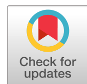
Original article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH



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Humoral immune response to SARS-CoV-2 mRNA vaccines is associated with choice of vaccine and systemic adverse reactions

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Purpose: Although the fast development of safe and effective messenger RNA (mRNA) vaccines against severe acute respiratory syndrome coronavirus 2 has been a success, waning humoral immunity has led to the recommendation of booster immunization. However, knowledge of the humoral immune response to different booster strategies and the association with adverse reactions is limited.
Materials and Methods: We investigated adverse reactions and anti-spike protein immunoglobulin G (IgG) concentrations among health care workers who received primary immunization with mRNA-1273 and booster immunization with mRNA-1273 or BNT162b2.
Results: Adverse reactions were reported by 85.1% after the first dose, 94.7% after the second dose, 87.5% after a third dose of BNT162b2, and 86.0% after a third dose of mRNA-1273. They lasted for a median of 1.8, 2.0, 2.5, and 1.8 days, respectively; 6.4%, 43.6%, and 21.0% of the participants were unable to work after the first, second, and third vaccination, respectively, which should be considered when scheduling vaccinations among essential workers. Booster immunization induced a 13.75-fold (interquartile range, 9.30–24.47) increase of anti-spike protein IgG concentrations with significantly higher concentrations after homologous compared to heterologous vaccination. We found an association between fever, chills, and arthralgia after the second vaccination and anti-spike protein IgG concentrations indicating a linkage between adverse reactions, inflammation, and humoral immune response.
Conclusion: Further investigations should focus on the possible advantages of homologous and heterologous booster vaccinations and their capability of stimulating memory B-cells. Additionally, understanding inflammatory processes induced by mRNA vaccines might help to improve reactogenicity while maintaining immunogenicity and efficacy.

Keywords: SARS-CoV-2, mRNA vaccines, Secondary immunization, Adverse reactions, Humoral immunity

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the ongoing pandemic of coronavirus disease 2019 (COVID-19) [1]. A global effort has been made to rapidly develop vaccines that protect against COVID-19 [2].

The messenger RNA (mRNA) based vaccines mRNA-1273 (Spikevax; Moderna Biotech Spain S.L., Madrid, Spain) and BNT162b2 (Comirnaty; BioNTech Manufacturing GmbH, Mainz, Germany; Pfizer Manufacturing Belgium NV, Puurs-Sint-Amands, Belgium) were the first SARS-CoV-2 vaccines approved in the United States [3,4] and Eu-

rope [5,6]. Both vaccines' nucleoside-modified mRNA is encapsulated in lipid nanoparticles and encodes the SARS-CoV-2 spike (S) protein stabilized in its prefusion conformation [7,8]. Immunity against the spike protein is expected to protect against COVID-19 [9]. Despite their similar composition, mRNA-1273 and BNT162b2 elicit slightly different immune responses. Vaccination with mRNA-1273 induces an antibody and type 1 helper T-cell–mediated immune response against the viral spike protein [7]. BNT162b2 additionally induces a specific cytotoxic T-cell response [10]. Nevertheless, both vaccines have demonstrated a comparable, high efficacy [11,12].

However, antibody levels after complete primary vaccination with mRNA vaccines wane over time [13-15]. Since neutralizing antibodies are expected to considerably contribute to protection against COVID-19, a decline raises concerns about waning immunity. Additionally, mRNA-1273 and BNT162b2 induced humoral immunity against SARS-CoV-2 variants is reduced [15,16]. To enhance and broaden immunity [15-18], booster vaccinations are now being administered. Yet knowledge of the effect of booster immunization on antibody levels particularly in health care workers and possible advantages of homologous and heterologous booster vaccination strategies is still limited.

Although the new technology and the fast development of mRNA vaccines against SARS-CoV-2 have given rise to safety concerns, several clinical trials have demonstrated acceptable safety with predominately mild to moderate adverse reactions [7,8,11,12,15,17-22]. Whether antibody levels are associated with adverse reactions has not been evaluated in clinical trials. Few studies on BNT162b2 vaccinated individuals [14,23-25] and mixed cohorts of mRNA-1273 and BNT162b2 vaccinated health care workers [26,27] indicate a relationship between antibody levels and adverse reactions. However, further investigations focusing on mRNA-1273 vaccinated individuals and booster immunization are lacking.
Considering higher COVID-19 mortality in older patients [28], the investigation of the influence of age on vaccine-induced antibody levels is of special interest. Despite immunosenescence immunization with mRNA-1273 has been shown to induce an age-independent humoral immune response [19-21]. In contrast, BNT162b2 elicits a lower humoral immune response in older individuals when applied as a prime dose [8,14,22] but an age-independent humoral immune when used for booster immunization [22,29]. Interestingly, adverse reactions have been reported to be less common among older people for both vaccines [8,11,12,14,20,22]. Evaluation of the association between adverse reactions and immunogenicity might help understand these contradictory observations.

