Does prior SARS-CoV-2 infection increase the risk of adverse effects after mRNA vaccination (BNT162b2) - the retrospective cohort study of physicians.

Keywords
vaccine, adverse effect, Covid19, BNT162b2, Pfizer-BioNTech

Abstract

Introduction
The COVID-19 pandemic has caused major changes in society. The prolonged lockdown led to economic collapse in many countries. Because of this reason, vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the only hope that may reduce spread of the virus. This study aimed to assess the relationship between the severity of adverse effects after COVID-19 vaccine and prior SARS-CoV-2 infection.

Material and methods
578 physicians vaccinated with two doses of BNT162b2 were included in the study. Via a form on the Google Form platform data about past SARS-CoV-2 infection and observed adverse effects after taking the vaccination were collected.

Results
The most common adverse effects were local symptoms (pain at the injection site, limitation of mobility of the upper limb). Pain at injection site occurred in 96,2% of cases after first dose of vaccination. Systemic symptoms (weakness, myalgia, fever) appeared less frequently however after second dose occurred statistically significantly more often than after the first one ($\chi 2 = 121.99, p < 0.001$). Statistically, symptoms appeared more often after the first dose in the group of doctors with previous SARS-CoV-2 infection ($\chi 2 = 10.85, p = 0.001$). Moreover, in this group, the severity of symptoms after first dose was greater ($p < 0.001$). However, an inverse relationship was observed after second dose of the vaccination ($p < 0.001$).

Conclusions
The severity of symptoms after the first dose of the vaccine is greater in people who had been infected with SARS-CoV-2 in the past than people not suffering from COVID-19, but after second dose this relationship is reversed.

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Key words: Adverse effect, BNT162b2, Covid19, Pfizer-BioNTech, vaccine.

Manuscript

Introduction:

New kind of pneumonia with a high potential of human transmission was first reported in Wuhan, Hubei, China in December 2019. The Chinese Center for Disease Control and Prevention and other associated institutions recognized the pathogen as a new type of coronavirus. In February 2020, the International Committee of Taxonomy of Viruses named this virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) based on the phylogenetic similarities of the coronavirus that caused the SARS epidemic in 2003. At the same time, The World Health Organization (WHO) announced COVID-19 name of this novel disease. WHO proclaimed a new coronavirus pandemic on 11 March 2020, due to elevated numbers of infections worldwide. COVID-19 has affected millions of people, until 8 May 2021, there has been reported over 156 million subjects globally (from more than 210 countries) with confirmed SARS-CoV-2 infection. So far 3.2 million deaths have been associated with COVID-19 disease. Poland is one of the most affected countries in the world, accompanied by more than 2.8 million confirmed cases with a mortality of 1848 people per million.[1] Infection of SARS-CoV-2 has a wide clinical spectrum from asymptomatic, mild upper respiratory tract illness (approximately 80% of all) to severe viral pneumonia with acute respiratory failure and deaths as a consequence. The most frequent symptoms are fever, cough, weakness, loss of smell and taste, myalgia, shortness of breath, headache, nausea, diarrhea.[2-4] High and easy transmission is caused by the upper respiratory mode of contagion, long incubation period, sustained time of viral shedding, widespread clinical symptoms, without typical and pathognomy sign and ability to spread the virus by infected people despite the absence of symptoms.[5] All these factors, combined with lack of an effective drug that could be used in the first period of the disease, resulted that globally the only way to stop the virus from spreading was a lockdown of the

