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Original article

The temporal course of T- and B-cell responses to vaccination with BNT162b2 and mRNA-1273

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ABSTRACT

Objectives: To investigate the response of the immune system (and its influencing factors) to vaccination with BNT162b2 or mRNA-1273.

Methods: 531 vaccinees, recruited from healthcare professionals, donated samples before, in between, and after the administration of the two doses of the vaccine. T- and B-cell responses were examined via interferon- γ (IFN- γ) release assay, and antibodies against different epitopes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (S1 and NCP) were detected via ELISA and surrogate neutralization assay. Results were correlated with influencing factors such as age, sex, prior infection, vaccine received (BNT162b2 or mRNA-1273), and immunosuppression. Furthermore, antinuclear antibodies (ANAs) were measured to screen for autoimmune responses following vaccination with an mRNA vaccine.

Results: No markers of immunity against SARS-CoV-2 were found before the first vaccination. Two weeks after it, specific responses against SARS-CoV-2 were already measurable (median \pm median absolute deviation (MAD): anti-S1 IgG 195.5 \pm 172.7 BAU/mL; IgA 6.7 \pm 4.9 OD; surrogate neutralization 39 \pm 23.7%), and were significantly increased two weeks after the second dose (anti-S1 IgG 3744 \pm 2571.4 BAU/mL; IgA 12 \pm 0 OD; surrogate neutralization 100 \pm 0%, IFN- γ 1897.2 \pm 886.7 mIU/mL). Responses were stronger for younger participants (this difference decreasing after the second dose). Further influences were previous infection with SARS-CoV-2 (causing significantly stronger responses after the first dose compared to unexposed individuals ($p \leq 0.0001$)) and the vaccine received (significantly stronger reactions for recipients of mRNA-1273 after both doses, $p < 0.05$ – 0.0001). Some forms of immunosuppression significantly impeded the immune response to the vaccination (with no observable immune response in three immunosuppressed participants). There was no significant induction of ANAs by the vaccination (no change in qualitative ANA results (p 0.2592) nor ANA titres (p 0.08) from pre- to post-vaccination).

Conclusions: Both vaccines elicit strong and specific immune responses against SARS-CoV-2 which become detectable one week (T-cell response) or two weeks (B-cell response) after the first dose.

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Introduction

Since its appearance in late 2019 [1], the worldwide spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to increasingly drastic public health measures with immense social, political, and economic consequences [2–4]. To achieve a sustainable containment of the pandemic, several vaccines against SARS-CoV-2 have been developed, BNT162b2 and mRNA-1273 being the first to be approved and administered since December 2020. While clinical data of these vaccines—both from the clinical trials [5–7] and ‘real-world’ data from their application in the field [8–10]—appear promising, their effects on the recipients’ immune systems remain to be studied further. On the one hand, the efficacy of the vaccines, as measured by the detection of assumed correlates (both humoral and cellular) of immunity against SARS-CoV-2, needs to be well characterized. On the other hand, possible autoimmune events associated with the vaccines should be closely monitored, especially as there is considerable uncertainty among the general population concerning mRNA-based vaccines owing to the novelty of their use in humans [11] as well as the unusually rapid process of their development and approval. To dispel this uncertainty, as well as to cast further light on the development of assumed immunity against SARS-CoV-2 after vaccination, is the goal of this study.

To this end, we examined the serological status of 531 vaccinees before, during, and after vaccination against SARS-CoV-2, measuring different components of the immune response to the vaccination: binding antibodies against different target antigens of SARS-CoV-2 (the S1-subunit of the spike protein (anti-S1) as well as the nucleocapsid protein (anti-NCP)), the neutralizing capacity anti-S1 IgG, and the specific T-cell response (via a SARS-CoV-2-specific interferon- γ release assay (IGRA)). Further, we examined antinuclear antibodies (ANAs) as a broad screening for the detection of antibodies against nuclear antigens, including mRNA. We hypothesized that: (a) prior to the vaccination, the seroprevalence would be low, (b) vaccinees would develop antibodies specifically against the S1-subunit of the spike protein (and not against NCP), (c) in addition to the antibody response, vaccinees would develop a specific T-cell response against SARS-CoV-2, and (d) vaccinees would show no development of antibodies against nuclear antigens, including RNA, as a consequence of the vaccination.

Methods

General design of the study

The study consisted of a series of tests performed on samples donated by the participants at different time points during the course of their vaccination against SARS-CoV-2. At the first time point (t_1), shortly before or after the first dose of the vaccine, the sera were tested for anti-SARS-CoV-2 antibodies, ANAs, as well as the T-cell response (via IGRA). For analytical purposes, all samples collected within 6 days after the first dose of vaccine were considered as t_1 (as not all participants were able to donate samples prior to the first dose). At a second time point (t_2), 2 weeks after the first dose of the vaccine, anti-SARS-CoV-2 antibodies (IgG, IgA and neutralizing antibodies) were measured again. At a third time point (t_3), 2 weeks after the second dose of vaccine, all participants were again tested for anti-SARS-CoV-2 antibodies (IgG, IgA and neutralizing antibodies), ANAs, and their T-cell response (IGRA).

