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Research Article

Induction of IgA Antibodies Against S1 Protein of SARS-CoV-2 after mRNA Vaccine

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Abstract :

Background

IgA class antibodies produced during SARS-CoV-2 infection showed high neutralizing activity and effective defense of mucous membrane surface. In common use of vaccines against SARS-CoV-2 the production and circulation of specific antibodies in IgA class is important. This study shows specific IgA antibodies after mRNA vaccine against SARS-CoV-2.

Material and Methods

Study included 649 health care workers divided into: group without SARS-CoV-2 virus infection (440 individuals) and group after SARS-CoV-2 virus infection (209 individuals). The occurrence of specific anti S1 IgA antibodies was showed with immunoassay.

Results

The non-infected group showed a stepwise increase of IgA levels after first and second vaccination, followed by a significant drop 3-6 months post-vaccination. Not surprisingly, the post-infected group mounted higher titers, after first and second vaccination in all check points with decline later.

Conclusions

The combination of infection and vaccination gave better response and longer memory of specific IgA antibodies production what suggest longer presence of secretory IgA on mucous surface with protective activity.

Keywords : specific IgA antibodies; SARS-CoV-2 S1 antigen; mRNA vaccine; serology; immune response

Abbreviations:

dIgA -Dimeric IgA
FcαRI - FC receptor
MALT - mucous associated lymphoid tissue,
pIgR - polymeric immunoglobulins receptor,
KIR - NK cells receptors,
DC - dendritic cells,
NET - neutrophil extracellular traps,

ADCC - antibody dependent cytotoxicity,
sIgA -secretory IgA,
IgAD - IgA deficiency,
RBD - receptor binding domain.

1. Introduction

The basic role of immunoglobulins IgA present on mucous surfaces is protection against the attachment of pathogens coming from the environments e.g., food, air and fluids. IgA circulating in serum is produced in bone marrow, spleen and lymph nodes, mainly as monomeric form with short half-life (4-6 days). Human monomeric IgA contains two subclasses – IgA1 and IgA2, distinguished by the length of the hinge region, numerous sequence differences in heavy chain constant regions and glycosylation patterns. The IgA2 is critical for mucosal defense, whereas IgA1 is important for serum IgA functions as suggested by the differential compartmental distribution. Both IgA subclasses show neutralizing and opsonizing pathogen activity in their localization. Mucous associated IgA2 subclass, is in dimeric form (dIgA), produced locally in mucous associated lymphoid tissue (MALT) with side-specific homing IgA-plasmablasts. The third form of IgA is secretory IgA (sIgA) containing a secretory component added to produced dIgA and cleaved during transcytosis through epithelial cells into the mucosal lumen. The IgA operates through binding to its matching Fc receptor (FcαRI) [1-4].

IgA functions and SARS-CoV-2 infection

After binding antigens with Fab binding sites, IgA neutralizes or blocks the activity of pathogens prevents their attachment to host epithelial cells. Moreover, IgA can neutralize toxins derived from pathogens, inhibiting development of symptoms associated with their detrimental activity. Fc□RI belonging to immunoglobulins Fc receptors family is expressed on innate immune cells like neutrophils, eosinophils, monocytes, macrophages, Kupffer cells and some subsets of dendritic cells (DC). Binding of IgA to Fc□RI activates Fc□RI on different cells stimulates their functions e.g., phagocytosis, superoxide generation, release extracellular traps (NET) by neutrophils, antibody dependent cytotoxicity (ADCC) by NK cells, release of cytokine and chemokines and antigen presentation by DC[1,2,4]. The antigen-specific IgA was noted after immunization bacterial antigens and also with viral antigen e.g., polio virus, influenza. The anti-viral role of IgA was suggested after finding HIV-specific IgA in sera of HIV infection survivors [1]. Moreover, selective IgA deficient patients demonstrate higher of mucosal infection and higher incidence of autoimmune diseases [5,6].

In SARS-CoV-2 infection the question of neutralizing activity of specific IgA was important due to protective role of IgA on surface mucous membranes. In experimental model of monoclonal antibodies IgA and IgG class expressed in transgenic mice, the neutralization activity of IgA was higher than IgG against authentic SARS-CoV-2 virus. This tendency was present all tested forms of IgA – monomeric, dimeric or secretory IgA [7].

