DECLINING NEUTRALIZING ANTIBODY LEVELS AFTER SARS-COV-2 MRNA VACCINATION: OBSERVATIONAL DATA FROM COMMUNITY POINT-OF-CARE TESTING SERVICE IN BRNO, CZECHIA

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SUMMARY

Objectives: Understanding immune response is critical for control of COVID-19 pandemic. However, recent studies show that vaccine-induced humoral immunity may not be long-lasting and weaker in SARS-CoV-2 variants of concern.

Methods: In May 2021, 253 self-nominated persons were tested for antibodies against SARS-CoV-2 in 1 to 104 days (mean 41, median 28) after two doses of Moderna and Pfizer-BioNTech vaccines in the city of Brno, Czechia. Two point-of-care iCHROMA™ II immunofluorescence assays were used: COVID-19 Ab against mix of SARS-CoV-2 nucleocapsid and spike proteins (IgG Ab); and COVID-19 nAb against S1-RBD protein (nAb). Results were analysed in relation to gender, age, vaccine, and past COVID-19 disease.

Results: Antibodies nAb were detectable in 92.9% (95% CI: 89.7–96.0) of vaccinees. We observed statistically insignificant decrease of positive results from 93.9% (95% CI: 89.5–98.3) and 97.0% (95% CI: 92.8–100.0) in the first and second month after vaccination, respectively, to 91.7% (95% CI: 83.8–99.5) and 78.3% (95% CI: 61.4–95.1) in the third and fourth month, respectively. Quantitative results showed decreasing level of nAb in both genders, age groups and vaccines. Higher levels of nAb were found in younger age group and in COVID-19 convalescents. IgG Ab showed little dynamics in time.

Conclusions: We found robust humoral response after vaccination with mRNA vaccines, however, decreasing nAb levels suggest that vaccine-induced humoral immunity is rapidly waning. This finding is relevant for adjustment of vaccination strategies with regard to inclusion of booster dose(s).

Key words: COVID-19, SARS-CoV-2, immune response, antibody, vaccine

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INTRODUCTION

The COVID-19 epidemic (infection caused by the new coronavirus SARS-CoV-2) originated in China at the end of December 2019 and gradually spread throughout the world. On 11 March 2020, the WHO declared the COVID-19 outbreak a pandemic (1). As of 12 June 2021, more than 176 million COVID-19 cases and 3.8 million deaths worldwide were reported (2). Czechia with more than 1.6 million COVID-19 cases and 30 thousand deaths occupied unfortunate third and fourth position globally, respectively (3).

Vaccination against SARS-CoV-2 is essential part of strategy containing COVID-19. The first and mostly used vaccines also in the Czech Republic were mRNA vaccines developed by Moderna and Pfizer-BioNTech. They are based on lipid nanoparticle delivery of mRNA encoding spike protein of SARS-CoV-2 isolated early in the epidemic in Wuhan, China. The mRNA-1273 vaccine (Moderna) showed 94% (95% CI: 89.3–96.8) efficacy in preventing COVID-19 illness with onset at least 14 days after the second injection (4) and BNT162b2 (Pfizer-BioNTech) showed comparable efficacy of 95% (95% CI: 90.3–97.6) in at least 7 days after the second injection (5) in phase 3 clinical trials. However, only limited data is available about the extent and duration of the antibody and overall immune responses after the mRNA vaccination as well as on its efficacy in real life so far.

Studies looking at immune response after SARS-CoV-2 infection show that humoral response is a complex and each component has its distinct kinetics. It has been reported that anti-SARS-CoV-2 serum antibodies peak in the first 2–3 weeks and then exhibit rapid decay during the few months after infection, and that production of spike-specific memory B cells may be limited (6, 7). Recent study on patients with past mild infection (n = 77) found rapid decline of anti-SARS-CoV-2 spike antibodies in the first four months after infection and then more gradually over the following seven months, however, they remain detectable at least 11 months after infection and the titres were correlated with the frequency of spike-specific memory B cells obtained from bone marrow aspirates and circulating B cells were detected also in plasma of the convalescent individuals (8). Relatively stable titre of IgG antibodies against spike protein and increasing level of

spike-specific memory B cells over 6–8 months after infection were reported (9). Nevertheless, there are concerns that humoral immunity against SARS-CoV-2, especially antibody plasma titres and circulating memory B cells, may be short-lived despite B cells immune memory persistent in organ compartments in convalescent patients.