Study population and vaccination programme

Participants were recruited from healthcare workers of a German university hospital, who were prioritized to receive a

vaccination against SARS-CoV-2 by the German SARS-CoV-2 vaccination roll-out campaign. More detailed information about the vaccination programme can be found in the [Supplementary Material](#).

For analytical purposes, data on age, sex and the specific vaccine received were collected from each participant. Other data, such as on immunosuppressive medication received by the participants, were disclosed voluntarily by some participants but not collected systematically.

All participants provided written informed consent. The study was approved by the University of Kiel institutional review board (AZ: D642/20). The study was conducted in accordance with the Declaration of Helsinki [12].

Anti-SARS-CoV-2 antibodies

Anti-S1 antibodies of the classes IgA and IgG, and anti-NCP IgG, were measured via ELISA using kits by EUROIMMUNE (Lübeck, Germany) according to the manufacturer’s instructions. Anti-S1 was chosen as the target antigen, as it is a main part of the immunogenic antigen induced via vaccination with BNT162b2 or mRNA-1273. Anti-NCP was chosen to detect possible unrecognized infections with SARS-CoV-2, as antibodies against NCP are not to be expected after vaccination. Further information on the interpretation of these assays can be found in the [Supplement Material](#).

Neutralizing antibodies (ELISA)

Neutralizing antibodies were examined via the SARS-CoV-2-NeutraLISA surrogate neutralization assay (EUROIMMUN, Lübeck, Germany), according to the manufacturer’s instructions. Further information on this assay can be found in the [Supplementary Material](#).

Interferon- γ release assay (IGRA)

The T-cell response to the vaccination against SARS-CoV-2 was examined using an interferon- γ release assay (IGRA; EUROIMMUN, Lübeck, Germany), according to the manufacturer’s instructions. Further information on the IGRA is provided in the [Supplementary Material](#).

Antinuclear antibodies (ANAs)

ANAs were examined as a broad screening for autoantibodies against nuclear structures at t_1 and t_3 . Indirect immunofluorescence microscopy (IIF) on the substrate HEp-20-10 (EUROIMMUN, Lübeck, Germany) was carried out according to the manufacturer’s instructions. More detailed information on the examination of ANA is provided in the [Supplementary Material](#).

Statistical analysis

For reporting averaged results, the median (measure of dispersion: median absolute deviation (MAD)) was used if not otherwise specified, as the dataset contained many outliers and skewed distributions.

Due to the abovementioned distribution of parts of the data, tests for statistically significant differences in continuous variables between two groups were performed mainly via the Mann–Whitney U test (unless otherwise specified). Tests for correlations between continuous variables were performed by calculating Spearman’s ρ . Statistical significance was assumed for p -values <0.05 . All statistical analyses were performed using the open-source software for statistical computing and graphics R

(version 4.0.4) with the integrated development environment RStudio (Version 1.1.463) [14].

Results

Study population and sample characteristics

Overall, 531 participants were recruited. Of these, 389 (73.3%) were female. The mean age at the time of receipt of the first vaccine dose was 42.2 years (SD \pm 12, range 18–67). There was no statistically significant difference in age between the sexes (t-test t 1.6954, df 269.45, p 0.09116). **Supplementary Material Fig. S1** shows the distribution of age groups in both sexes; 481 participants (90.6%) received BNT162b2 and 50 (9.4%) mRNA-1273, as determined by the availability of the vaccines.

Most but not all samples were collected at the time scheduled by the study protocol. The median absolute deviations (MADs) of the day of sample collection for the different time points were: $t_1 \pm 1.5$ days, range –6 to 27 days (of these, only those collected up until day 6 post-vaccination were included in calculations of the baseline serological status, as no vaccine-induced antibodies were to be expected within this time frame); $t_2 \pm 0$, range 9–37, and $t_3 \pm 0$, range 39–77).

Four hundred and twenty-six participants (80.3%) donated samples at all three time points; 82 (15.4%) did so at only two time points, and 23 (4.3%) at only one time point.

All medians (with median absolute deviation and respective group sizes) of all measured values at all time points can be gathered from **Table 1**.

Temporal course of the immune responses to the vaccination against SARS-CoV-2

The first component of the immune response to become detectable was the T-cell response as measured via IGRA, the medians of which first crossed the threshold for positivity (200 mIU/mL IFN- γ) in samples collected on day 7 after vaccination, at 1083 ± 914 mIU/mL. It was followed by anti-S1 IgA (crossing the threshold of 1.1 (OD ratio) at day 10 with 1.23 ± 1.3 (OD ratio)) and anti-S1 IgG (crossing the threshold of 35.2 BAU/mL at day 12 at 128.6 ± 150.4 BAU/mL) as well as neutralizing antibodies (also crossing the threshold of 35% at day 12 with $35 \pm 11.9\%$) (see **Fig. 1**). At t_2 , the responses reached a plateau, with IFN- γ and IgA showing a tendency to decrease again after peaks in samples collected 9 and 17 days post-vaccination, respectively. At t_3 , all measured responses exhibited significantly higher values ($p < 0.0001$) than at t_2 . All time points being considered, all responses showed highly significant correlations of medium to strong effect sizes with the number of days after vaccination (see **Fig. 2**).