The present study aims at expanding the knowledge of humoral immune response after primary and booster immunization and of the association between humoral immune response and adverse reactions in health care workers who were vaccinated with mRNA vaccines against SARS-CoV-2.

Materials and Methods

Trial design and participants

The retrospective study's cohort consisted of 105 health care workers who were primarily vaccinated twice with 100 µg mRNA-1273. In accordance with national recommendations, booster immunization with either 50 µg mRNA-1273 or 30 µg BNT1273 was offered between 6 to 10 months after complete primary immunization. Written informed consent for vacci nation and participation in the study was obtained from each participant. Sample and data acquisition were approved by the Medical Ethics Committee of the University Hospital RWTH Aachen (EK 093/20). Each participant was asked to complete a questionnaire regarding local and systemic adverse reactions and inability to work after the first, second, and third vaccination. Local adverse reactions include pain at the injection site, local swelling, and redness. Fatigue, headache, fever, chills, myalgia, arthralgia, diarrhea, vomiting, rash and pruritus, edema, and being bedridden are summarized as systemic adverse reactions. Participants graded the severity of symptoms as mild, moderate, or severe and stated the approximate beginning and duration of each symptom. Fever was classified as mild, moderate, or severe for temperatures <38.5°C, 38.5°C–39.5°C, and >39.5°C, respectively. Serum was collected at three-time points (TP) to measure anti-S-immunoglobulin G (IgG) concentrations (TP1: 2 to 3 weeks after complete primary immunization, TP2: 5 to 8 months after complete primary immunization but before booster immunization, TP3: at least 2 weeks after booster immunization). Additionally, at TP1 inhibition in a surrogate virus, a neutralization test was measured. According to anti-S-IgG concentrations, the participants were stratified into high-responders (top quartile) and low-responders (bottom quartile). Of the 92 participants who had blood drawn at TP1 and answered the questionnaire 23 were stratified in each quartile. At TP3 BNT162b2 and mRNA-1273 vaccinated participants were evaluated sepa-

rately to avoid bias. For BNT162b2 vaccinated individuals who had blood drawn at TP3 and completed the questionnaire (n=32), each quartile contained eight participants. Among exclusively mRNA-1273 vaccinated participants who had blood drawn at TP3 and turned in the questionnaire (n=42), 10 were classified as low- and high-responders, respectively. To maximize the sample size mRNA-1273 and BNT162b2 vaccinated participants were also analyzed together. This did not change the findings described below (data not shown).

Antibody measurements

To measure total anti-S-IgG concentration, we performed the Liaison SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Saluggia, Italy) as recommended by the manufacturer [30]. For the measurement of neutralizing antibodies, we used a surrogate SARS-CoV-2 neutralization test (SARS-CoV-2 Surrogate Virus Neutralization Test Kit; Genscript Biotech, Piscataway, NJ, USA) according to the manufacturer's instructions. The method has been described in detail previously [31]. Sera prediluted by 1:20 were used.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 27.0 for Windows (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as absolute numbers or frequencies and are compared between groups using Fisher's exact test. Effect size is reported as odds ratio (OR) and 95% confidence interval (CI). Metric variables are given as median (interquartile range, IQR) or arithmetic mean±standard deviation. We tested for normal distribution by qualitative evaluation of histograms and using the Kolmogorov-Smirnov test. Due to skewed distribution and identification of several outliers, metric variables are compared between two groups using a two-sided Mann-Whitney U test for unpaired variables. Correlation between metric variables was assessed using Spearman's correlation. All p-values below 0.05 are considered significant.

Results

Study population

The questionnaire was completed by 94 participants after each of the two injections of the primary immunization and by 81 participants after the booster immunization. At TP1, TP2, and TP3 (details: Materials and Methods section), blood for antibody measurements was drawn from 93, 90, and 87 participants, respectively. All participants had two doses of mRNA-1273 administered for primary immunization. Of the participants who had blood drawn at TP3, 51.7% had received mRNA-1273 and 41.4% BNT162b2 as booster vaccination. And 6.9% did not specify the vaccine. The participants' age ranged from 21 to 73 years with a mean of 49.8±13.1 years

