groups ( $p < 0.0001$ ). The mean titer of the younger group increased more than 10-fold (3702.0 BAU/ml) and ranged from 81.6—32000.0 with no participant testing below cut-off (Figure 1B). While the mean titer for elderly vaccinees increased to 1332.0 BAU/ml (0—16891.0 BAU/ml), 10.6% of the participants in this group still had titers below the cut-off.

The comparison of SARS-CoV-2 spike specific IgG titers showed an extremely significant ( $p < 0.0001$ ) difference between the two age groups, after both the first and second vaccination, suggesting an attenuated antibody response in the group of elderly vaccinees > 80 years of age. While the gap in mean values narrowed after



the second vaccination, which in particular underlines once again the necessity of a second vaccination, several elderly participants remained below the detection limit of the anti-SARS-CoV-2 assay. A general age-dependent negative correlation in SARS-CoV-2 spike specific IgG after both vaccinations is noticed throughout the entire cohort (Figure 1D/1E).

### **Elderly vaccinees showed reduced SARS-CoV-2 neutralizing capacity compared to younger vaccinees**

We next determined the neutralization capacity in our cohort after the first and second dose of vaccination. At 17—19 days after the first vaccination, the majority of participants, regardless of their age, failed to display neutralizing antibody titers. In the group of younger vaccinees, 16.1 % displayed neutralizing antibodies with titers ranging between 1:10 to 1:2560. In the group of elderly vaccinees, only 1.2 % had developed neutralizing antibodies after the first vaccination (Figure 2A).

After the second dose, a neutralization titer was attained by 97.8% of the younger vaccinees. In the elderly group, 68.7% showed titers ranging from 1:10 to 1:320. Remarkably, in 31.3% of the elderly vaccinees neutralizing antibodies were not detectable after the second vaccination, and thus, were potentially without seroprotection (Figure 2B).

### **The severity of post-vaccination reactions does not correlate with antibody response**

To assess differences in post-vaccination reactions between the age groups and to evaluate a potential correlation with antibody titers, medical questionnaires were completed at the two collection time points.

After the first vaccination, half of the younger cohort (51.6%) reported no reactions to the vaccination, the remaining vaccinees recorded reactions with a score ranging between 1 and 4 of combined reactions. In turn, 93.9 % of elderly vaccinees reported no post-vaccination reactions; the remaining 6.1% reported either one or two of the scored reactions (Figure 3A).

After the second dose, only 25.8% of the younger vaccinees had no post-vaccination reactions. While 38.7% of this group reported only one of the scored post-vaccination reactions, 35.5% reported a combination of reactions scoring between 2 and 6. Among the elderly, 83.1% reported no reaction, and the remaining 16.9% of this group reported combined reactions up to a score of 3 (Figure 3B). However, there was no general correlation between vaccination-induced SARS-CoV-2 spike specific IgG or neutralizing antibody production and the presence or absence of individual post-vaccination reaction reports.

## Discussion

The SARS-CoV-2 pandemic has led to the development of various vaccines and vaccine strategies, which have been made available to the public by either emergency use designation or conditional marketing authorization. Inevitably, data on populations that are difficult to enroll, including immunocompromised or cohorts <16 years or >80 years who might show reduced vaccine reactivity, are limited. The main goal of this real-life study was to investigate the immunogenicity of the current vaccination strategy in the most vulnerable group of vaccinees (>80 years old) compared to those younger than 60 years who received the Biontech/Pfizer BNT162b2 COVID-19 vaccination. We compared the induction of immune responses in these two age groups after the first and second vaccination by measuring vaccine-induced SARS-CoV-2 spike specific IgG and SARS-CoV-2 neutralizing antibodies. While the majority of both young and elderly vaccinees raised IgG responses after their second vaccination, the induction of ELISA-IgG and in particular neutralizing antibody levels were significantly lower in the elderly vaccinees.

The main differences between the two groups are likely a consequence of immunosenescence, which describes the reduced adaptive immune responses in the elderly [29]. It is well described that elderly individuals not only have higher rates of morbidity due to infection but also respond less to vaccination [30-32], mainly due to a decline in cellular as well as humoral immunity. For vaccinations including the influenza vaccine, this limitation is bypassed by increasing the vaccine doses [33].