Studies reporting about immune response from real situation vaccinations share the same concern although recent findings show that while some sera from convalescent patients may have substantially reduced neutralization activity against virus, sera from vaccinated individuals are highly effective in neutralizing it (10). However, weaker immune responses and higher number of non-responders among older individuals were reported. The study modelling decay of antibodies found half-time of antibodies varying from 43 to 173 days depending on the assay and model used (11). Although humoral response was found robust, neutralizing antibody levels were declined in week 6 as compared to week 1 after full vaccination and the level was lower in older individuals (12). After the second vaccination, only 69% of the elderly (> 80) had detectable neutralizing antibodies in contrast to 98% in the younger group (< 60) (13). Another study showed also lower magnitude of memory B cell responses with increased age (14).

Although clinical trials showed high efficacy of mRNA vaccines, it is important to consider effectiveness from real-life studies. Analysis of nearly 4,000 healthcare personnel from the United States vaccinated with mRNA-1273 vaccine (Moderna) and BNT162b2 (Pfizer-BioNTech) from December 2020 to March 2021 showed 90% effectiveness against SARS-CoV-2 infection after full immunisation ≥ 14 days after the second dose (15). Nationwide study analysing data from Scotland from December 2020 to February 2021 found 91% effectiveness against COVID-19 disease and reduced COVID-19 hospital admissions at 28–34 days post-vaccination (16). In Israel, 95% effectiveness against SARS-CoV-2 infection was found in nationwide study during four months of vaccination from January to April 2021, and even higher efficacy (97–98%) was found against symptomatic disease, (critical) hospitalisation or death (17). Regional study from Spain showed lower efficacy of 66% against SARS-CoV-2 infection, 82% against symptomatic infection, and 95% against hospitalisation after the second dose, highlighting lower effect of vaccines in older age groups ≥ 60 years (18). Recently, emergence of novel circulating SARS-CoV-2 variants of concerns (VOC) raised questions on effectiveness of vaccination strategy worldwide. VOC have shown substantial reduction of neutralization activity of both convalescent and vaccine sera (19–22).

In this paper, we report data from diagnostic screening of antibodies against SARS-CoV-2 in individuals vaccinated with 2 doses of mRNA vaccines in Brno, Czechia.

MATERIALS AND METHODS

Sample

During 3 days from 30 April to 2 May 2021, 253 persons vaccinated with mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) vaccines were tested for antibodies against SARS-CoV-2 once at the time of 1 to 104 days after the second dose. Testing was performed within SARS-CoV-2 antigen community testing centre of Spolecnost Podane ruce in Brno city, Czechia. Participants were self-nominated following advertisement of the testing in local media in Brno city. A short list of demographic data (gender, age) and anamnestic data on vaccination (type of vaccine, date of first and second vaccination and past COVID-19 disease) was collected from tested persons. Data on the chronic comorbidities or immunosuppressive therapy were not collected. Testing was anonymous, all subjects provided informed consent.

Assays

System iCHROMA™ II was used. It is a portable point-of-care system by Boditech Med Inc. on the principle of time-resolved fluorescent lateral flow immunoassay (TRFLFA). Two tests were used:

- iCHROMA™ COVID-19 Ab uses a sandwich immunodetection method. Fluorescence labelled conjugates of mix of SARS-CoV-2 nucleocapsid and spike proteins in a dried detection buffer binds to antibody (Ab) in a sample, forming antibody-antigen complexes, and migrates onto nitrocellulose matrix to be captured by the other immobilised anti-human IgG and anti-human IgM on test strip. The more antigen-antibody complexes lead to stronger fluorescence signal by the detector antigen which is processed by the iCHROMA™. The iCHROMA™ processes the signal using a cut off index of 0.9–1.1, results <0.9 are interpreted as negative, results between 0.9 and 1.1 are interpreted as indeterminate, and results >1.1 are interpreted as positive.
- iCHROMA™ COVID-19 nAb test is a specific test for the neutralizing antibodies (nAb) against SARS-CoV-2 S1 protein of receptor-binding domain (S1-RBD). It uses a competitive immunodetection method. Neutralizing antibody in the sample binds to the fluorescence labelled S1-RBD antigen in a detection buffer forming complexes and migrates through a nitrocellulose matrix to which ACE-2 receptor protein is covalently immobilized. Binding of fluorescence labelled antigen to ACE interferes with its binding to the neutralizing antibody. The more neutralizing antibodies there are in the sample, the less free labelled antigen remains, resulting in an inhibition of fluorescence signal. Working range of inhibition is 10–100% with ≥ 30% inhibition is interpreted as positive result.