In a recent clinical study of 64 healthcare workers infected with SARS-CoV-2, monomeric IgA antibodies, specific for S1 spike protein, were assayed in serum, in tears, nasal fluid and saliva, representing mucosal secretory IgA (sIgA). A high level of serum IgA was noted in patients with severe course of SARS-CoV-2 infection, rapidly increasing after symptom's onset [8]. Notable, IgA specific for S1 protein in serum patients with mild course was in low level and decreased within one month. Analyses of sIgA mucosal secretions showed specific sIgA antibodies in asymptomatic individuals or with mild course of disease what suggested the local mucous reaction in the absence of systemic IgA production seen as circulating serum antibodies. Disease severity, gender, rather than age, played an important role in antibody levels. However, there was no relation in time and level, between systemic and local mucosal IgA responses [3,7].

Like in many other viral infections, antibodies to SARS-CoV-2 antigens are produced in all immunoglobulins' classes. Increase of IgA antibodies level in serum strongly correlated with increase of IgG level in sera of 101 SARS-CoV-2 adult patients (76 PCR positive and 25 pandemic survivors). The correlation between IgG and IgA antibodies levels suggested the used of IgA ELISA test as a confirmation of seropositivity during viral infection. Furthermore, the high level of IgA antibodies was helpful to detect SARS-CoV-2 infection in patients with low level of IgG anti S1 protein antibodies [9].

Neutralization of virus is critical for inhibition of virus replication and spreading. Adjusting the amount of IgA to IgG, the potency of neutralization was higher in antibodies of IgA then IgG. The high neutralization activity was shown for circulating monomeric IgA in serum and for secretory IgA purified from bronchial lavage and saliva at different periods of symptomatic SARS-CoV-2 infection. The assay of sIgA neutralization activity showed high potency in late stage of disease, up to 6 weeks after onset of symptoms. Comparison of equivalent amount of IgA subtypes and IgG suggested a highest neutralization activity of sIgA, lower activity of monomeric IgA and IgG [3,5,10,11]. Early occurrence of mucosal sIgA with high neutralization activity represents an important first line of defense against viruses including the SARS-CoV-2. Effectiveness of this compartmental activity is crucial for virus entry into cells, replication and development of clinical symptoms. Vaccines against SARS-CoV-2 are inducing cellular and humoral response to viral proteins with production of specific antibodies, mainly IgG class [10,12]. In the present study S1 protein IgA specific antibodies were tested aiming to explore their post mRNA vaccine activity, in relation to prior symptomatic or non-infected SARS-CoV-2 individuals.

2. Materials and Methods

Patients

The healthcare workers of the University Children Hospital in Krakow, Poland were included in the present study of IgA antibodies production to SARS-CoV-2 S1 spike protein, after vaccinations. Blood samples were withdrawn from the personal who recieved BioNtech-Pfizer BNT162b2 vaccine in two scheduled doses.

The cohort included 46 men and 636 women (682 all together). The age of the volunteers was 20-40 years old (386), 50-60 years old (233), 70-80 years old (9). Sample were collected according protocol showed in Figure 1.