Of note, at t_2 , 22 participants did not yet develop an anti-S1 IgG response, and 190 did not develop levels of neutralizing antibodies considered to be reactive. At t_3 , the same is true for only three participants (see 'Influence of Immunosuppression' below).

Influence of different factors on the immune response to the vaccination against SARS-CoV-2

Influence of age

There is a highly significant inverse correlation of medium effect size between values and age at t_2 for both anti-S1 IgG ($R = -0.5$, $p < 0.0001$) and neutralizing antibodies ($R = -0.4$, $p < 0.0001$). At t_3 , the same correlation can be observed with only small effect sizes for both anti-S1 IgG ($R = -0.26$, $p < 0.0001$) and neutralizing antibodies ($R = -0.23$, $p < 0.0001$; see **Fig. 3**). For anti-S1 IgA, this correlation can only be shown at t_2 ($R = -0.32$,

Table 1
Average values (reported via medians \pm median absolute deviation) for all measured markers at all time points, including the respective group sizes, for the whole cohort and the following subgroups: women, men, participants previously infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), participants having received BNT162b2, and participants having received mRNA-1273

Group	t_1 (0–6 days after first dose)			t_2 (14 days after first dose)			t_3 (14 days after second dose)			
	IFN- γ (mIU/mL)	Anti-S1 IgA (OD ratio)	Anti-S1 IgG (BAU/mL)	Neutralizing antibodies (%)	Anti-S1 IgA (OD ratio)	Anti-S1 IgG (BAU/mL)	IFN- γ (mIU/mL)	Anti-S1 IgA (OD ratio)	Anti-S1 IgG (BAU/mL)	Neutralizing antibodies (%)
Whole cohort	14.3 \pm 21.2	0.3 \pm 0.2	<1	5 \pm 5.9	6.7 \pm 4.9	195.5 \pm 172.7	1897.2 \pm 886.7	12 \pm 0	3744 \pm 2571.4	100 \pm 0
Women	12.6 \pm 18.7	0.3 \pm 0.2	<1	6 \pm 4.4	6.3 \pm 4.9	190.4 \pm 167	1859.3 \pm 958.8	12 \pm 0	3830.4 \pm 2585.7	100 \pm 0
Men	21.7 \pm 32.1	0.3 \pm 0.3	<1	4 \pm 4.4	8.2 \pm 5.3	219.8 \pm 187.9	1901.6 \pm 883.2	12 \pm 0	3564.8 \pm 2495.5	100 \pm 0
Previously infected	1875.4 \pm 906.5	3.7 \pm 4.5	110 \pm 39.4	40 \pm 5.9	12 \pm 0	3753.6 \pm 3415.9	2203.6 \pm 401.7	12 \pm 0	3323.2 \pm 517.1	100 \pm 0
BNT162b2	12.7 \pm 18.8	0.3 \pm 0.2	<1	6 \pm 4.4	6.2 \pm 4.8	183.4 \pm 155.4	1807.2 \pm 1016.9	12 \pm 0	3654.4 \pm 2571.4	100 \pm 0
mRNA-1273	18.4 \pm 23.4	0.5 \pm 0.2	<1	3 \pm 5.9	11.0 \pm 1.4	512 \pm 415.1	2471 \pm 35.4	12 \pm 0	4926.4 \pm 3598.6	100 \pm 0