Manufacturer declares 95.8% sensitivity and 97.0% specificity for iCHROMA™ COVID-19 Ab, and 91.9% sensitivity and 100.0% specificity for COVID-19 nAb test. There are comparative data on iCHROMA™COVID-19 IgG Ab with the Abbott Architect SARS-CoV-2 IgG assay showing an overall agreement of 95%, with a sensitivity of 100% and a specificity of 90% of the iCHROMA™ COVID-19 IgG antibody assay (23).

Data Analysis

Both tests are semi-quantitative, we used both quantitative (strength of TRFLFA signal or its inhibition) and qualitative (N = negative, P = positive, I = indeterminate) results in the analysis. We report just results of IgG Ab and nAb. The post-vaccination period was divided into four-week intervals in which quantitative and qualitative results of antibodies were explored in association with gender, age group (< 60, ≥ 60), vaccine type (Moderna, Pfizer-BioNTech), and past COVID-19 disease (confirmed or alleged,

no disease). Data were analysed in IBM SPSS Statistics 25; 95% confidence intervals (95% CI) for frequencies are constructed on the basis of approximation by normal distribution.

RESULTS

Demographic and Anamnestic Data

Of total 253 persons, 177 were females and 76 males. They were aged 16 to 83 years (females 16–82, mean 43.5, median 43; males 20–83, mean 46.5, median 45). Twenty-six were vaccinated with Moderna and 227 with Pfizer-BioNTech, 1 to 104 days (Moderna 15–47, Pfizer-BioNTech 1–104) prior testing (mean 41, median 28). Thirty-one reported confirmed disease and seven reported alleged (referred to as suspected) COVID-19 disease in the past; in 37 persons this information was unknown. Demographic and anamnestic data of the sample by time after vaccination is reported in Table 1.

Antibody Testing

Quantitative and qualitative results of IgG Ab in time after the second dose of vaccine by gender, age, vaccine brand, and COVID-19 disease in the past are provided in Figure 1 and Table 2.

Quantitative and qualitative results of nAb in time after second dose of vaccine by gender, age, vaccine brand, and COVID-19 disease in the past are provided in Figure 2 and Table 3.

DISCUSSION

Although our results show high variability of individual humoral responses, they suggest overall robust response to mRNA vaccination since neutralizing antibodies against S1-RBD protein (nAb) were detectable in 92.9% (95% CI: 89.7–96.0) of vaccinated subjects. However, they suggest decreasing levels of nAb over first four months following two doses of mRNA vaccines. Decrease was found in both genders and age groups. Higher inhibition of fluorescence signal indicating overall higher levels of neutralizing antibodies was found in younger group and in COVID-19 vaccinees reporting past COVID-19 disease (means in those with hybrid immunity response). In qualitative results of nAb, our results indicate a decrease from 93.9% (95% CI: 89.5–98.3) and 97.0% (95% CI: 92.8–100.0) of positive results in the first and second month after vaccination, respectively, to 91.7% (95% CI: 83.8–99.5) and 78.3% (95% CI: 61.4–95.1) in the third and fourth month, respectively, though the decrease is not statistically significant as CIs are overlapping. However, quantitative results show steadily decreasing level of nAb during the first four months following vaccination with two doses of mRNA vaccines. IgG antibodies against mix of nucleocapsid and spike proteins (IgG Ab) showed (with exception of convalescent subjects) overall little dynamics in time.