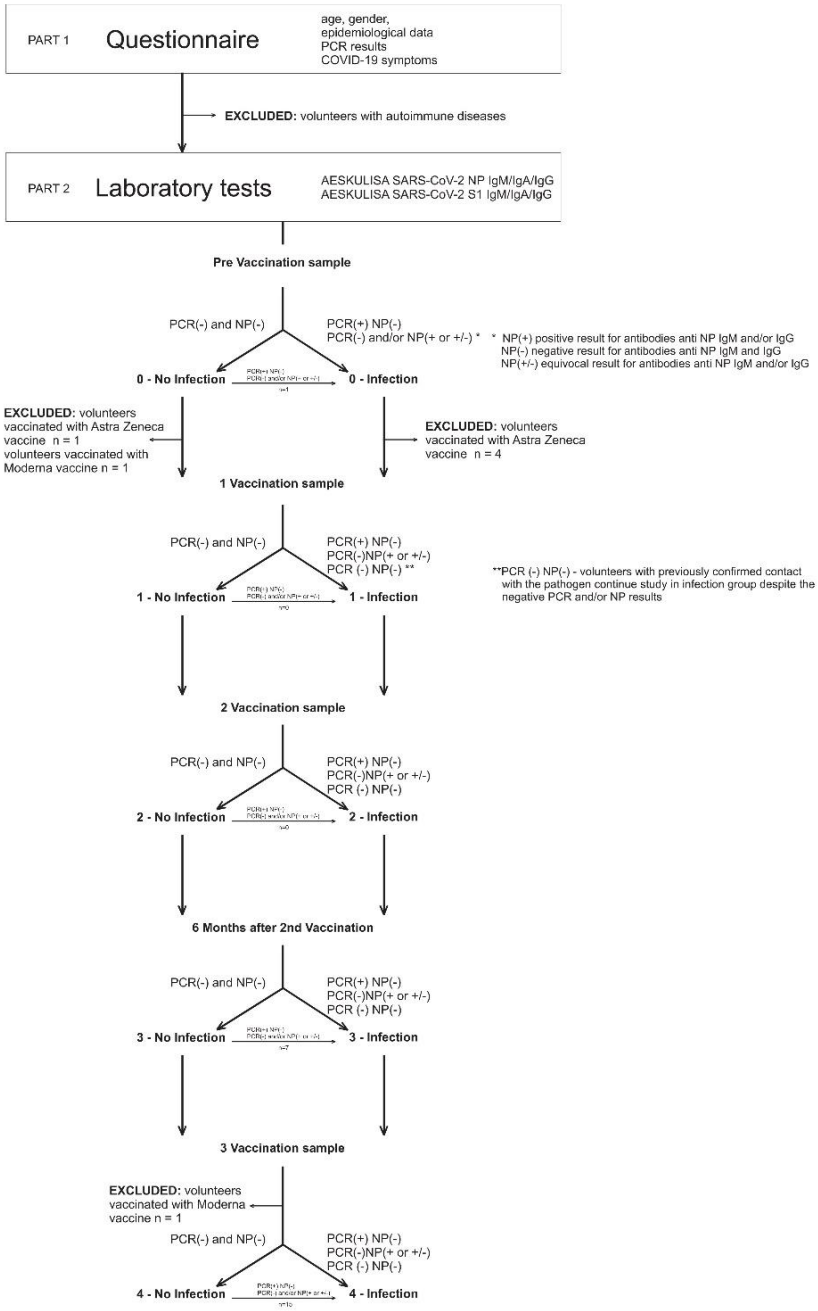
Staff self-reported data on SARS-CoV-2 exposure history, PCR results, signs and symptoms of COVID-19, comorbidities, treatment used, vaccination complications and vaccine tolerance were recorded based on individual questionnaire. Ethical approval was obtained from the Jagiellonian University Medical College Ethics Committee No KBE 1072.6120.61.2021.

Clinical symptoms of SARS-CoV-2 infection of the participating volunteers are shown in Table 1. In the covid-19 infected group (219), the PCR test was performed in 132 (60,2%) with positive results in 128 cases and negative results in 14 cases. In the non-infected group (463), the PCR test was performed in 102 (22,0 %) of the participants and all results were negative. All samples were also checked for presence of anti NP antibodies (IgM and IgG) to identify volunteers with SARS-CoV-2, however, only the IgA results are perently reported.

Staff were grouped into those with evidence of prior infection i.e., the positive and borderline anti-spike or anti-nucleocapsid antibody test (AESKULISA®) or positive PCR prior to the first dose of the vaccine.

Additionaly, positive anti-nucleocapsid antibody test after the second dose of the vaccine, were included. Indications for PCR smears were: contact with virus (patients (mainly children), family, social contacts) or presence of slight or unspecific symptoms suggesting possible SARS-CoV-2 infection. The second non-infected group included volunteers without antibodies to NP, part of them with negative PCR smear results and without any history of possibile contact with SARS-CoV-2 virus. (Figure 1)

Fig.1 Study design



Blood samples were collected from the participants according to the following our worked out schedule:
1-3 days before the administration of the first vaccination for several participants – check point 0
3 weeks (19 - 22 days) after the administration of the first vaccination – check point 1
Within 14 - 22 days and > 22 days after the administration of second vaccination – check point 2.

Figure 1: Study Desing

More than 6 months (170 – 214 days) after the administration of the second vaccination – check point 3. Majority of samples were collected before the end of 6 months, only 15 samples were added later [12].

The time period between the first and the second dose of vaccine was about 3 weeks. The staff immunization program started at the end of December 2020, initially with the Pfizer-BioNTech BNT162b2 vaccine, and since March 2021, part of the staff was vaccinated with AstraZeneca ChAdOx1nCoV-1. Only serum samples of volunteers vaccinated with the Pfizer vaccine were analyzed for IgA antibody titer.