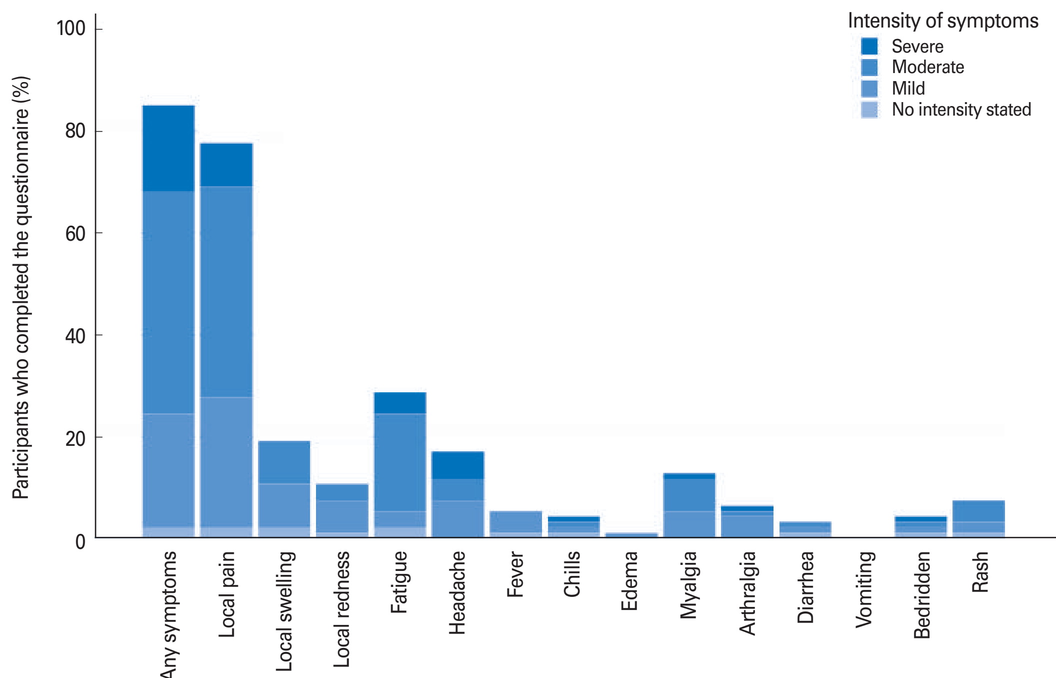

Fig. 1. Frequency and intensity of adverse reactions after the first vaccination with messenger RNA (mRNA)-1273.

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and a median of 54 years (IQR, 40.5–59.0 years). Of the participants, 75.2% were older than 40 years, and 45.7% were older than 55 years. And 83.8% of the participants were female.

Adverse reactions after first, second, and third vaccination

After the first vaccination, 85.1% of the participants reported symptoms. The symptoms were predominately graded as mild to moderate (Fig. 1). In contrast, 94.7% of the partici-

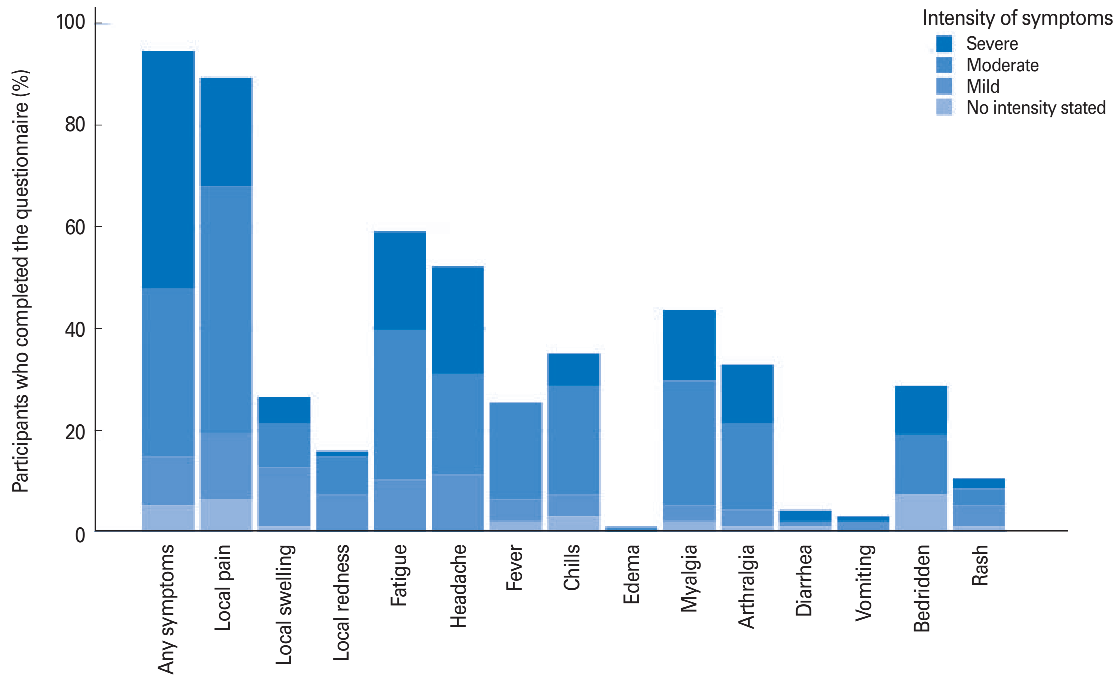

Fig. 2. Frequency and intensity of adverse reactions after the second vaccination with messenger RNA (mRNA)-1273.