society, meaning very restrictive rules of movement. Additionally, many obligatory rules have been put into effect to slow the transmission of the virus by wearing the protective masks, using sanitaries, closing schools, restaurants or restriction of travel by closing borders, which finally have contributed to reducing the number of COVID-19 cases as well as mortality.[5][6] It's unlikely the pandemic appears to abruptly end, and the prolonged lockdown has devastating medical, economic, and social consequences, thus are urgently needed safe and effective vaccines to contain the pandemic.[7–10] Numerous SARS-CoV-2 preventive vaccine projects were initiated immediately after the published genome of this virus, including e.g. technologies that generate inactivated virus vaccine, viral protein subunits vaccine, messenger RNA (mRNA) vaccine, DNA plasmid vaccine, and recombinant human adenovirus.[11] The first remedy was approved by Food and Drug Administration (FDA) was the Pfizer-BioNTech COVID-19 vaccine (BNT162b2). For purpose of this study only this product was described in this effort. Trials have shown that the mRNA vaccine is safe and well-tolerated for preventing SARS-CoV-2 infection. There is based on lipid nanoparticle formulated (LNP) mRNA vaccine technology permits the transport of genetic information to the antigen-presenting cell. The response is reinforced by an adjuvant effect. BNT162b2 encodes the SARS-CoV-2 full-length spike protein, which stimulates both cellular and humoral immune responses. The reported efficacy rates were 95%.[12][13] Healthcare workers are at greater risk of being infected with SARS-COV2, thus in Poland, they were the first group that was vaccinated by Pfizer-BioNTech product.[14][15] Despite that the BioNTech coronavirus vaccine notice as good results in real observation as having been previously described in clinical trials[16], there is a risk that the pandemic won't stop. There is a great number of people who do not want to be vaccinated. This fact can be caused by increasing acts of the anti-vaccination movement especially by internet networks and social media.[17] One of the reasons may be not complete information about possible side effects after vaccination and fear about their occurrence, which is exacerbated by various popular myths.[18] The available clinical trial data showed that the observed adverse effect after the vaccine was of varying intensity depend on e.g age of the participants.[13]

This study aimed to assess the relationship between the severity of adverse effects after Pfizer-BioNTech COVID-19 vaccine and prior SARS-CoV-2 infection.

Material and methods:

Our survey was performed from 15 March to 10 April 2021. Five hundred seventy eight physicians have been enrolled in the survey. The study was carried out via a form, posted on the internet on the Google Form platform, this form was posted on special physician's network groups. Administrators of this group, during registration, verify medical license number of group members. Authors created for this study their own questionnaire. The study was performed anonymously, without collecting patients' personal data. Exclusion criteria were: non-physician, vaccination with an other than Pfizer-BioNTech product and administration of only one dose of vaccine. The study was conducted as a survey that did not fullfill the medical experiment criteria, therefore, did not require Bioethical Committee approval. Decision number: PCN/0022/KB1/61/21 revised by The Bioethics Committee of the Medical University of Silesia. The study group was divided into subgroups depending on the prior SARS-CoV2 infection.

Study questionnaire

The questionnaire contained the following: demographic data (age, gender); anthropometric data (body, mass, height); concomitant diseases: hypertension, hyperthyroidism, hypothyroidism, type 1 or type 2 diabetes, bronchial asthma, rheumatic diseases, chronic colitis, and place to take other; smoking. A section about COVID-19 if a patient suffered that: date of received the positive result of RT-PCR test, symptoms, taken medicine, duration of hospitality, support by oxygen. Part of vaccination included information about the type of vaccine, date of taking both doses, adverse effect after the first and second dose with time of duration, severity and additional medicines taken. Severity was measured with the scale (0 to 10 where 0 is no symptoms and 10 is symptoms that limited normal life) how severe they were. We divided the severity scale range for three groups: mild 1-4, moderate 5-7, and severe 8-10.

Statistical analysis

The collected data were processed via the Statistica TIBCO Software Inc.(2017) version 13.3 program, licensed by the Medical University of Silesia in Katowice. The Shapiro-Wilk test was used to assess the normality of distributions. Continuous variables with non-normal distribution were presented using medians and interquartile ranges (IQR). To compare quantitative variables, the U Mann-Whitney test was used. Between-group differences were evaluated using the chi-square test for categorical variables. We assumed a p-value of less than 0.05 as statistically significant.

Results

Study group characteristics

The study involved 578 physicians. Among the respondents there were 460 (79.6%) women and 118 (20.4%) men. 217 respondents (37.5%) indicated that they suffered from chronic diseases, the most common of which was hypothyroidism (N=75; 13%), hypercholesterolemia (N=43; 7.4%) and hypertension (N=41; 7.1%). 49 (8.5%) from the whole study group also declared that they suffer from obesity (BMI≥30), and 129 (22.3%) from overweight (BMI≥25). The characteristics of the group are presented in Table I.