Laboratory assays

The serological analyses were performed in the facilities of AESKU.Diagnostics GmbH & Co. KG in Wendelsheim, Germany, using the AESKULISA® SARS-CoV-2 S1 IgA immunoassay according to the manufacturer instructions. The present study is a part of of an extended project on the serological response to the mRNA-based vaccine where antibody isotypes like anti-IgG S1, IgM S1, IgG NP, IgM NP were analyzed. Only the IgA antibodies results are presently reported as a main aim of this paper.

Statistical analysis

GraphPad Prism version 6.01 was used for statistical analyses. Kruskal-Wallis test was conducted to identify any significant changes in categorical variables over time and between groups. Non-parametric Mann-Whitney (Wilcoxon) test was used to compare quantitative data over time or between groups, respectively.

3. Results

In the non-infected group, serum IgA level, before vaccination (time 0) was low (0.9 U/ml). As expected, IgA antibodies level was higher in the group after prior infection (mean value 6,5 U/ml) with maximal individual value 28.1 U/ml (Table 2). The number of individuals tested before vaccination in those two groups was low (13 in the naïve, 17 infected participants, respectively) because the program of vaccination was introduced earlier than the present study. The response in IgA antibodies to first dose of vaccine was higher in the infected group, when compared to the response in the non-infected group (mean value - 28,0 U/ml and 11,6 U/ml respectively, $p<0.0001$). Following the second vaccine, the level of specific IgA titers increased markedly in the noninfected group. In contrary, increase noted in participants after SARS-CoV-2 infection was small (28,0 U/ml – 35.8 U/ml) (Table 2, Figure.2). Analysis of individual induction of IgA antibodies production after vaccines showed the highest value of 262,4 U/ml, noted in non-infected group.

The analysis of decline of IgA specific antibodies level showed a significant decrease in the non-infected group (mean value 5,9 U/ml - below the limit of cut off), ($p<0.0001$) (Table 2, Figure.2 and 3). Interestingly, in the infected group, level of specific IgA antibodies decreased also, but the mean value was 13,0 U/ml, significantly above the level of IgA specific antibodies in the non-infected group. It should be stressed that in both groups, the decrease of IgA antibodies level tested after two vaccinations and after 6 months was statistically significant ($p<0.0001$) with still higher level in group after infection. The statistical analysis of IgA level after first and second vaccine dose within the non-infected group showed a significant increase ($p<0.01$) between these two check points. In the group of participants, after SARS-CoV-2 infection, the difference between mean value of response to first and second dose of vaccine did not reach a statistical significance. The difference in IgA level between initial level and response to first vaccine in both groups was high, but due to discrepancy of participants numbers, the statistical analysis wasn't performed (Figure.2 and 3).