Though post-infection and post-vaccination immune response is complex and includes both humoral and cellular mechanisms, antibodies against Spike proteins (which are key in vaccine-induced immunity) are in general considered a proper indicator of humoral capacity to neutralize the virus and reasonable correlate of overall humoral immunity in SARS-CoV-2 (8) as well as in other infectious diseases (24). In our results, nAb levels indicate a decrease over time while IgG Ab do not – this might be partly explained by the previous exposure to the wild virus which is indicated by overall higher levels found in subjects with reported previous infection.

A key question is what titre of post-vaccination antibodies is protective. Analysis comparing immune response and protective effect between vaccinees and convalescents estimated 50% protective effect against any infection at 20% (95% CI: 14–28) and against severe infection at 3% (95% CI: 0.7–13) of mean level of neutralization antibodies found in convalescents (25). However, efficacy of vaccination was questioned with emergence of VOC – particularly multiple mutants (Beta, Gamma, Delta) in the spike receptor-binding domain (RBD) have been found more transmissible, pathogenic and virulent and posed a serious concern over efficacy of vaccines (26–28). Recently emerged Omicron variant which has spread globally also in highly vaccinated populations from November 2021 has shown extreme resistance against currently used vaccines – vaccine effectiveness waned rapidly, with very limited vaccine effects seen from 20 weeks after the second dose of any vaccine and with rapidly waning protection against symptomatic disease also after a booster dose with mRNA vaccines (29). However, mRNA vaccines were found highly effective

Table 1. *Sample demographic and anamnestic data by time after vaccination (N = 253)*

Subgroup		Time after vaccination				Total
		0–3 weeks	4–7 weeks	8–11 weeks	12–15 weeks	
Gender	Female	76	52	35	14	177
	Male	40	14	13	9	76
Age	< 60	78	53	43	22	196
	≥ 60	38	13	5	1	57
Vaccine	Moderna	22	4	0	0	26
	Pfizer-BioNTech	94	62	48	23	227
COVID-19 in the past	Confirmed/suspected	14	15	6	3	38
	No COVID-19 disease	80	45	37	16	178
	Unknown	22	6	5	4	37
Total		116	66	48	23	253