Table I

COVID-19 infected

Of all the surveyed, 348 (60.2%) had been infected with SARS-CoV-2 in the past. There is a statistically significant relationship between greater body weight and a greater risk of SARS-CoV-2

Table II

infection ($p < 0.05$). For this reason, in the group of overweight people, people suffering from COVID-19 were statistically more often observed ($\chi 2 = 7.4$, $p < 0.05$). Only 6 people (1.7%) required hospitalization because of severe course of infection. Among people who were infected 338 (97.1%) declared symptomatic infection. The most common symptoms are olfactory disorders (72.1%), weakness (70.1%) and headache (59.2%). The characteristics of the symptoms are presented in Table II.

Adverse effects after vaccination

All surveyed physicians were vaccinated with 2 doses of Pfizer-BioNTech COVID-19 vaccine on the day of completing the form. 549 (95%) people reported adverse effects after taking 1 dose, and 526 people reported adverse effects after taking 2 doses of Pfizer-BioNTech COVID-19 vaccine. Overall, nobody had any adverse effects that resulted in hospitalization. The most common adverse effects were local symptoms in the form of pain at the injection site (in 528 cases (96.2%) after first dose and in 447 (85%) after second dose) and limited mobility of the upper limb (in 264 cases (48.1%) after first dose and in 170 cases (32.3%) after second dose).Among the systemic symptoms the most frequent were weakness (in 168 cases (30.6%) after first dose and in 254 cases (48.3%) after second dose) and muscle pain (in 127 cases (23.1%) after first dose and in 199 (37.8%) after second dose). This symptoms in our group are most common in younger participants ($p < 0.01$ for pain at the injection site, $p < 0.001$ for limited mobility of the upper limb and $p < 0.05$ for weakness). Attention should also be drawn to the fact that statistically systemic symptoms occurred more frequently after taking the second dose than after taking the first one ($\chi 2 = 121.99$, $p < 0.001$). Characteristics of the adverse effects are presented in Table III.

Table III

Previous COVID-19 infection vs severity of post-vaccination symptoms

Importantly in the group of people who had suffered from COVID-19 in the past after taking the first dose of the vaccine, adverse effects appeared statistically significantly more often (in 339 cases) than in the group of physicians who were not infected with SARS-CoV- 2 in the past (in 210

cases) ($\chi 2 = 10.85$, $p = 0.001$). However, in the case of the second dose, no statistically significant differences were found in the frequency of symptoms in the group of patients with and without COVID-19 in the past ($\chi 2 = 1.2$, $p > 0.05$). Attention is also drawn to the fact that the surveyed doctors who were not infected with the SARS-CoV-2 virus before vaccination reported a greater severity of adverse effects after taking the second dose of vaccination than in the group of people who did not suffer from COVID-19 ($\chi 2 = 52, 55$, $p < 0.001$) (Fig. 1).

Fig 1

The differences in the severity of adverse effects in these two study groups are also noteworthy. After the first dose of vaccination, people who had been infected with SARS-CoV-2 in the past reported more pronounced severity of symptoms compared to the group of people not suffering from COVID-19 ($p < 0.001$). The situation was completely different after taking the second dose of vaccination, after which the severity of symptoms was greater in the group of people who did not suffer from COVID-19 ($p < 0.001$). The exact data are shown in Figures 2 and 3.

Fig 2 and3

Discussion

The novel coronavirus has caused a worldwide challenging and threatening pandemic COVID-19 with huge health and economic losses. In December 2019, no one expected the coronavirus pandemic to reach such size and spread worldwide, so far over 156 million people have been infected, and 3.2 million of them pass away.[1][19]

As it seems the only way to stop spreading and harvesting its deadly toll is the vaccination. Worldwide were developed some vaccines against SARS-CoV-2. The first two vaccines available in Poland (by Pfizer-BioNTech and Moderna) are messenger RNA (mRNA) vaccines. mRNA vaccines are created as microscopic capsulated lipid nanoparticles containing inside the genetic modification messenger RNA that which is responsible for encodes for a portion of the SARS-CoV-2 S spike or “S” protein. The lipid layer protects and delivers the mRNA to muscle cells after injection. At human cells, mRNA is released and translated into viral proteins. Those proteins are

displayed on the cell surface, which induces the immune response.[20][21] Vaccinations are one of the most valuable medical achievements contributing to the extinction of many diseases.[22] However, the same as any pharmacological product, they can trigger adverse reactions in the body. According to the definition, the adverse vaccine reactions are "any health disorders that may be related to the vaccine taken, that occurred within 4 weeks after administration".[23]