The notion that humoral vaccination responses are impaired with increasing age is well depicted in our cohort, as the mean titer of SARS-CoV-2 spike specific IgG remained 2.8-fold lower after the second vaccination for the elderly group of vaccinees compared to the younger cohort (Figure 1B). Additionally, a general intra- and inter-group trend in negative correlation between age and IgG titer is visible after both vaccinations (Figure 1C/1D). More importantly, a similar age-dependent trend can be seen for SARS-CoV-2 specific neutralizing antibody titers: While neutralization antibody titers were attained by 97.8% of the younger vaccinees, 31.3% of the elderly remained without neutralization antibody titers after the second vaccination (Figure 2B).

The lack of neutralizing antibody responses in about one-third of the elderly group raises the questions whether the effectiveness of vaccine-induced immune protection may be transferred to this population without explicit testing. In a large cohort study using the Biontech/Pfizer vaccine BNT162b2 and the related BNT162b1 vaccine candidate, the humoral responses in two adult age groups (18-55 and 65 to 85 years) were compared after the second vaccination. They reported that immunogenicity as measured by antibody responses including neutralization titers was lower in the elderly cohort and also discussed immunosenescence as potential cause [34]. The role of neutralizing antibodies is in particular crucial since neutralizing antibody levels correlate with protection against many viruses including SARS-CoV-2 in humans [35, 36] and recent data suggest that high neutralizing titers are particularly important for protection against novel circulating SARS-CoV-2 variants conferring immune escape [37-39].

Currently, different vaccination schedules for the same vaccines have been adopted in several countries. These include a delay of the second vaccination, as implemented by the UK or Israel, to allow for the initial primary vaccination to a larger proportion of the population, a strategy that is controversially discussed [40, 41]. The observation that single-dose vaccinees broadly lacked neutralizing antibody responses in our cohort raises the question, whether these individuals might still acquire infections and may transmit the disease while remaining asymptomatic. This assumption is supported by recent results of a large Israeli study which reports a 46% effectiveness in preventing a documented infection 14 to 20 days after the first dose, the BNT162b2 vaccine [13]. Smaller studies report similar results with

incomplete Biontech/Pfizer vaccinations [16, 17]. However, other large scale population studies on the experience with COVID vaccinations report that even after the first mRNA SARS-CoV-2 vaccination, a significant decrease in hospitalizations and severe disease is seen in the overall vaccinated population, but also the >80 year old group [38]. These reports emphasize that not only direct protection of vulnerable groups but also indirect protection by generating a community immunity can contribute to the decrease of severe COVID cases, hospitalizations and death, which ultimately eases the economic burden of the pandemic. However, it is not yet clear how long this protective effect of mRNA vaccination lasts, hence monitoring effectiveness after the vaccine deployment is inevitable [42].

Our data presented here suggests that it might be necessary to have strategies at hand to overcome possible age-related limitations for COVID-19 vaccination. Moderna has recently demonstrated an increased immune response determined by higher binding and neutralizing antibody titers by increasing the dose of the second vaccination from 25  $\mu$ l to 100  $\mu$ l [14]. Strategies to enhance immunogenicity such as the use of adjuvants, application of increased amounts or multiple doses of the same vaccine, or the combination of different vaccines for a heterologous prime/boost should be rapidly tested and implemented in COVID-19 vaccination protocols where necessary.

This study provides insight into age-dependent limitations of immune responses elicited after the first and second dose of the BNT162b2 vaccine. By comparing similar-sized cohorts of vaccinees aged < 60 years and > 80 years, we found that more than 30% of elderly vaccinees did not attain neutralizing antibody responses after their second vaccination. Despite the fact that the elderly age group is most vulnerable, this population was underrepresented in previous studies. Nevertheless, promising studies show that even after the first vaccination with the mRNA vaccines, at least severe courses of COVID-19 are attenuated.

## Notes

Author contributions: Conceptualization: HS, OA, MA, LM, Formal analysis: OA, WM, Investigation: LM, MA, WM, ID, LW, RG, JP, JH, AR, DR, OA, HS, Writing – original draft preparation: HS, OA, MA, LM, Writing – review and editing: LM, MA, WM, ID, LW, RG, JP, JH, AR, DR, PNO, RR, SH, AW, CM, RG, JT, OA, HS, Supervision: HS, OA, MA, LM

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**Table 1:** Characteristics of the study population.