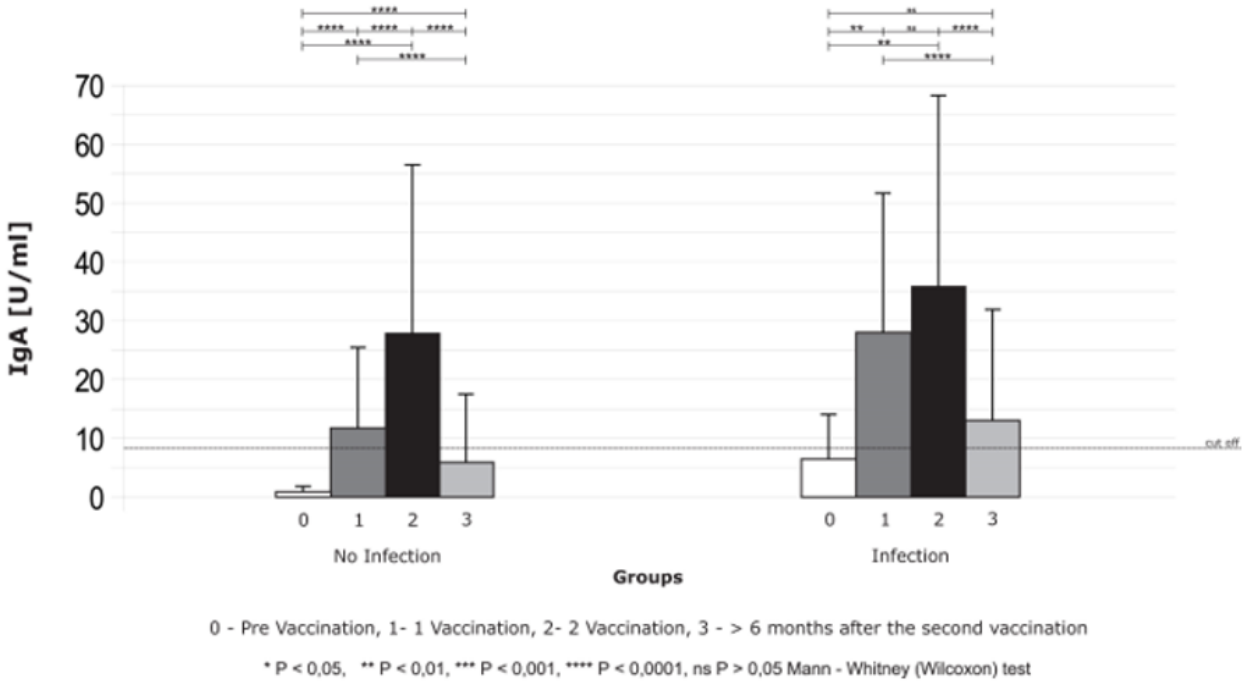


Figure 2: Antibodies IgA class produced Post Vaccination according to prior infection of SARS-Cov-2

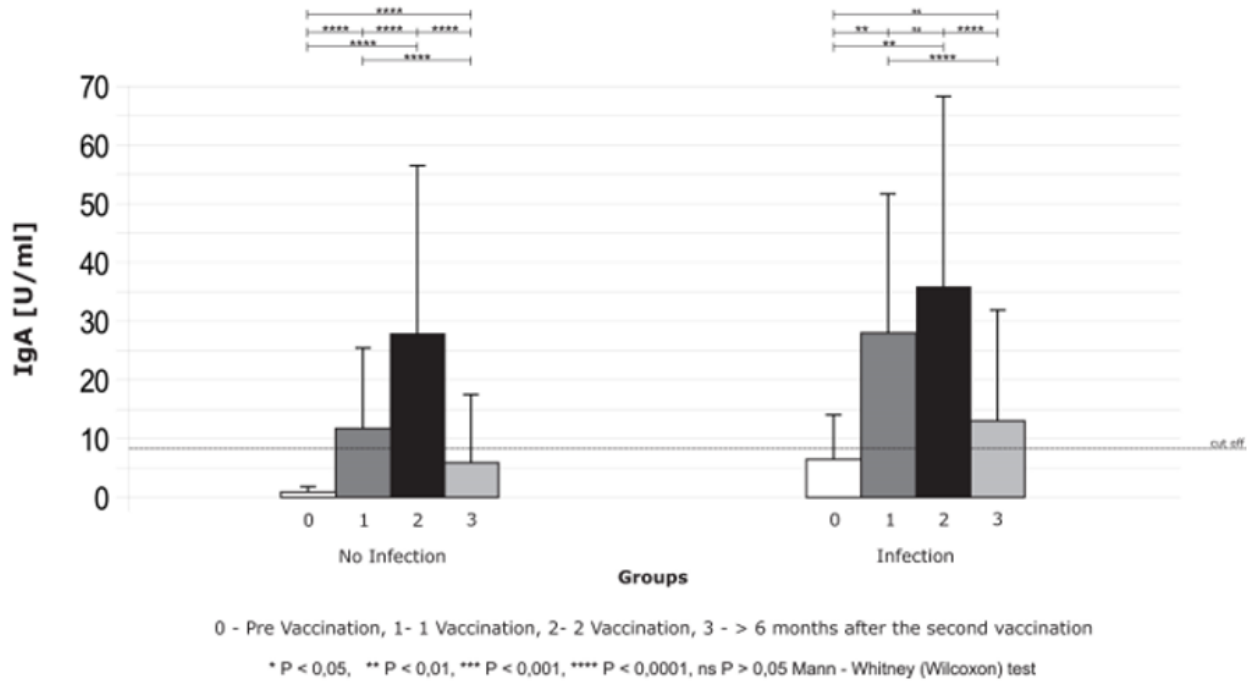


Figure 3: Antibodies IgA class produced Post Vaccination according to prior infection of SARS-Cov-2. Summary of the data set – the minimum, first quadrlle, median, third quadrlle and the maximum.The median is represented by the line in box

The comparison of gG specific antibodies level and IgA showed similar tendency with gentle differences. After first dose of vaccine increase of IgA level was relatively higher in non-infected group as compare to IgG response. In people after contact with SARS-CoV-2 virus, there was no increase of IgG level after second dose of vaccine with deep decrease 6 months later (Table 2, Figure.4).