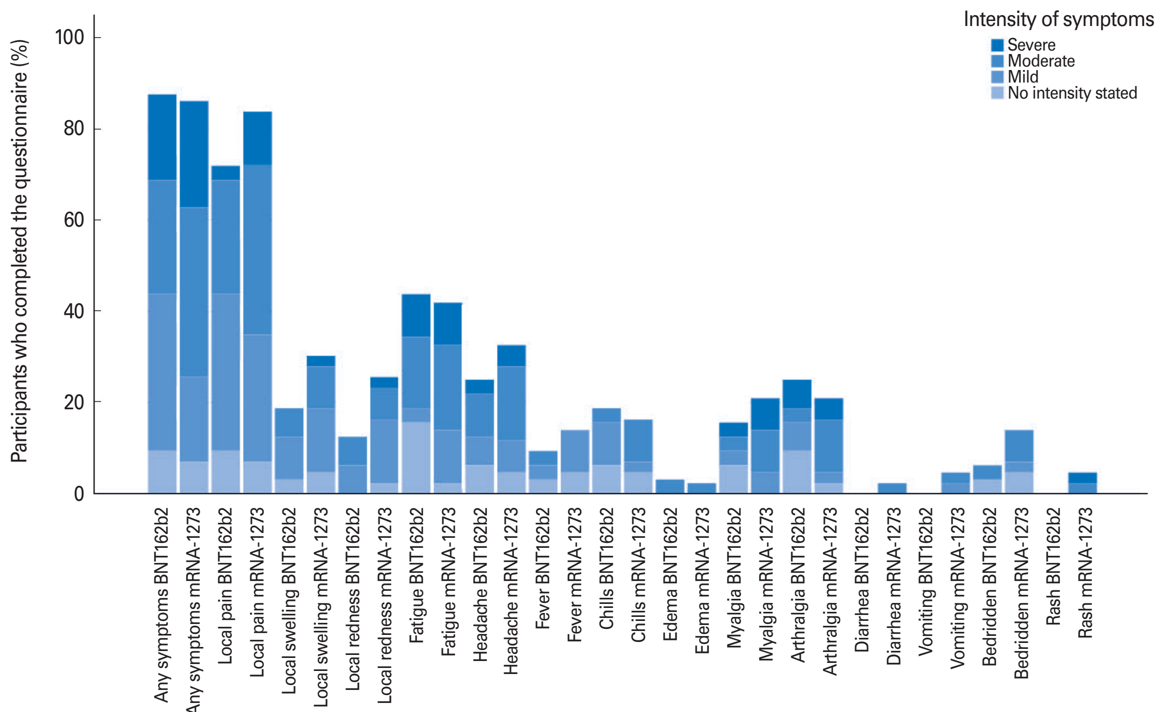

Fig. 3. Frequency and intensity of adverse reactions after the third vaccination with messenger RNA (mRNA-1273) or BNT162b2.

pants stated to have had symptoms after the second vaccination. Symptoms after the second vaccination were characterized as rather moderate to severe (Fig. 2). Most symptoms tended to be more common after the second than after the first immunization. After the booster immunization symptoms were reported by 86.0% of the participants who received mRNA-1273 and by 87.5% of the participants who received BNT162b2. The frequency and intensity of adverse reactions were numerically similar among participants who received mRNA-1273 and BNT162b2 as booster immunization (Fig. 3). The frequency of symptoms after the third immunization tended to be lower than after the second but higher than after the first dose for most symptoms except for local pain, local swelling, diarrhea, and rash. The intensity of symptoms after booster vaccination was comparable to the first immunization.

Symptoms started 5 hours (IQR, 2–8 hours) after the first vaccination, 4 hours (IQR, 2–7 hours) after the second vaccination, 6 hours (IQR, 2–12 hours) after the third vaccination with BNT162b2, and 4 hours (IQR, 1–8 hours) after the third vaccination with mRNA-1273, lasting for 44 hours (IQR, 25–67 hours), 47 hours (IQR, 36–71 hours), 60 hours (IQR, 25–74 hours), and 44 hours (IQR, 34–64 hours), respectively. After the first, second, and third vaccination 6.4%, 43.6%, and 21.0% of the health care workers were temporarily unable to work. Inability to work lasted a median of 1 day (IQR, 1–2 days) after each vaccination.

Humoral immune response

At TP1 all participants had anti-S-IgG concentrations above the test-specific cut-off of 39 BAU/mL with a mean of 3,373± 1,410 BAU/mL. Inhibition in the surrogate neutralization test exceeded the test-specific cut-off of 20% for all participants with a mean of 70.45%±18,80%. At TP2 and TP3 mean anti-S-IgG concentrations were 645±514 BAU/mL and 9,949±7,950 BAU/mL, respectively. At both time points, all participants far exceeded the test-specific cut-off (Fig. 4). At TP2 anti-S-IgG concentrations had decreased to 0.16 times (IQR, 0.13–0.23 times) the concentrations at TP1. At TP3 anti-S-IgG concentrations were 13.75 times (IQR, 9.30–24.47 times) higher than at TP2 and 2.28 times (IQR, 1.84–3.63 times) higher than at TP1.