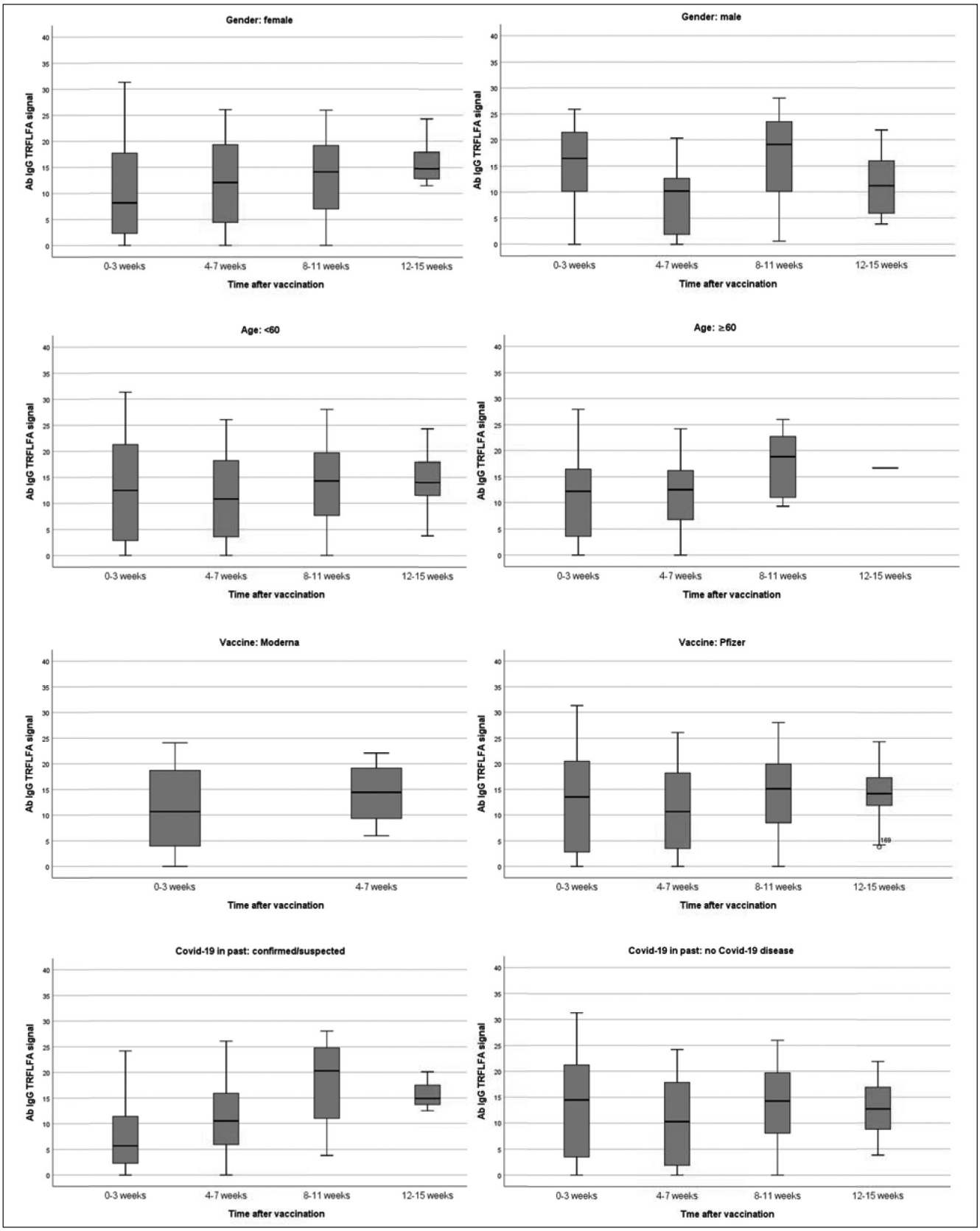

Fig. 1. *IgG Ab TRFLFA signal by time after vaccination and by gender (1st raw), age (2nd raw), vaccine brand (3rd raw) and COVID-19 disease in the past (4th raw).*