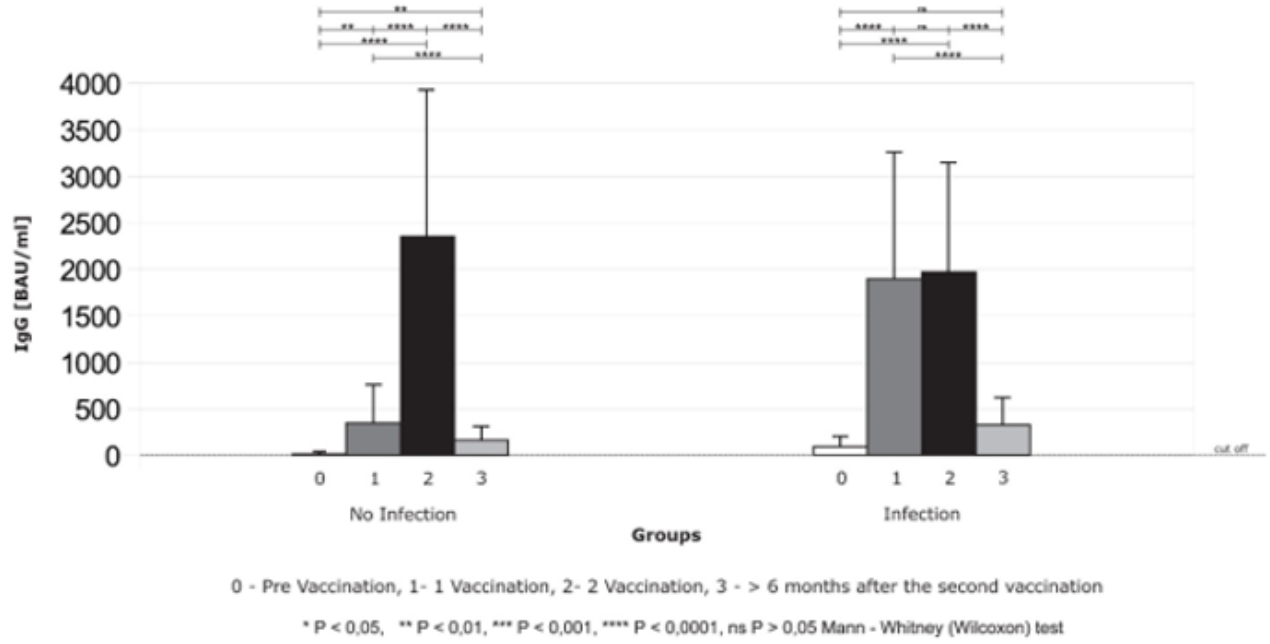


Figure 4: Antibodies IgG class produced post vaccination according to prior infection of SARS- Cov-2

The further analysis of decrease of specific antibodies level with time (selected periods in days) showed no difference between infected and non-infected in IgG antibodies decline in comparison to IgA, when level of specific gA antibodies in people after infection was declining slowly with higher level at the end of observation time (Figure. 5).