A few methods are being used to contain the spread of the virus and help counter the COVID-19 pandemic: reducing viral transmission (quarantine, face masks, social distancing, use of sanitizers, etc); trying to use different drugs, and finally vaccines.[24] Reduced opportunities for work and meetings cause psychological and economic consequences. [25] Another important issue is the fact that constantly educating about the course and the health hazards related to COVID-19 the society is needed. Study by Kulesza W. et.al showed that increasing the medical knowledge of SARS-CoV2 infection may contribute to compliance with the restriction, and stop spread of the virus, thus contributing to the inhibition of the epidemic.[26]

Therefore herd immunity is needed to avoid them. To achieve it a high percentage of society should have an immune response. Vaccination is the best way to reach it. It is very important to encourage people to get vaccinated, because the increasingly frequent phenomenon among the society is the widespread hesitancy toward or downright rejection of vaccination. The risk of occurs on potential adverse effects should be full transparency and reliable. Regulation of law ought to include information with instruction, how companies should inform patients. The style of presented information has a strong influence on making decisions about therapies and perceptions of their effect. For example, we can provide the probability of not occur this effect or emphasize information that adverse effect like fever, chills, muscle pain, or fatigue are normal reactogenic reaction and indicates that the immune system has been stimulated and it is properly responding to the vaccine.[27][28] There is worth mentioning the example of influenza vaccination, which has been widely used for many years. Despite the different mechanisms of action, adverse effects from influenza vaccines are similar to those against COVID-19, and include pain in the injection site,

weakness, and myalgia. This fact additionally confirms the safety of the vaccination against COVID-19 compared to previous influenza vaccinations.[29]

Our study was made to establish if there is a relationship between adverse effects, their severity after Pfizer-BioNTech vaccine, and prior COVID-19 disease. Large multicenter, placebo-controlled, observer-blinded, pivotal efficacy trial showed that a two-dose regimen of BNT162b2 (30 μg per dose, given 21 days apart) was found to be safe and 95% effective against COVID-19.[13] Our research showed which adverse effects occur the most frequently after first and second dose of vaccination and their severity depending on the history of COVID-19 disease. We described that adverse effects were presented more often after first dose in the group of physicians who suffered from COVID-19 disease in the past than in the group of physicians who were not infected with SARS-CoV- 2 ($p= 0.001$). Results of our study are similar to Tissot N et. al. which has the same observation about side effects after the first dose at people with COVID-19 disease history. Their research group was significantly older than ours (Tissot N et. al. study mean age was 55.4 and in our study was 33). Therefore, we can assume that age of people is not a factor influencing the study result.[30] However, in the case of second dose, no statistically significant differences were found in the frequency of symptoms in the group of patients with and without history of COVID-19.

The worth of attention is also fact that the surveyed physicians who were not infected with the SARS-CoV-2 before vaccination reported greater severity of adverse effects after taking the second dose of vaccination than in the group of people who suffered from COVID-19 ($p<0.001$). It may be related to antibody production and stimulation of the immune system depending on prior exposure to the virus Recent research reports that individuals who had has prior contact with SARS-CoV2 reached similar antibody levels after the first dose vaccine, like was seen in infection-naive persons after two doses.[31]

In our study, we also evaluated occurred adverse symptoms after vaccine. The most common

symptom presented after the first dose were local reactions like pain at the site of injection reported by 91% subjects. The next one occurring in 45% participants was the limitation of the mobility of an upper limb. These data confirm reports published by Fernando B. Polack's et al. which showed that among BNT162b2 recipients, pain at the injection site within 7 days after an injection was the most frequently reported local reaction and occurred in 71% for older than 55 and 85% for younger participants.[13] The difference may be due to the age of the study group, the median of age in our cohort was lower and the intensity of local symptoms in both studies our and Polack's study decreased with age. In our work pain at the site of injection was more common in younger participants and the same for limitation of the mobility of an upper limb. Also, survey from Saudi Arabia performed by Alghamdi AN et. al. has the same observation about the local symptoms of side effects and their severity after the vaccine. It could suggest that ethnic origin does not affect the severity and incidence of side effects.[32] Systemic reactogenicity events were reported more commonly by younger vaccine recipients than by older (over 55 years) and occurs more often after second dose. The explanation could be mobilization of the immune system. Re-contact with the virus in the form of a vaccine causes more severe systemic adverse effects. As it was described by Krammer F et.al. vaccine recipients with immunization acquired by COVID-19 after first dose of vaccine had systemic adverse effects at higher frequencies than those infection-naive. Likewise, the antibodys levels in plasma were 10 to 45 times higher at this persons.[33] Results in many clinical trials are also similar.[13]