Spearman's correlation indicated a strong positive correlation between anti-S-IgG concentrations at TP1 and TP2

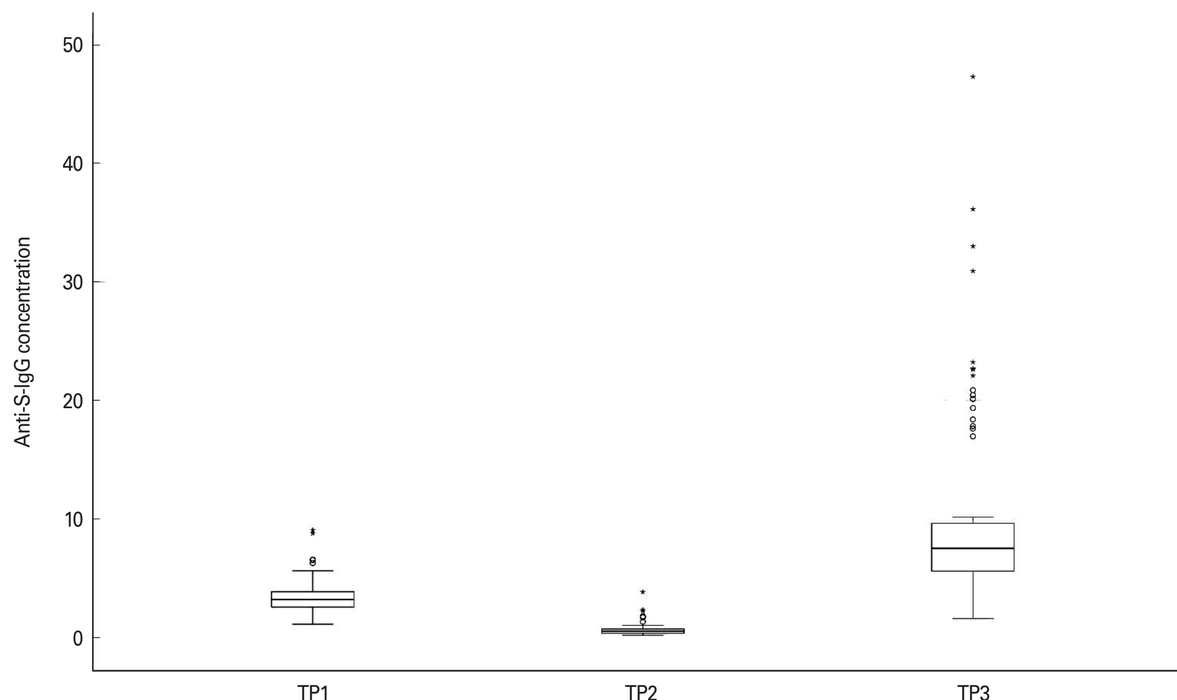

Fig. 4. Box plots of anti-S-immunoglobulin G (IgG) concentrations 2 to 3 weeks after primary immunization (TP1), 5 to 8 months after primary immunization (TP2) and at least 2 weeks after booster immunization (TP3). Horizonal bars and boxes denote median and interquartile range. Whiskers equal lower and upper quartile±1.5 times the interquartile range. Circles depict outliers outside the lower and upper quartile±1.5 times the interquartile range. Asterisks represent extreme outliers outside the lower and upper quartile±3 times the interquartile range. TP, time points.

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(r=0.620, p<0.001) (Fig. 5) and a weak, but significant correlation between anti-S-IgG concentrations at TP1 and TP3 (r=0.295, p=0.008) (Fig. 6). There was no significant correlation between anti-S-IgG concentrations at TP2 and TP3 (p=0.057) (Fig. 7).

At TP3 mRNA-1273 vaccinated individuals had significantly higher anti-S-IgG concentrations than BNT162b2 vaccinated participants (p=0.021). Age, sex distribution, and anti-S-IgG concentrations at TP2 were comparable between participants booster vaccinated with mRNA-1273 or BNT162b2 (Table 1).

Association of antibody levels with adverse reactions and age

Comparison of low- and high-responders at TP1 showed a significantly higher frequency of fever (p=0.023; OR, 6.11; 95% CI, 1.41–26.41), chills (p=0.002; OR, 8.91; 95% CI, 2.25–35.33), and arthralgia (p=0.007; OR, 9.63; 95% CI, 1.82–50.89) after the second immunization among high-responders (Table 2). All other adverse reactions and inability to work after the second vaccination were not significantly associated with high and low anti-S-IgG concentrations at TP1. There was no significant association between adverse reactions and inability to work after the first immunization and low- and high-responders at TP1 (data not shown).

The frequencies of adverse reactions and inability to work after the third vaccination were not significantly different in high- and low-responders at TP3, neither among BNT162b2 nor among mRNA-1273 vaccinated participants.