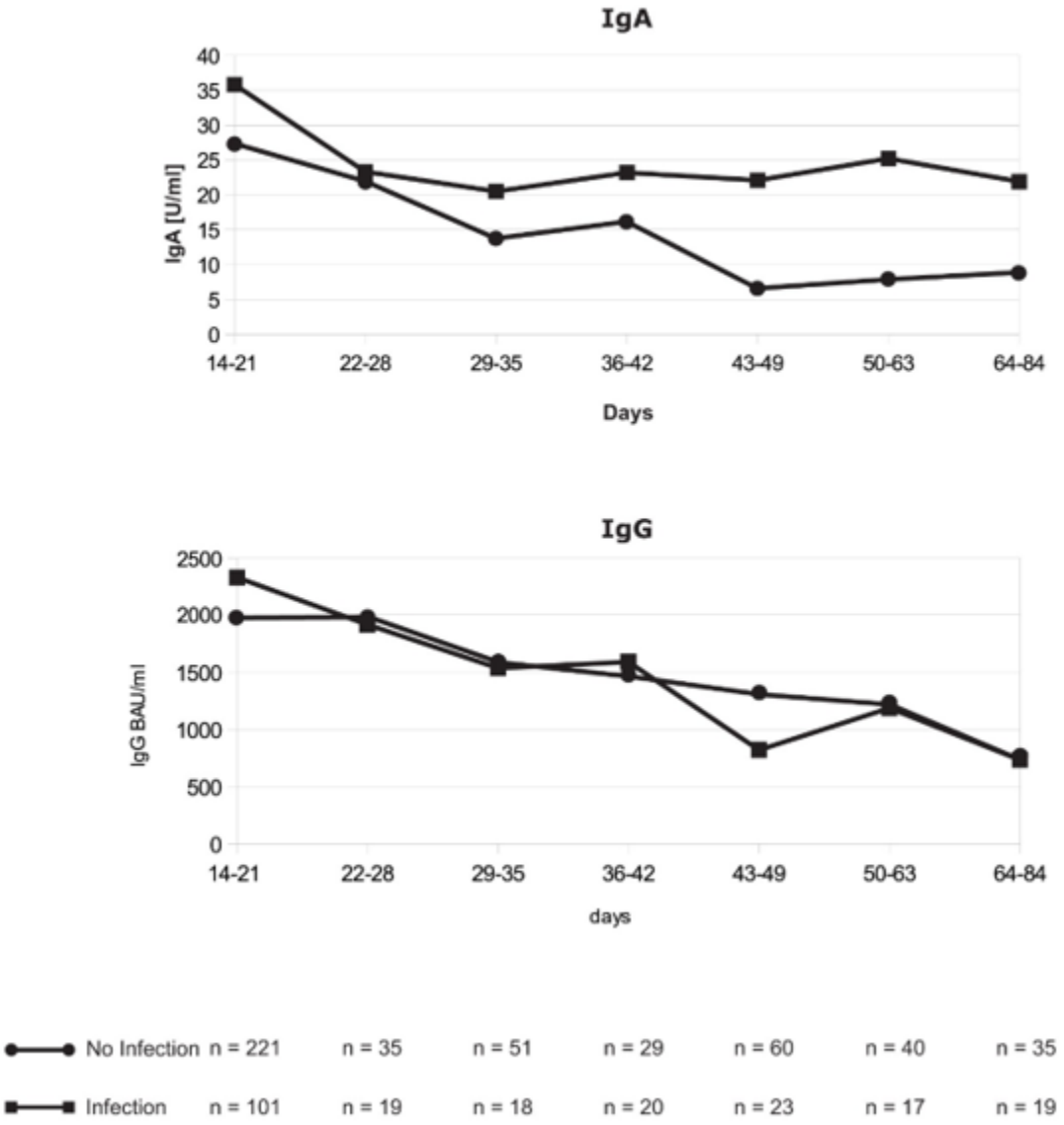


Figure 5: Changes of antibodies levels produced post vaccination after the second dose

4. Conclusions

1. The production and lasting of specific IgA antibodies to SARS-CoV-2 S1 protein is better after prior contact with virus and mRNA vaccine than after vaccine only.
2. mRNA vaccine is inducing IgA producing memory B cells for longer time as compare to IgG, what is associated with better protection of mucous membranes against SARS-CoV-2.

5. Discussion

The effect of two consecutive mRNA vaccinations against SARS-CoV-2 on specific IgA antibodies production was shown in people with or without infection of SARS-CoV-2. There was increase of IgA antibodies level after first followed with second dose of vaccine with decline in 6 months period thereafter. This pattern is know from studies of IgG antibodies production after mRNA vaccine. However, there are some differences between response in IgG immunoglobulin and IgA

immunoglobulin as well as between people with or without virus infection. The results of our study showed better and longer production of specific IgA antibodies to SARS-CoV-2 antigen after infection even mild, supported with vaccination thereafter. These results are comparable to other observations, despite of different time between vaccination and assay of specific antibodies occurrence [14,15]. The possible explanation of differences between IgA response in people with history of prior SARS-CoV-2 infection and people without contact with virus is based on differences between variety of antigens presented by virus during

infection in opposite to one antigen selected for vaccine. The time and dynamic of IgA antibodies decrease in serum was shown as different from IgG level, what might be associated with half-time of IgA circulation in serum or different regulation of production [9,13].