In our analysis, the most occurred symptoms in COVID-19 were olfactory disorders, weakness and headache. These results are similar to other research from the world.[2–4] However, we observed that the asymptomatic course of the disease was significantly less frequent than described by other scientists, e.g Kenji Mizumoto et.al had examined that it was 51.7%, and Hiroshi Nishiura et.al reported 30.8% asymptomatic infection.[34] In our study only 2.9% (N=10) people declared it. The difference may arise from the fact that the survey took part only physicians, which could recognize symptoms correctly, without ignoring any, even the least disruptive. We believe that a properly

collected medical interview is crucial for right diagnosis and it would allow the referral on RT-PCR test faster.

We would like to emphasize that one of the study limitations could be the recruitment method of participants, in order to remain anonymous except for the appropriate selection in the survey, we resigned on verifying that persons included in the study were actually physicians. We relied on verification by administrators of network groups.

Conclusions:

Our study showed that the severity of symptoms after the first dose of the vaccine is greater in people who had been infected with SARS-CoV-2 in the past than people not suffering from COVID-19. However, people who had not suffered from COVID-19 previously presented more severe adverse effects after the 2nd dose. Additionally, we suggest that a thorough medical interview is essential and if carried out correctly, it may reduce the percentage of diagnosed "asymptomatic courses", which will allow being referred for tests faster, preventing the spread of the virus.

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Table I . Study group characteristics