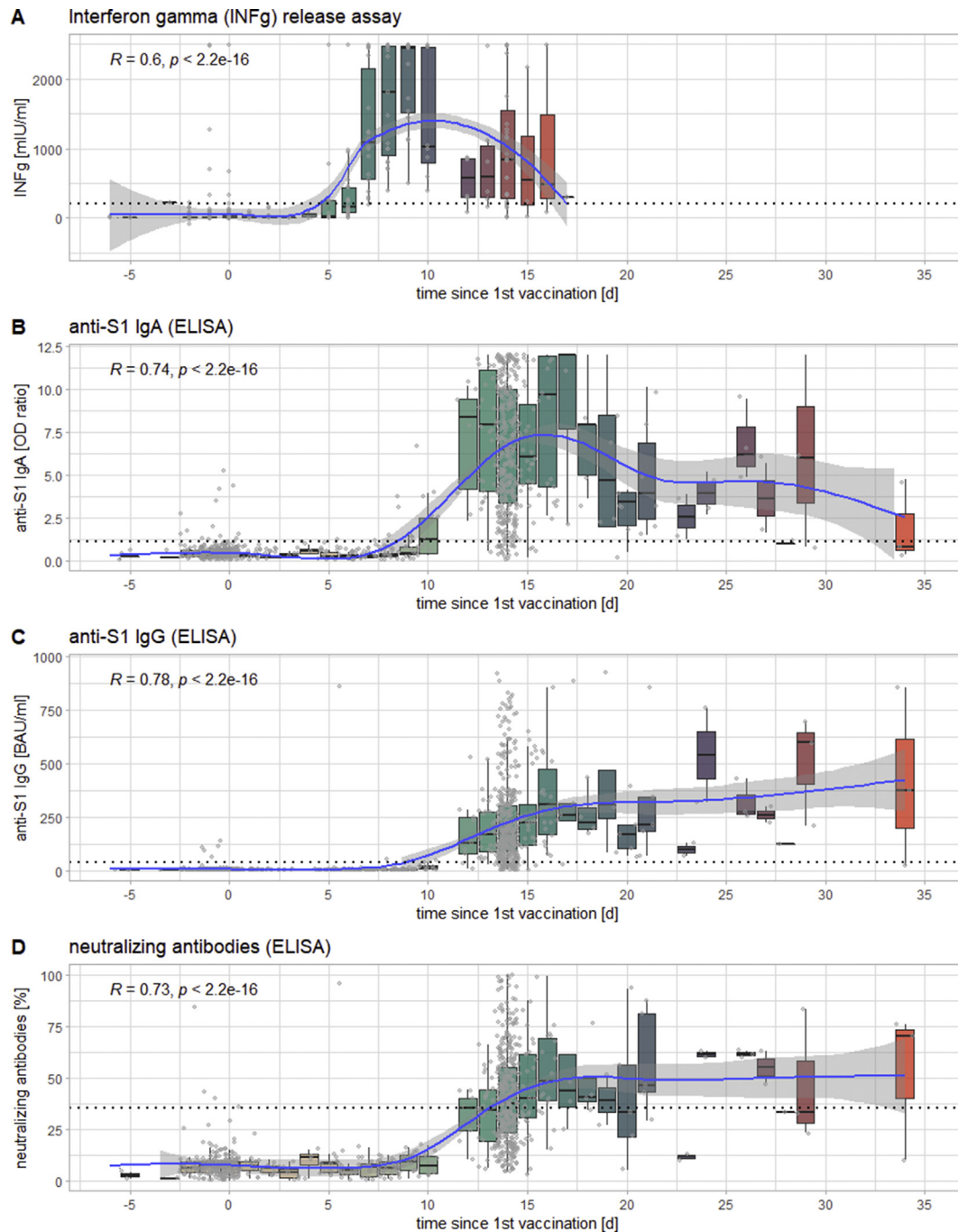


Fig. 1. Timeline of the inter-individually measured kinetics of the different markers of the immune response to the first dose of the vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presented as a function of days after the administration of the first dose: T-cell response as measured via interferon- γ release assay (IGRA) (panel A), anti-S1 IgA (panel B), anti-S1 IgG (panel C), and neutralizing antibodies (panel D). Each box-plot represents 1 day from administration of the first dose, the jittered dots represent each individual measurement. The blue line indicates the smoothed means, with a grey confidence band of 95%. In the upper left-hand corner of each panel is Spearman's ρ for the correlation of x (days since first dose) and y (levels of the respective marker) of each panel, as well as its p -value. The dotted line indicates the respective cut-offs for positivity/reactivity of the different markers.

$p < 0.0001$). For IFN- γ via IGRA (which was not performed at t_2) an inverse correlation with age of only negligible effect size can be observed at t_3 ($R = -0.13, p 0.004$).

Influence of prior infection with SARS-CoV-2

We could identify five participants with a self-reported, anamnestic history of coronavirus disease 2019 (COVID-19). These individuals already showed detectable immune responses against

SARS-CoV-2 (including anti-NCP IgG) at t_1 (anti-S1 IgG 110 ± 39.4 BAU/mL; anti-S1 IgA 3.7 ± 4.5 (OD ratio); neutralizing antibodies $40 \pm 5.9\%$; IFN- γ (IGRA) 1875.4 ± 906.5 mIU/mL), which increased dramatically in size at t_2 (anti-S1 IgG 3753.6 ± 3415.9 BAU/mL; anti-S1 IgA 12.0 ± 0 (OD ratio); neutralizing antibodies $100 \pm 0\%$), reaching levels observed only after the second dose of the vaccination in previously uninfected individuals. For anti-S1 IgA, IgG and neutralizing antibodies, this difference between previously infected