**Figure 1**

SARS-CoV-2 spike protein specific antibody titers were determined using Euroimmun Anti-SARS-CoV-2-QuantiVac-ELISA. Antibody titers below the detection limit were set to 1.0. **A** and **B** Antibody titers 17—19 day after first (A) and second (B) vaccination are shown. Boxes span the interquartile range; the line within each box denotes the median and whiskers indicate the 2.5 and 97.5 percentile values. **C** The pairwise comparison of IgG antibody titers within the two analysed age groups are shown. **D** and **E** Linear correlations between participant's age and SARS-CoV-2 specific antibody titer after first vaccination (D) and second vaccination (E). Results < 25.6 BAU/ml as negative (red area),  $\geq 25.6$  BAU/ml  $\leq 35.6$  BAU/ml as indeterminate (orange), and > 35.6 BAU/ml were considered positive. For comparison of two groups either two-tailed parametric unpaired t-tests or paired t-test were performed. Correlation was analysed by simple linear regression. P-values < 0.05 were considered statistically significant. P-Values are depicted in the figures.

**Figure 2**

Neutralization antibody titers were determined as described in the methods section. The frequencies of individuals with a certain neutralizing antibody titer after the first vaccination (A) and the second vaccination (B) are shown.

**Figure 3**

Post-vaccination reaction scores after first (A) and second (B) vaccination were determined as the sum of cumulative reactions using to the predefined categories (see method section).

Characteristics	< 60 years of age (younger vaccinees)	> 80 years of age (elderly vaccinees)	Total
<b>Total N (%)</b>	91 (53%)	85 (47%)	176 (100%)
<b>Gender</b>			
Male N (%)	29 (32%)	23 (27%)	52 (30%)
Female N (%)	62 (68%)	62 (73%)	124 (70%)
<b>Mean years (min - max)</b>	42.2 (19.5 - 59.5)	87.9 (80.1 - 100.5)	