At TP1 and TP2, there was no significant Spearman's correlation between age and anti-S-IgG concentration (p=0.238, p=0.971, respectively) (Fig. 8). Neither for BNT162b2 nor for mRNA-1273 vaccinated participants, anti-S-IgG concentrations at TP3 significantly correlated with age (p=0.123, p=

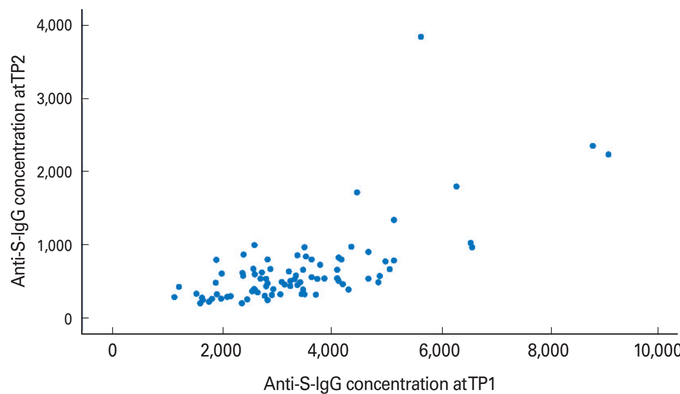

Fig. 5. Scatter plot of anti-S-immunoglobulin G (IgG) concentrations at TP1 and TP2 expressed in BAU/mL. Correlation was assessed by Spearman's correlation coefficient (r=0.620, p<0.001). TP, time points.

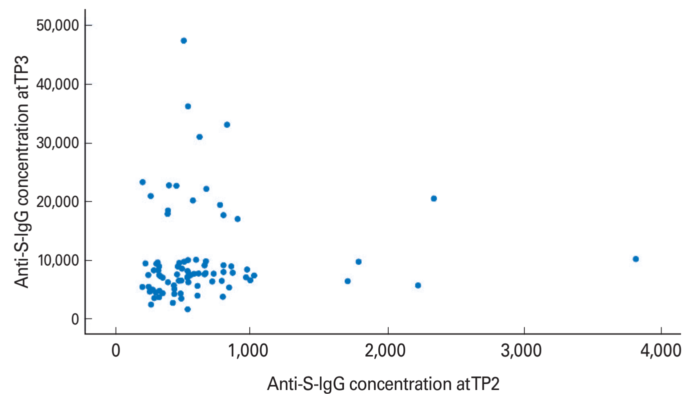

Fig. 7. Scatter plot of anti-S-immunoglobulin G (IgG) concentrations at TP2 and TP3 expressed in BAU/mL. Correlation was assessed by Spearman's correlation coefficient (r=0.209, p=0.057). TP, time points.

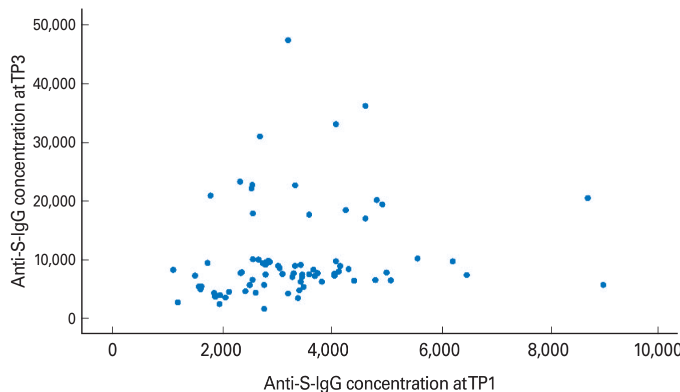

Fig. 6. Scatter plot of anti-S-immunoglobulin G (IgG) concentrations at TP1 and TP3 expressed in BAU/mL. Correlation was assessed by Spearman's correlation coefficient (r=0.295, p=0.008). TP, time points.

Table 1. Age, sex, and anti-S-IgG concentrations before (TP2) and after (TP3) booster immunization with BNT162b2 or mRNA-1273

Variable	Booster immunization	
	BNT162b2	mRNA-1273
Anti-S-IgG at TP3[a)] (BAU/mL)	8,071±5,999	11,305±8,757
Anti-S-IgG at TP2 (BAU/mL)	673±660	626±428
Age (yr)	48±15	54±8
Sex		
Male	19.4	11.1
Female	80.6	88.9

Values are presented as mean±standard deviation or %.
IgG, immunoglobulin G; TP, time points; mRNA, messenger RNA.
[a)]Indicates a significant difference between individuals booster vaccinated with mRNA-1273 and BNT162b2 (p=0.021).

Table 2. Adverse reactions after the second vaccination with mRNA-1273 among low- and high-responders after the second vaccination (TP1)

	No/yes	Anti-S-IgG concentration at TP1	
		Low-responders (n=23)	High-responders (n=23)
Fever	No	87.0 (20)	52.2 (12)
	Yes	13.0 (3)	47.8 (11)
Chills	No	82.6 (19)	34.8 (8)
	Yes	17.4 (4)	65.2 (15)
Arthralgia	No	91.3 (21)	52.2 (12)
	Yes	8.7 (2)	47.8 (11)

Values are presented as % (number of participants).
TP, time points; mRNA, messenger RNA; IgG, immunoglobulin G.