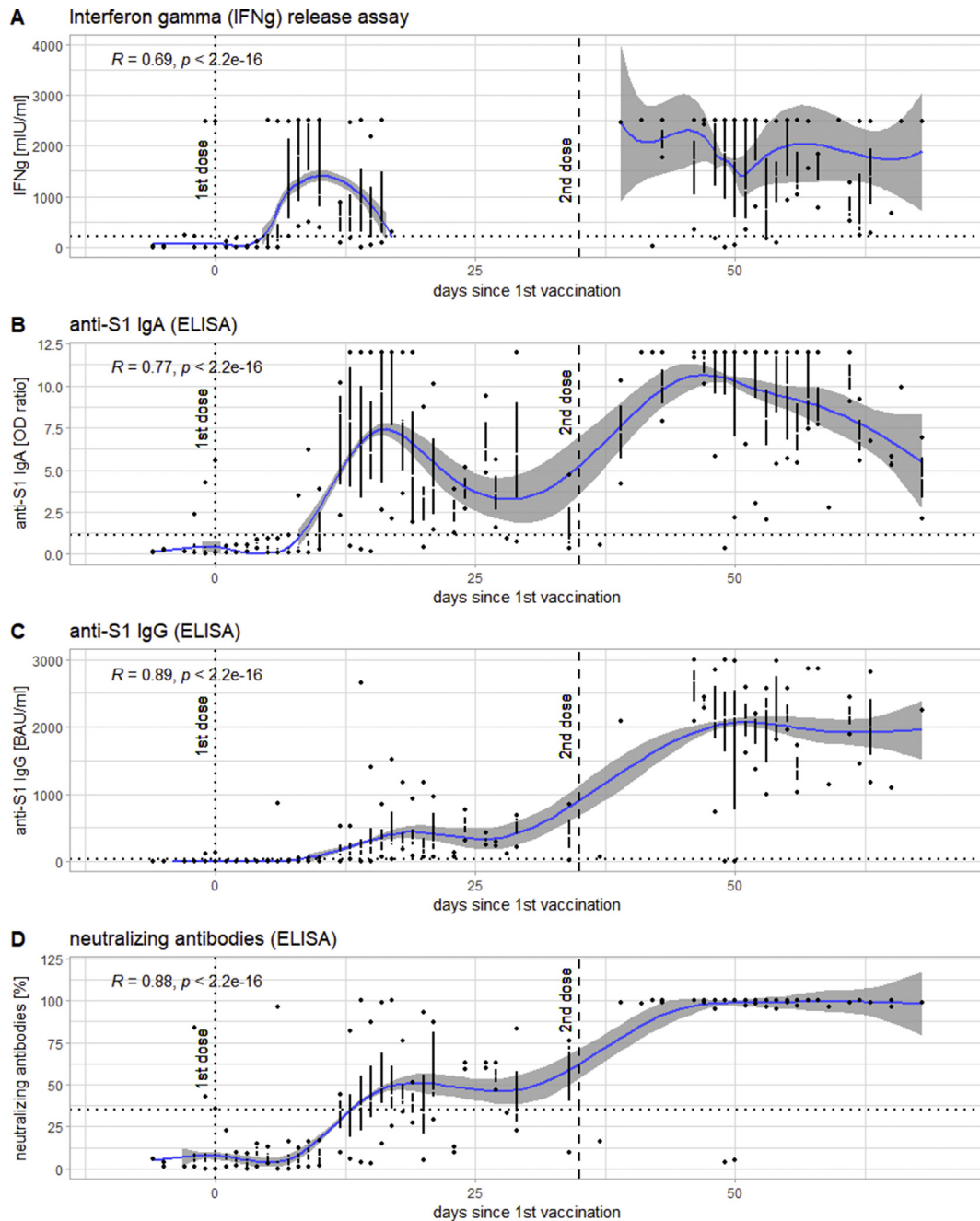


Fig. 2. Levels of the different serological markers in the course of the administration of both doses of the vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presented as a function of days since the first dose of the vaccine: interferon- γ release assay (IGRA) (panel A), anti-S1 IgA (panel B), anti-S1 IgG (panel c), and neutralizing antibodies (panel D). The results for each day are represented as a Tuftes boxplots (the line representing the interquartile range (IQR), the gap in it the median, the dots above and below the ends of the whiskers). The blue line indicates the smoothed means with a 95% confidence band around it. The dotted line indicates the time of the first dose, the dashed line that of the second dose of the vaccine. In the upper right-hand corner is Spearman's ρ for the correlation between x and y for the whole period of time examined.

and uninfected individuals at t_2 is statistically significant ($p \leq 0.0001$). At t_3 , their responses (especially anti-S1 IgG 3323.2 ± 517.1 BAU/mL) did not increase further in size.

Influence of immunosuppressive medication

Eleven participants disclosed receiving immunosuppressive medication. While eight of these (receiving dimethylfumarate, methotrexate, adalimumab or certolizumab) did not show reduced immune responses compared to the rest of the cohort, three participants (receiving rituximab, fingolimod and mycophenolate plus

belatacept, respectively) showed no immune response at any time point. Of note, information about immunosuppressive medication received by the vaccinees was not collected systematically but relied on the voluntary disclosure of this fact by participants during the course of the study.