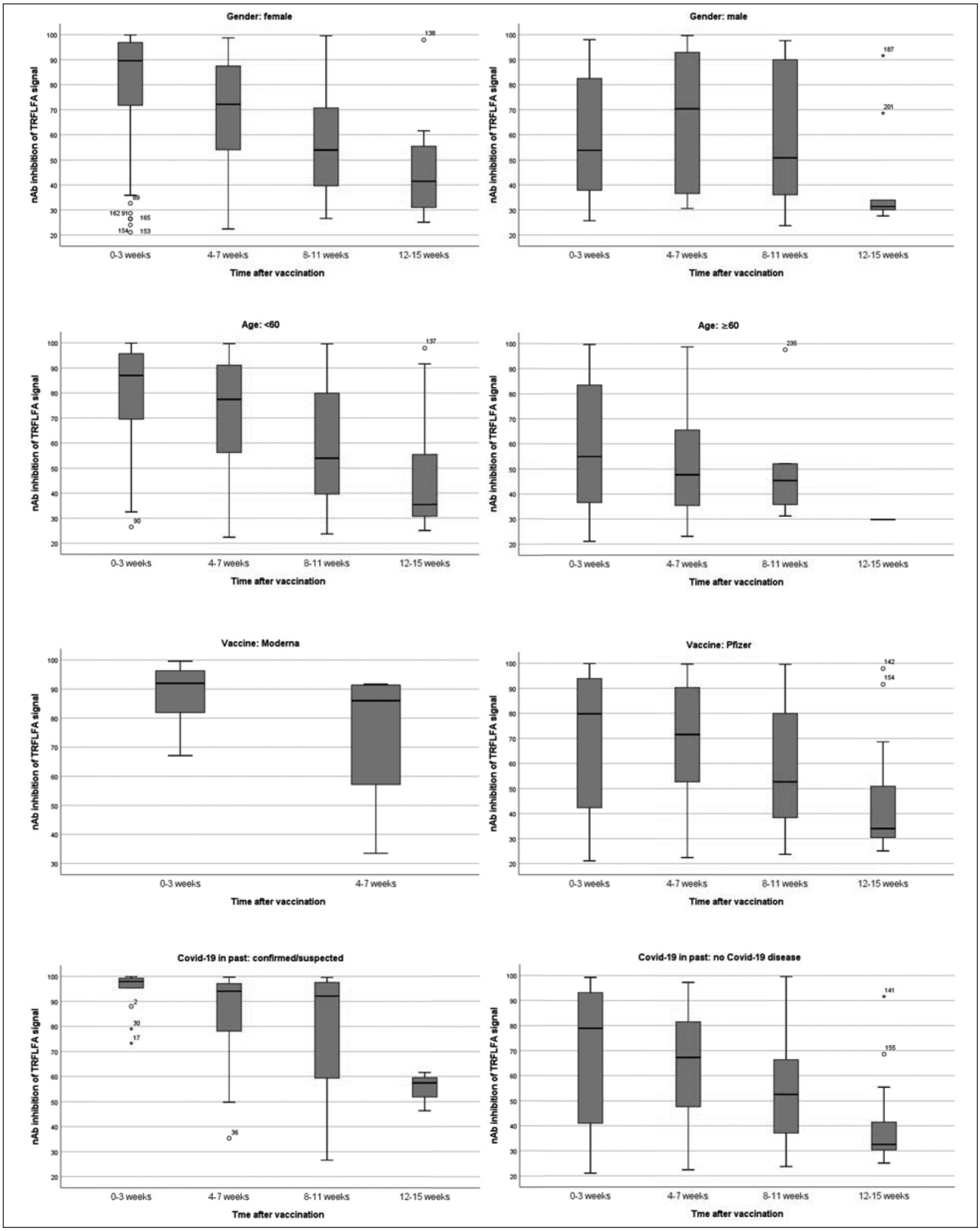

Fig. 2. *nAb inhibition of TRFLFA signal (%) by time after vaccination and by gender (1st raw), age (2nd raw), vaccine brand (3rd raw) and COVID-19 disease in the past (4th raw).*

Table 2. *Qualitative results of IgG Ab by time after vaccination and by gender, age, vaccine brand and COVID-19 disease in the past – % (95% CI) of positive results*

Subgroup		Time after vaccination				Total
		0–3 weeks % (95% CI)	4–7 weeks % (95% CI)	8–11 weeks % (95% CI)	12–15 weeks % (95% CI)	
Gender	Female	82.9 (74.4–91.4)	84.6 (74.8–94.4)	94.3 (86.6–100.0)	92.9 (79.4–100.0)	86.4 (81.4–91.5)
	Male	90.0 (80.7–99.3)	78.6 (57.1–100.0)	92.3 (77.8–100.0)	100.0	89.5 (82.6–96.4)
Age	< 60	84.6 (76.6–92.6)	84.9 (75.3–94.5)	93.0 (85.4–100.0)	95.5 (86.8–100.0)	87.8 (83.2–92.3)
	≥ 60	86.8 (76.1–97.6)	76.9 (54.0–99.8)	100.0 (–)	100.0 (–)	86.0 (76.9–95.0)
Vaccine	Moderna	90.9 (78.9–100.0)	100.0 (–)	–	–	92.3 (82.1–100.0)
	Pfizer-BioNTech	84.0 (76.6–91.4)	82.3 (72.7–91.8)	93.8 (86.9–100.0)	95.7 (87.3–100.0)	86.8 (82.4–91.2)
COVID-19 in the past	Confirmed/suspected	85.7 (67.4–100.0)	93.3 (80.7–100.0)	100.0 (–)	100.0 (–)	92.1 (83.5–100.0)
	No COVID-19 disease	87.5 (80.3–94.7)	77.8 (65.6–89.9)	91.9 (83.1–100.0)	100.0 (–)	87.1 (82.2–92.0)
Total		85.3 (78.9–91.8)	83.3 (74.3–92.3)	93.8 (86.9–100.0)	95.7 (87.3–100.0)	87.4 (83.3–91.4)

Table 3. *Qualitative results of nAb by time after vaccination and by gender, age, vaccine brand and COVID-19 disease in the past – % (95% CI) of positive results*