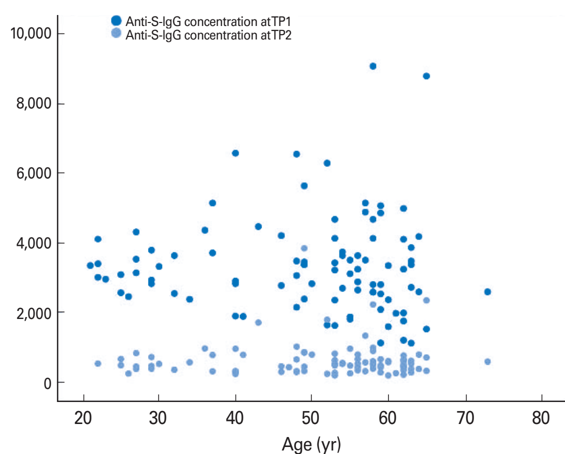

Fig. 8. Scatter plot of age expressed in years and anti-S-immunoglobulin G (IgG) concentrations at TP1 and TP2 expressed in BAU/mL. Correlation was assessed by Spearman's correlation (TP1: p=0.238, TP2: p=0.971). TP, time points.

0.632, respectively) (Fig. 9).

Correlation between inhibition in neutralization test and anti-S-IgG concentration

For normalization anti-S-IgG concentrations and inhibition in the neutralization test measured at TP1 were divided by the test-specific cut-offs. Normalized inhibition was plotted against normalized anti-S-IgG concentration (Fig. 10). Spearman's correlation indicated a strong correlation between neutralizing antibodies and anti-S-IgG (r=0.806, p<0.001).

Discussion

The present study aimed at evaluating the humoral immune response to primary and booster immunization with mRNA vaccines against SARS-CoV-2 in health care workers and the

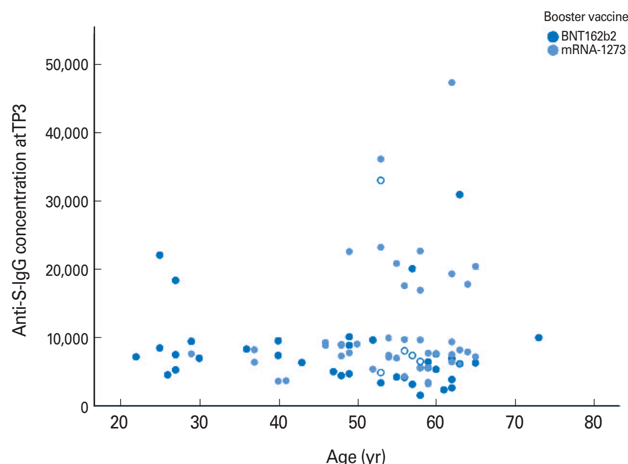

Fig. 9. Scatter plot of age expressed in years and anti-S-immunoglobulin G (IgG) concentrations at TP3 expressed in BAU/mL. Correlation was assessed by Spearman's correlation (BNT162b2: p=0.123, messenger RNA [mRNA]-1273: p=0.632). Individuals not specifying booster vaccine were excluded from correlation analysis and are represented by white circles. TP, time points.

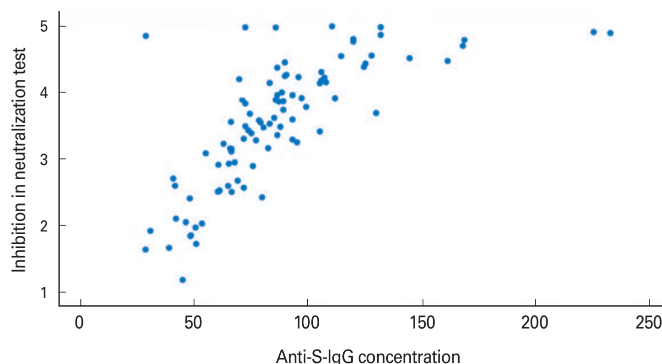

Fig. 10. Scatter plot of normalized anti-S-immunoglobulin G (IgG) concentrations and inhibition in a surrogate neutralization test at TP1. Correlation was assessed by Spearman's correlation coefficient (r=0.806, p<0.001). TP, time points.

association with adverse reactions.

The frequency of symptoms observed after the first and second vaccination with mRNA-1273 was as expected from the phase 1 to 3 trials with adverse reactions being more common and severe after the second immunization [7,11,19,20]. However, local pain, fatigue, headache, fever, chills, myalgia, and arthralgia were classified as more severe. Adverse reactions after the booster immunization occurred more commonly than after the first vaccination but did not reach the extent of adverse reactions after the second vaccination. Compared to clinical trials on the booster vaccination [15,17,18,21,22], we observed lower rates of headache, fatigue, myalgia, arthralgia, and chills but higher rates of local

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redness and swelling and a higher intensity of local pain, especially after mRNA-1273 booster vaccination. Differences in the clinical trials might be explained by our cohort consisting exclusively of health care workers, who might rate health issues differently than the general population. Notably, adverse reactions after a third dose of mRNA-1273 or BNT162b2 were comparable while previous studies have reported conflicting results [21,32]. We found symptoms to begin mainly within the day of vaccination. Symptoms after the first and second vaccination lasted shorter than in phase 2 and 3 trials on primary vaccination with mRNA-1273 [11,20]. Of note, symptoms after booster vaccination with BNT162b2 lasted longer compared to vaccinations with mRNA-1273. While most of our participants were able to work after the first dose, almost half and a quarter of them were temporarily absent from work after the second and third doses, respectively. While one study reported about a quarter of the participants requiring time off work without differentiating between the first and second vaccination [33], another study found slightly more participants temporarily unable to work than in our study, both after the first and the second immunization [34]. Taken together, the observed moderate to high frequency and intensity of adverse reactions, the beginning and duration and the high rate of temporary inability to work after the second and third immunization should be considered when scheduling vaccinations, especially among essential workers.