Influence of the vaccine received (mRNA-1273 versus BNT162b2)

At t_2 , significantly higher values ($p < 0.0001$) could be measured for anti-S1 IgG (512 ± 415.1 versus 183.4 ± 155.4 BAU/mL), anti-S1 IgA (11.0 ± 1.4 versus 6.2 ± 4.8 (OD ratio)) and neutralizing

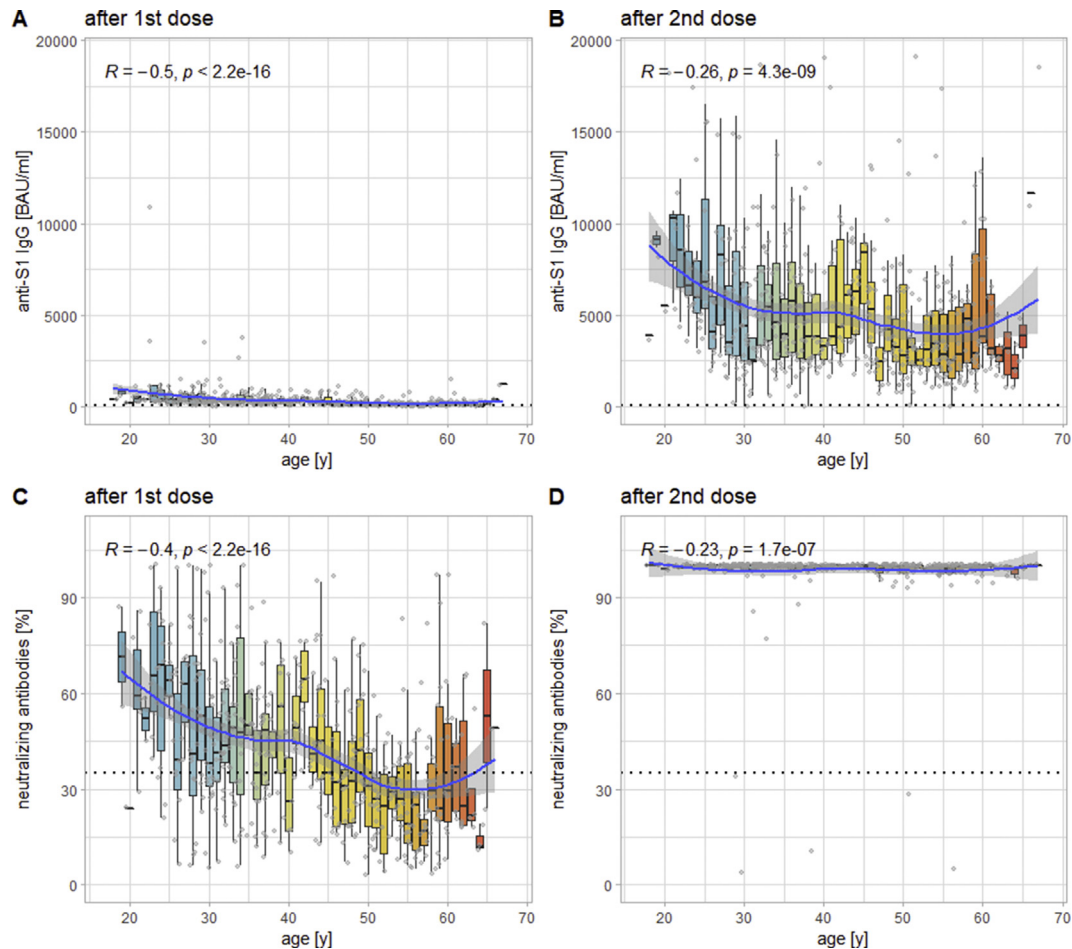


Fig. 3. Levels of anti-S1 IgG (panel A) and neutralizing antibodies (panel B) as a function of recipients' age at t_2 (14 days after the first dose of vaccine); panels C and D show the same analysis for t_3 (14 days after the second dose of the vaccine). Each box-plot represents 1 year, each (jittered) point one individual measurement. The blue line indicates the smoothed means with a 95% confidence band. The dashed lines indicate the respective cut-offs for positivity. In the upper left-hand corner is Spearman's ρ for the correlation between recipients' ages and levels of the different markers.

antibodies (60.5 ± 25.2 versus 37 ± 23.7) for patients receiving mRNA-1273 compared to BNT162b2. At t_3 , this difference could still be shown for anti-S1 IgG ($p = 0.0453$) and for IFN- γ via IGRA (which was not performed at t_2 ; $p = 0.0051$). Importantly, these differences cannot be explained by age differences between recipients of different vaccines as statistical analyses revealed none (t-test $t = -1.245$, $df = 58.821$, $p = 0.2181$). See Fig. 4 for this comparison for anti-S1 IgG and neutralizing antibodies.

Influence of sex

At no time point was there any relevant difference in any of the measured immune responses between the two sexes (no participant having self-declared a non-binary sexual identity).

Anti-nuclear antibodies (ANAs)

The detailed results of the examination of ANAs can be found in the [Supplementary Material](#). In brief, no short-term induction of ANAs after vaccination against SARS-CoV-2 could be seen.

Discussion

In general, the results of this study show that adults develop strong and specific immune responses to both examined anti-SARS-CoV-2 mRNA vaccines, at both the T- and the B-cell levels. Almost all participants developed high levels of all examined

markers, while there was no evidence of a vaccine-associated induction of antinuclear antibodies.