Subgroups		Time after vaccination				Total
		0–3 weeks % (95% CI)	4–7 weeks % (95% CI)	8–11 weeks % (95% CI)	12–15 weeks % (95% CI)	
Gender	Female	93.3 (87.7–99.0)	96.2 (90.9–100.0)	94.3 (86.6–100.0)	78.6 (57.1–100.0)	93.2 (89.5–96.9)
	Male	95.0 (88.2–100.0)	100.0 (–)	84.6 (65.0–100.0)	77.8 (50.6–100.0)	92.1 (86.0–98.2)
Age	< 60	98.7 (96.2–100.0)	98.1 (94.5–100.0)	90.7 (82.0–99.4)	81.8 (65.7–97.9)	94.9 (91.8–98.0)
	≥ 60	83.8 (71.9–95.7)	92.3 (77.8–100.0)	100.0 (–)	0.0 (–)	85.7 (76.5–94.9)
Vaccine	Moderna	100.0 (–)	100.0 (–)	–	–	100.0 (–)
	Pfizer-BioNTech	92.6 (87.2–97.9)	96.8 (92.4–100.0)	91.7 (83.8–99.5)	78.3 (61.4–95.1)	92.1 (88.6–95.6)
COVID-19 in the past	Confirmed/suspected	100.0 (–)	100.0 (–)	83.3 (53.5–100.0)	100.0 (–)	97.4 (92.3–100.0)
	No COVID-19 disease	91.1 (84.9–97.4)	95.6 (89.5–100.0)	91.9 (83.1–100.0)	81.3 (62.1–100.0)	91.5 (87.4–95.6)
Total		93.9 (89.5–98.3)	97.0 (92.8–100.0)	91.7 (83.8–99.5)	78.3 (61.4–95.1)	92.9 (89.7–96.0)

in preventing VOC-related hospital admissions (83% to 87%), though booster dose was required to achieve protection against Omicron variant similar to the protection against previous VOCs achieved after two-doses scheme (30).

Our results echo results of previous studies showing that humoral immunity against SARS-CoV-2 may not be long-lasting after mRNA vaccination and may weaken in time (11, 12). It is worrying also because the lack of neutralizing capacity correlates with an increased risk of fatal outcomes (31) and neutralizing potency is a strong predictor of survival (32). In line with our results, other studies also show lower humoral response (12–14) and lower vaccine efficacy in older individuals (18).

Methodological Limitations

Presented dynamics of antibody response is not based on individual follow up, so that there was a big variation in sampling interval after the vaccination and sampling was not performed in defined timepoints after the second dose in each individual. Antibody dynamics is based on comparison of antibody levels between groups based on sampling interval, and so there is the risk of confounding results with differences between groups in different time periods following the vaccination. However, stratified analysis shows consistency of our results across different strata by gender, age, vaccine brand, or past COVID-19 infection. We could not adjust our results for the chronic comorbidities or immunosuppressive therapy since these data were not available.

We did not have serological data to control for SARS-CoV-2 infection prior vaccination; just anamnestic data on suspected or confirmed COVID-19 were available. Thus, it was impossible to fully control for booster effect of vaccination in individuals previously exposed to wild virus. Taking into account high prevalence of reported COVID-19 cases in Czechia (more than 1.6 million cases so far) and substantial undocumented (up to 70%) part of SARS-CoV-2 infections (33), we can assume quite high proportion of vaccinees previously exposed to the wild virus. This can also partly explain individual variability in humoral responses to mRNA vaccination and perhaps also lack of dynamics in levels of IgG Ab, which are mix including also antibodies against nucleocapsid of the virus.

Strong Points

Our sample size (n = 253) is quite big as compared to previously published studies on antibody response in persons vaccinated against SARS-CoV-2. Also, although non-representative, our

sample is recruited in non-clinical setting and brings real-world evidence from community setting using point-of-care testing.

CONCLUSIONS

Understanding immune memory after infection and after vaccination against SARS-CoV-2 is critical for future development of the COVID-19 pandemic. Our results show robust humoral response in majority of persons vaccinated with mRNA vaccines. However, our results suggest also rapid decrease of neutralizing antibodies levels in the first four months after completed vaccination. Although immunity is complex and immune memory is a key element of humoral response after exposure to the wild virus, our results suggest that vaccine-induced humoral immunity may not be long-lasting. This highlights importance of booster doses and their role in future control strategies and vaccination schemes at the individual and population level.

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Conflict of Interests

None declared

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Authors' Contribution

JV and SKV were involved in organisation of testing and data collection. VM designed data analysis and concept of the paper. All authors participated in draft paper.

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