The schedules of vaccination are based on serial assays of occurrence, high level and following decrease of antibodies level in serum after infection and/or vaccines. Data are associated mainly to production and lasting of antibodies to anti-S1 spike protein and/or anti RBD antigen (receptor binding domain). The study of 26 healthcare workers infected with SARS-CoV-2 showed systemic decrease of IgA neutralizing antibodies within 3 months after onset of SARS-CoV-2 symptoms. Similar pattern of anti S1 spike protein antibodies decrease was noted against the RBD antigen. Compared to IgA antibodies, the level of IgG antibodies, in similar periods of observation, showed more stable level in IgA antibodies circulating in serum as monomeric [14]. The presence of monomeric IgA antibodies was thought as representative for all forms of IgA including dimeric form associated with mucous membranes. It was shown is study of secretory IgA occurrence in typical compartments e.g. breast milk during lactation as marker of mucous presence in breast ducts [8,13,14]. Vaccines containing mRNA induce cellular host expression of S1 spike protein followed with adaptive immune response, including production of specific antibodies and occurrence of specific memory T and B cells [15]. The study of specific T lymphocytes showed strong response of CD4+ subpopulation contributed to RBD- binding IgG and antibodies titer. These cells showed increased expression of CD40L (ligand) important for signaling and activating B cells. Vaccines provide long-term protection via generation of memory B cells leading to stimulation of long-lived plasma cells producing specific antibodies. The presence of memory B cells producing specific antibodies in IgG (IgG1, IgG2) class to S full length protein and RBD was shown as wells as production of IgM specific antibodies. There are no data about IgA specific antibodies and memory B cells contributed to this type of antibodies [15].

Cumulating data of antibodies occurrence and lasting after vaccinations suggested higher level of antibodies in people with high pre-vaccination level (after infection even asymptomatic), however, the decrease was significant within 3 months after vaccination without relation to level before vaccination [16,17]. The time of specific antibodies production in both antibodies' isotypes (IgG and IgA) after vaccine, is important for protection against re-infection and represents state of immune system ready for immediate reaction. Within mechanisms involved in protection against re-infections memory T and B cells are playing basic role supporting long-time protective activity of immune system [10,14,18].
The IgA specific antibodies are usually thought as one type, however, different role and activity is presented by subtypes – IgA1 and IgA2. The analysis of IgA antibodies in subclasses IgA1 and IgA2 after vaccination in 27 subjects without contact of SARS-CoV-2 and 19 patients after infection, showed increased level after first vaccine in IgA1 class in both studied groups. IgA2 antibodies titer was below cut - off in subjects without SARS-CoV-2 infection in contrast to increase of IgA2 antibodies in patients after infection [19]. The main role of sIgA is protection of mucous membrane surface, however, it is largely understudied in the context of the SARS-CoV-2 using mucous membrane for entering through ACE2 receptor [20,21]. There is different prevalence of SARS-CoV-2 infections associated with expression of ACE2 receptor – in adult people the nasopharynx and the respiratory tracts were extensively explored, in opposite to children when the intestinal route represent a major port of entry for the virus [22,23,25]. IgA mucosal response is effective in virus neutralization, correlating with disease severity, even in absence of systemic IgA specific antibodies production [3, 23,24,26]. However, the role of IgA is important but not only one in response to SARS-CoV-2 infection, as patients with selected IgA deficiency (IgAD) are not prone to more frequent infection or more severe course of disease [27].
Our study of IgA and IgG specific antibodies production showed better response to vaccine after contact with SARS-CoV-2 virus and longer lasting reasonable level of IgA specific antibodies more than 6 months after second dose of mRNA vaccine. However, there are some limitations to the present study. It includes only IgA monomer, leaving the question about neutralizing capacity of dimeric IgA and secretory IgA on the mucosal surfaces.

The profile of antibodies production in response to vaccines showed systematic increase after consecutive dose of vaccine in majority of people without contact with virus. In people after infection (symptomatic or asymptomatic) this first contact is inducing response, in consequence of this, the first dose of vaccine is working as booster showing highest possible response. The tendency to low or no increased of antibodies production after second dose of vaccine in people after infection was similar in many observations including showed results in our group after infection. It can be summarized, that after a natural occurring SARS-CoV-2 infection, the reactive immunity response is stronger and remains longer than after S1 mRNA vaccine only. These observations are indicating an idea of repeating vaccinations (third and next), especially for people in high risk of re-infection (e.g. health care workers, teachers and others). The problem is in schedule for following vaccinations – time between doses, checking of antibodies level and test for memory T and B lymphocytes specific for SARS-CoV-2 antigens.

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