While the T-cell response (IFN- γ via IGRA) became detectable 7 days after the first dose of the vaccine on average, the B-cell response (anti-S1 IgA and IgG) did so at 10 or 12 days post-vaccination, respectively. Others have found timelines very similar to ours in intra-individual measurements [15]. This timeline observed by us can be correlated with the clinical observation that the cumulative incidences of unvaccinated and vaccinated individuals start to diverge 12 days [6,8] to 14 days [16] after the first dose. In agreement with our data, this divergence is likely explained by the emergence of measurable levels of anti-SARS-CoV-2 IgG at exactly this point. This assumption is further supported by the fact that one of our participants tested positive for SARS-CoV-2 via PCR 10 days after having received the first dose of BNT162b2. One day prior to this, they had donated a sample already showing a strong T-cell response but at that time no anti-S1 IgG, which suggests that the T-cell response alone, as measured via IGRA, is not sufficient to convey immunity against SARS-CoV-2. Furthermore, the fact that vaccine-induced clinical protection against SARS-CoV-2 becomes detectable at the same time as anti-S1 IgG suggests that relatively low levels of anti-S1 IgG and neutralizing antibodies might already convey at least some degree of clinical protection (median anti-S1 IgG titre between days 12 and 35 after the first dose of the vaccine 193.3 ± 167.9 BAU/mL; median

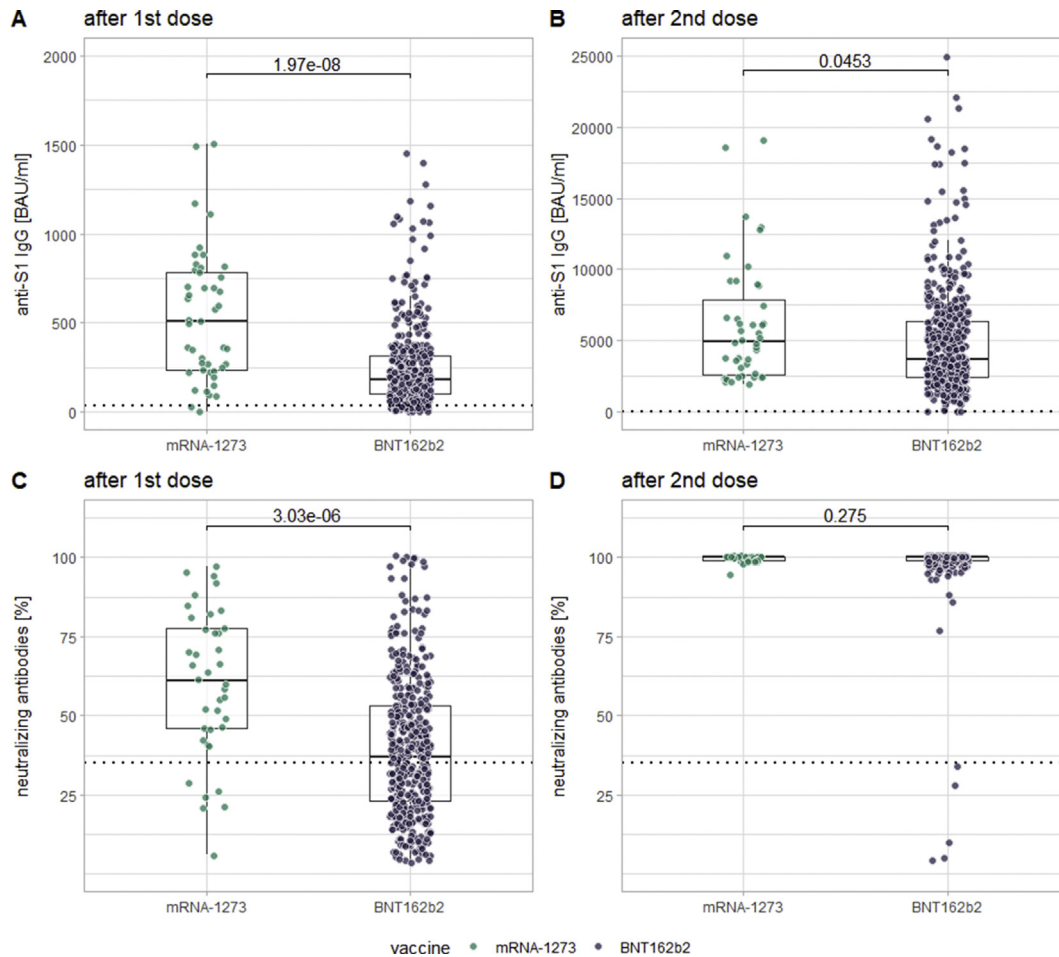


Fig. 4. Comparison of levels of anti-SARS-CoV-2 IgG (panels A and B) and neutralizing antibodies (panels C and D) in between recipients of the two different examined mRNA-vaccines, both after the first dose (panels A and C) and after the second dose (panels B and D) of the respective vaccines.

level of inhibition for the same time frame $38 \pm 23.7\%$). This assumption is supported by findings that even low levels of neutralizing antibodies convey protection against SARS-CoV-2 [17].