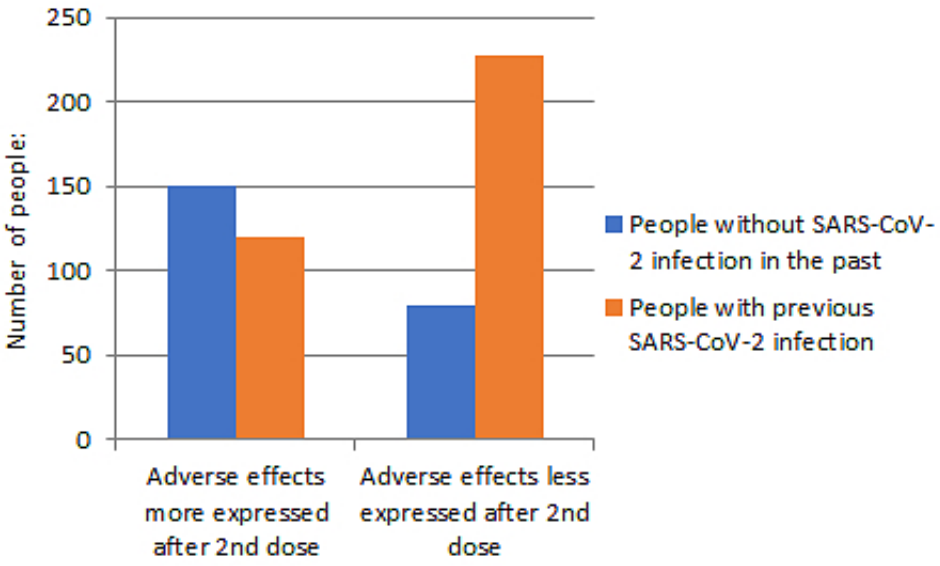
		Diagnosed COVID-19 in past		
	All subjects [N = 578]	**Yes [N = 348]**	**No [N = 230]**	**Statistical significance (p)**
Men [N(%)]	118 (20.4%)	71 (20.4%)	47 (20.4%)	0.99
Women [N(%)]	460 (79.6%)	277 (79.6%)	183 (79.6%)	0.99
Age [years]	33 (28-42)	34 (29-42)	31 (28-42)	0.1
≤30 [N(%)]	225 (38.9%)	125 (35.9%)	100 (43.5%)	0.06
31-40 [N(%)]	196 (33.9%)	128 (36.8%)	68 (29.6%)	0.07
41-50 [N(%)]	93 (16.1%)	56 (16.1%)	37 (16.1%)	0.99
51-60 [N(%)]	50 (8.7%)	32 (9.1%)	18 (7.8%)	<0.05
>60 [N(%)]	14 (2.4%)	7 (2%)	7 (3%)	0.42
Body mass [kg]	65 (57-77)	65.5 (58-78)	64 (55-75)	<0.05
Height [cm]	169 (164-175)	169 (164- 175)	168.5 (164-174)	0.86
BMI [kg/m^2]	22.6 (20.5-25.9)	22.8 (20.6-26.3)	22.3 (20,1-24,8)	<0.05
Overweight [N(%)]	129 (22.3%)	91 (26.1%)	38 (16.5%)	<0.01
Obese [N(%)]	49 (8.5%)	35 (10%)	14 (6%)	0.09
Smokers [N (%)]	108 (18.7%)	60 (17.2%)	48 (20.1%)	0.27
Past	57 (9.8%)	31 (8.9%)	26 (11.3%)	0.34
Active	51 (8.8%)	29 (8.3%)	22 (9.5%)	0.77
Co-morbidity [N (%)]	217 (37.5%)	126 (36.2%)	91 (39.6%)	0.41
Hypothyroidism	75 (13%)	44 (12.6%)	31 (13.5%)	0.77
Hypercholesterolemia	43 (7.4%)	25 (7.2%)	18 (7.8%)	0.77
Hypertension	41 (7.1%)	20 (5.7%)	21 (9.1%)	0.12
Asthma	24 (4.2%)	14 (4%)	10 (4,3%)	0.84
Allergies	19 (3.2%)	8 (2.3%)	11 (4.7%)	0.1
Polycstic ovary syndrome	10 (1.7%)	5 (1.4%)	5 (2.1%)	0.5
Reumatological diseases	6 (1%)	5 (1.4%)	1 (0.4%)	0.24
Hyperthyroidism	6 (1%)	3 (0.8 %)	3 (1.3%)	0.6
Oncological disorders	4 (0.7%)	2 (0.6%)	2 (0.9%)	0.67
Diabetes melitus type 2	4 (0.7%)	3 (0.8%)	1 (0.4%)	0.54
Heart failure	3 (0.5%)	1 (0.3%)	2 (0.9%)	0.34
Inflammatory bowel diseases	2 (0.3%)	2 (0.6%)	0	0.24
Chronic kidney disease	2 (0.3%)	2 (0.6%)	0	0.24