We confirmed the decline of antibody levels after complete primary immunization with mRNA-1273 over time [13,15]. However, anti-S-IgG concentrations 5 to 8 months after the second vaccination still far exceeded the test-specific cut-off in all participants. Booster immunization led to an almost 14-fold increase of anti-S-IgG concentrations with antibody levels about 2 times higher than after the second vaccination. The observed increase is in the range of the previously described increase of binding and neutralizing antibodies [15,17,18,21,22]. However, previous studies mainly focused on homologous booster vaccination strategies, and studies on heterologous booster vaccination especially with mRNA-1273 as the prime dose are limited. In our study, a heterologous vaccination scheme with mRNA-1273 as prime and BNT162b2 as booster vaccination was also effective but resulted in significantly lower antibody concentrations than homologous mRNA-1273 vaccination. One prospective study found numerically higher neutralizing and binding antibody levels after homologous vaccination with mRNA-1273 compared to heterologous vaccination with mRNA-1273 and BNT162b2 but was not designed for direct inter-group comparison [21]. A stronger humoral immune response to homologous vaccination could be explained by a more effective stimulation of memory B-cells. Nevertheless, heterologous vaccination with mRNA-1273 as prime and BNT162b2 as boost might offer immunological advantages, e.g., by inducing an additional cytotoxic T-cell response [10]. Therefore, further prospective and randomized studies are needed to evaluate the advantages and disadvantages of homologous and heterologous vaccination strategies. Interestingly, antibody levels after booster immunization were only weakly correlated with antibody levels measured directly after primary immunization and not correlated with antibody levels measured before booster immunization. An explanation might be the independency of antibody response and generation of memory B-cells which presumably account for the humoral immune response to booster vaccination [26].

Previous studies have found an association between adverse reactions and humoral immune response among BNT162b2 vaccinated individuals [14,23-25] and in mixed study populations of BNT162b2 and mRNA-1273 vaccinated participants [26,27]. Particularly systemic adverse reactions after the second vaccination showed to be associated with antibody levels. We observed an association between fever, chills, and arthralgia after the second vaccination and anti-S-IgG concentrations after the complete primary vaccination. Our results support the hypothesis that systemic adverse reactions after the second dose are associated with antibody levels not only in BNT162b2 but also in mRNA-1273 vaccinated individuals. Higher frequencies of systemic adverse reactions likely indicate a stronger inflammation [35] which might either be the triggering factor for antibody induction or the result of a stronger immune response.

Considering higher COVID-19 mortality in older patients, investigation of the immune response to mRNA-1273 in older individuals is crucial [28]. In our study humoral immune response was independent of age. This is in line with the observation that mRNA-1273 elicits an age-independent immune response [19-21] but contradictory to trials on BNT162b2 that observed a lower humoral immune response in older individuals [8,14]. However, previous studies focusing on booster immunization showed no correlation between age and humoral immune response to booster vaccination with BNT162b2 [22,29]. Possible explanations for an age-independent immune response include the activation of memory B cells either against SARS-CoV-2 or endemic human coronaviruses

[19,36] and improvement of immunogenicity compared to traditional vaccine approaches [37].

Limitations of this study are the small sample size, the predominance of female participants, and the limited age range. While the composition of our study cohort might be representative of the health care system it does not represent the general population and therefore generalization of our findings is limited. Additionally, national booster vaccination strategies changed over the time course of our study. Due to our retrospective study design, this influenced the choice of vaccine depending on availability, age, and primary vaccination.

In summary, our study showed that adverse reactions after the second and third doses of SARS-CoV-2 mRNA vaccines are common in health care workers resulting in almost half and a quarter of them being unable to work after the second and third dose, respectively. Furthermore, we found both homologous booster immunization with mRNA-1273 and heterologous booster immunization with mRNA-1273 and BNT162b2 to increase binding antibody concentrations with significantly higher levels after homologous booster vaccination. We did not find a correlation between age and humoral immunogenicity supporting the suitability of mRNA vaccines across age groups. Finally, we have demonstrated an association between the frequency of fever, chills, and arthralgia after the second vaccination with mRNA-1273 and anti-S-IgG concentrations after complete primary immunization indicating a linkage between systemic adverse reactions, inflammation, and humoral immune response. Further understanding of the underlying processes might help to improve vaccine reactogenicity while maintaining immunogenicity.

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