The levels of all examined markers increased significantly after the second dose of the vaccine. This increase, and the fact that a considerable share of participants did not develop levels of anti-S1 IgG and/or neutralizing antibodies considered to be reactive after the first dose of the vaccine, are strong arguments in favour of administering both doses of the vaccine to all recipients, especially older ones. While older vaccinees have a general tendency to develop lower anti-S1 IgG titres and levels of neutralizing antibodies than younger vaccinees, this discrepancy is much more pronounced after the first dose of the vaccine than after the second one. Most likely, this is due to immune responses being delayed but also less pronounced in older individuals, a phenomenon generally summarized under the term immunosenescence [18]. A delay in immune responses of older recipients would explain why the age dependency of the markers examined by us is greater after the first dose of the vaccine, while a generally weaker response would explain why this dependency persists after the second dose. The same mechanisms may also underlie the heightened risk in older patients of developing a severe course of COVID-19 [19–21]. Therefore, while all age groups profit from the second dose, in regard to the levels of markers examined by us, older vaccinees do so even more; other studies have shown that this trend continues beyond the age groups we examined [22]. Nevertheless, there is as

yet no evidence to show that different antibody levels translate to different levels of clinical protection against SARS-CoV-2.

Further, three participants did not develop any immune response at any time point, most likely as a consequence of immunosuppressive medication. Although the mechanisms of immunosuppression were very different between these three, both B- and T-cell responses were absent for all of them. Although it can't be proved serologically, it must to date be assumed that a missing seroconversion translates to missing clinical protection against SARS-CoV-2. Other studies have also shown an impaired immune response to vaccination with BNT162b2, especially in patients with a liver or kidney transplant [23–25]. To counter possible adverse effects of a false sense of security it is therefore critical to identify non-responders to the vaccination, as is usual for other vaccines as well. Other forms of immunosuppressive medication did not affect immune responses to the vaccination against SARS-CoV-2, as has been shown previously [26].

In our cohort, a vaccination with mRNA-1273 elicited somewhat stronger immune responses than BNT162b2. It is doubtful, however, whether this translates to better clinical protection, as the differences (especially in neutralizing antibodies at t_3), while statistically significant, are very small. Clinical data seem to suggest a very comparable efficacy for both vaccines [9].

A further observation of our study is that individuals with a history of COVID-19 develop much higher antibody levels already after the first dose of vaccine compared to unexposed recipients.

While this has been shown before [27–30], we were also able to show that these vaccinees do not benefit further from a second dose of the vaccine, which could potentially be employed more efficiently if administered to another unexposed vaccinee.

An interesting side note of the examination of ANAs in our cohort is the unusually high prevalence of the pattern AC-2. Considering the fact that AC-2 and its target antigen DFS70 are negatively associated with the presence of autoimmune diseases [31], this observation serves to show that non-specific findings increase in frequency when tests are ordered without preselection. To avoid unnecessary diagnostics and therapy, a correct interpretation of these findings is all the more important.

Our study has several limitations. Information on immunosuppressive medication, while being reported voluntarily by several participants, was not collected systematically. Neither was information collected about possible medical conditions, especially autoimmune ones, or other medication received by the participants. The impact of these factors may therefore have been underestimated, or not recognized at all. The proportion of participants receiving mRNA-1273 was considerably smaller, possibly underestimating the differences between the two vaccines. The temporal course of the immune response after vaccination was gained through inter-individually gathered data. Ideally, intra-individual measurements in short (ideally daily) intervals after the vaccination would be performed. Also, the interval between the second dose of the vaccine and the last collection of blood from was relatively short at 2 weeks. However, another follow-up measurement with a longer interval is in the planning at the time of writing. Lastly, our participants having been recruited from a population of employed individuals of working age, there may have been a bias towards more healthy individuals in our cohort.

In conclusion, we were able to show that mRNA-1273 and BNT162b2 elicit strong and specific immune responses that were significantly enhanced after the second dose. Important influencing factors were age, prior infection, immunosuppression, and the vaccine received. In light of recent evidence showing the antibody responses to the vaccines to be sustained [32,33], and the vaccines to be clinically effective [5,6,8–10], our findings are encouraging indications that the available vaccines against SARS-CoV-2 may contribute decisively the containment of the COVID-19 pandemic.

Author contributions

RM, DP, SS, K-PW, BS, FL and RJ designed the study. RM, JD, SE, JR and SG contributed to the recruitment of participants. The described vaccinations were performed under the direction of SG. The assays were performed by RM, DP, KS, VH, DZ and CK. Data analysis was performed by RM, KS, VH and DZ. The manuscript was written by RM, with support from all authors. All authors have read and approved the final version of the manuscript.

Transparency declaration

KS, VH, DZ and CK are currently employees of the EUROIMMUN AG (Lübeck, Germany). All other co-authors have no conflicts of interest to declare. No external funding was received for this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.09.006>.

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