Table II. Occurance of symptoms during SARS-CoV-2 infection

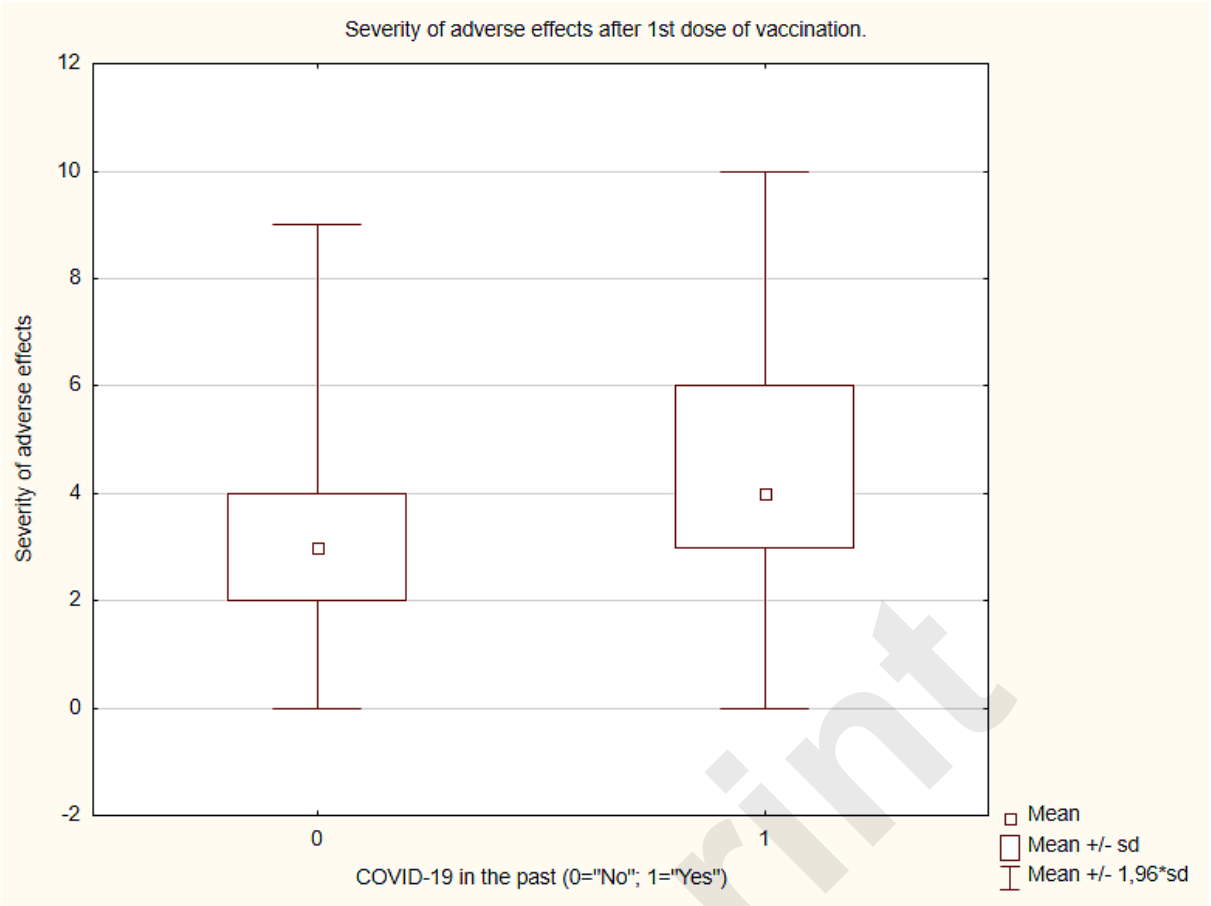
	Allsubjects [N = 338]
Olfactory disorder [N(%)]	251 (72.1%)
Weakness[N(%)]	244 (70.1%)
Headache [N(%)]	206 (59.2%)
Musclepain [N(%)]	201 (57.7%)
Taste disturbance [N(%)]	193 (55.5%)
Cough [N(%)]	166 (47.7%)
Decrease in exercise tolerance [N(%)]	156 (44.8%)
Low-grade fever [N(%)]	138 (39.7%)
Concentration disorders [N(%)]	122 (35.1%)
Rhinitis [N(%)]	116 (33.3%)
Fever [N(%)]	112 (32.2%)
Sinusitis [N(%)]	93 (26.7%)
Dyspnoea [N(%)]	50 (14.4%)
Diarrhoea [N(%)]	46 (13.2%)
Nausea [N(%)]	35 (10%)
Abdominal Pain [N(%)]	30 (8.6%)
Skin disorders [N(%)]	18 (5.1%)
Decrease in saturation below 92% [N(%)]	14 (4%)