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Figure 1

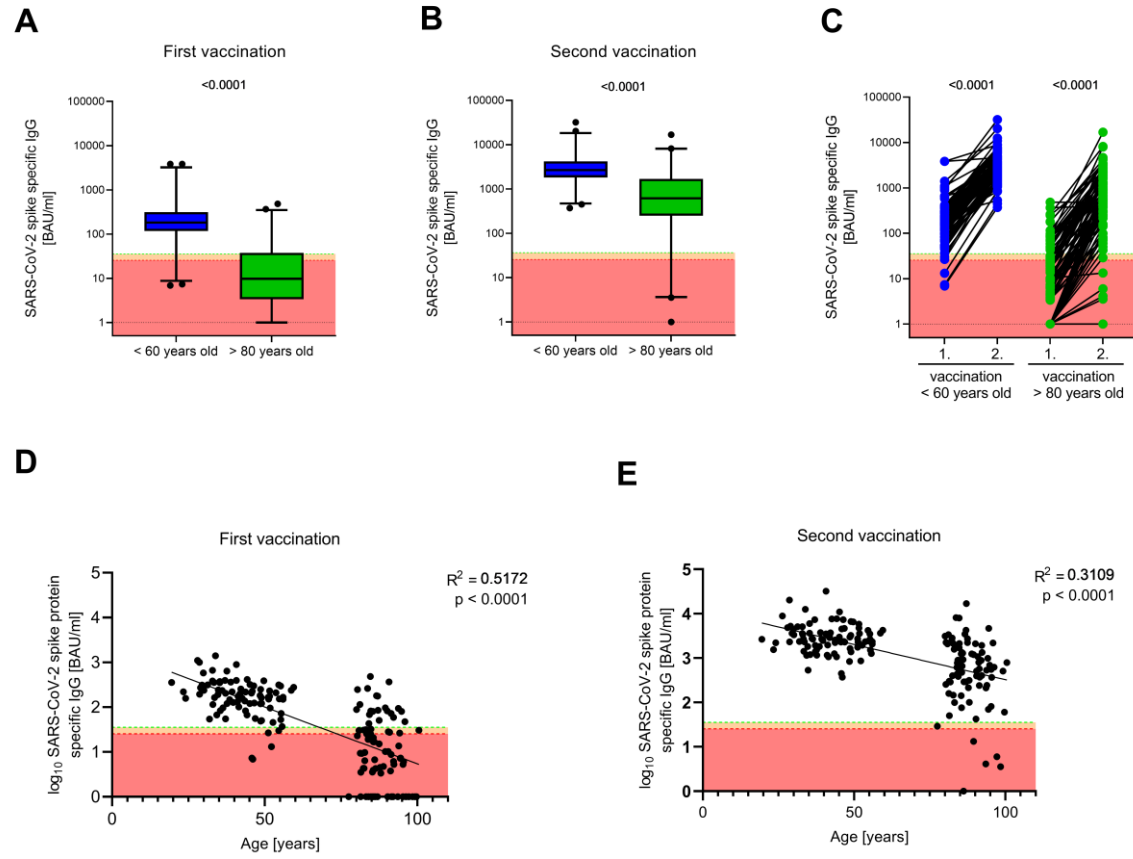


Figure 2

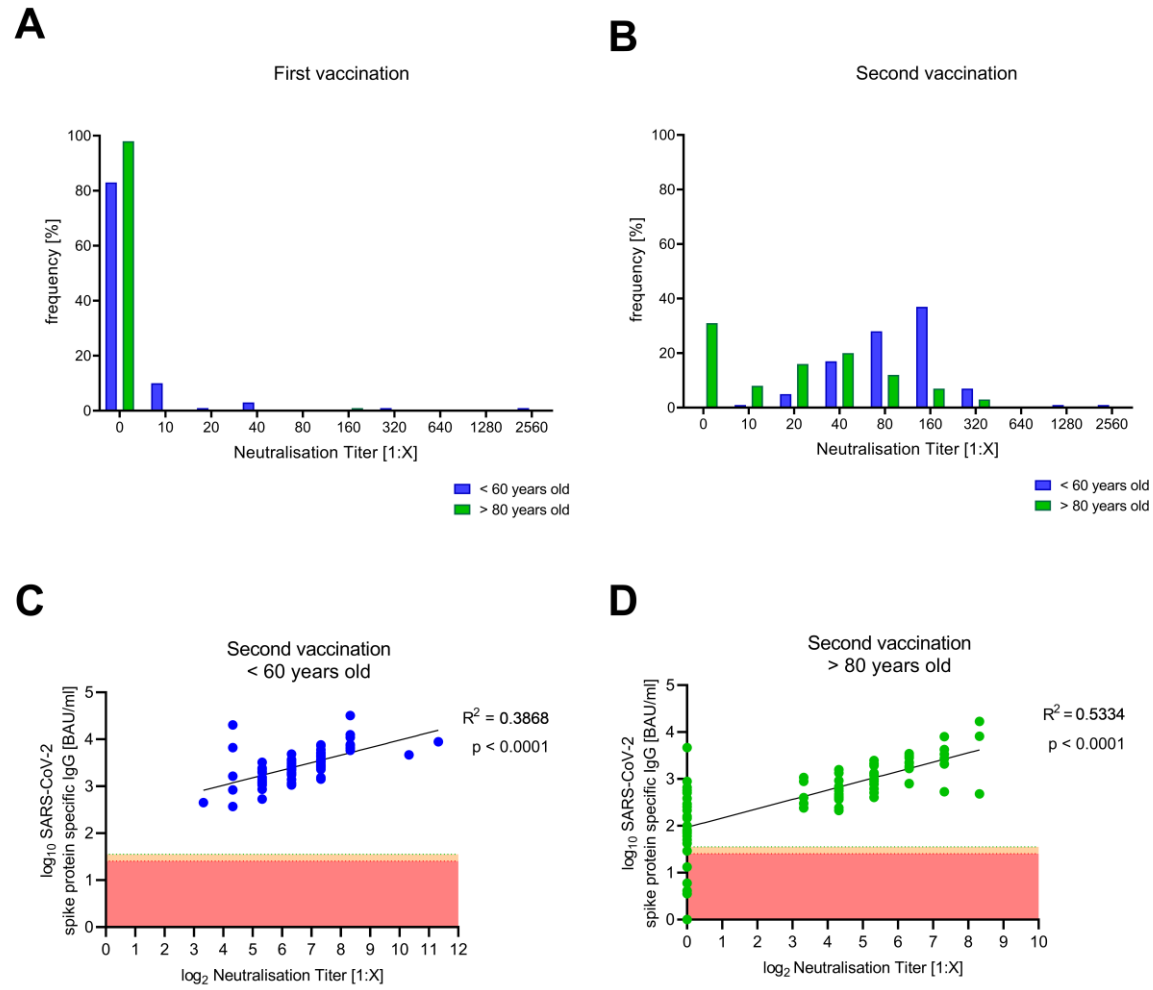


Figure 3