Table III. Occurance of adverse effects after vaccination

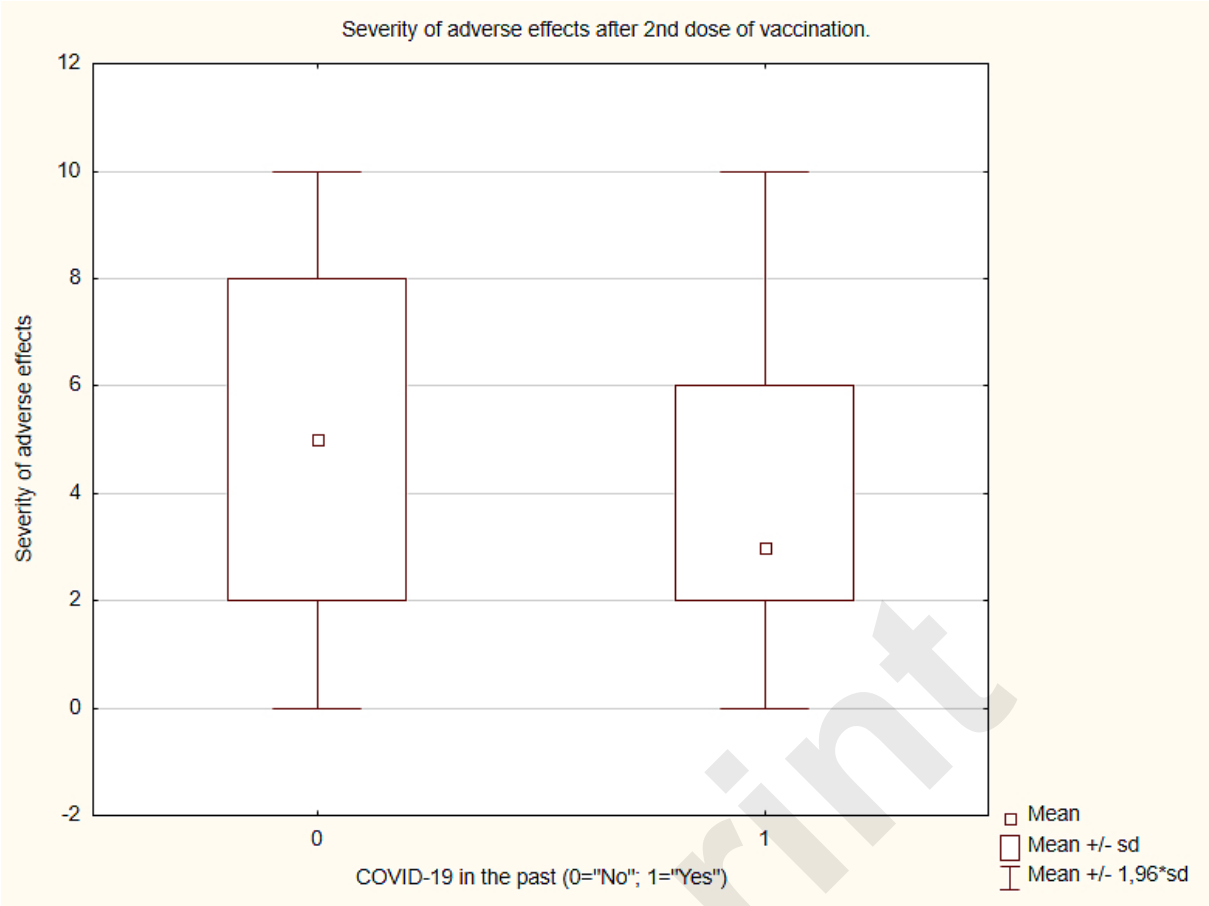
	First dose of vaccination [N = 578]	**Second dose of vaccination [N = 578]**
Pain at the injection site [N(%)]	528 (96.2%)	447 (85%)
Limitation of mobility of the upper limb [N(%)]	264 (48.1%)	170 (32.3%)
Weakness [N(%)]	168 (30.6%)	254 (48.3%)
Muscle pain [N(%)]	127 (23.1%)	199 (37.8%)
Somnolence [N(%)]	103 (18.8%)	129 (24.5%)
Reddening at the injection site [N(%)]	86 (15.7%)	56 (10.6%)
Schivers [N(%)]	83 (11.1%)	166 (31.6%)
Arthralgia [N(%)]	53 (9.6%)	120 (22.8%)
Lymohadenopathy[N(%)]	39 (7.1%)	61 (11.6%)
Concentration disorders [N(%)]	37 (6.7%)	71 (13.5%)
Fever [N(%)]	30 (5.5%)	106 (20.2%)
Headache [N(%)]	27 (4.9%)	33 (6.3%)
Nausea [N(%)]	23 (4.2%)	41 (7.8%)
Insomnia [N(%)]	6 (1.1%)	0 (0%)
Abdominal pain [N(%)]	6 (1.1%)	20 (3.8%)
Skin disorders [N(%)]	5 (0.9%)	16 (3%)
Diarrhea [N(%)]	0 (0%)	13 (2.5%)



Severity of adverse effects after the second dose of the vaccine compared to the adverse effects after the first dose in the group of people with and without previous COVID -19 disease



Severity of adverse effects after the first dose of the vaccine in the group of people with and without previous COVID -19 disease. (p <0.001)



Severity of adverse effects after the second dose of the vaccine in the group of people with and without previous COVID -19 disease. ($p < 0.001$)