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Safety of Pfizer-BioNTech COVID-19 mRNA vaccine in the elderly

Short title: Artur Cieślewicz et al., Safety of Pfizer-BioNTech COVID-19 mRNA vaccine in the elderly

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ABSTRACT

Introduction: COVID-19 is an infectious viral disease that has affected more than 775 million people and has caused more than 7 million deaths worldwide. According to scientific data, the patient's age is the most important factor influencing the risk of severe disease course, including a substantially higher risk of death. Therefore, developing and distributing COVID-19 vaccines have become crucial in protecting this age group. Another thing typical for the elderly is that they usually suffer from many ailments, so polypharmacy is a common phenomenon among them.

Objective: The study aimed to analyze adverse reactions that occurred after administration of the Pfizer BioNTech vaccine against SARS-CoV-2 in a group of elderly individuals. Moreover, the relationship between the occurrence of adverse reactions and the pharmacotherapy used was examined.

Material and methods: The information concerning post-vaccination adverse effects, COVID-19 in the past, and current pharmacotherapy was collected via the analysis of medical documentation of 200 people aged 60 years or older. Statistical analysis was performed using StatSoft Statistica 13.1 software.

Results: Twenty-three participants reported adverse effects after vaccination (including fatigue, fever, and pain at the injection site) while 177 did not. The participants taking such drugs as agents acting on the renin-angiotensin system, analgesics and anti-inflammatory drugs, antithrombotic agents, calcium channel blockers, diuretics, drugs for acid-related disorders, lipid modifying agents, mineral supplements, psychoanaleptics, psycholeptics, and vitamins were less likely to experience adverse effects post-vaccination.

Conclusions: Adverse effects in the elderly population are rare and do not pose a threat to the health and life of the patient. Chronic pharmacotherapy may influence the risk of experiencing adverse effects.

Keywords: COVID-19 vaccine, pharmacotherapy, safety, the elderly

Introduction

According to the WHO (World Health Organization) data, COVID-19 (coronavirus disease 2019) has affected more than 775 million people and has caused more than 7 million deaths worldwide [1]. The risk factors for the severe course of the disease include male sex, obesity, smoking, and comorbid and chronic conditions; however, age is the most important factor [2–6]. Older people are at risk of COVID-19 complications and death: according to CDC (Centers for Disease Control and Prevention) data, the risk of death becomes substantially higher in people aged 50+ years compared to 18–29 years old (from 25 times higher in patients aged 50–64 years to 340 times higher in those ages 85+ years) [7]. As a result, the development and distribution of COVID-19 vaccines have become crucial in protecting this age group. Vaccination efforts have focused on prioritizing the elderly, recognizing their vulnerability, and the need to reduce the disease burden within this population [8].

COVID-19 vaccines have been extensively studied and proven to be safe and effective in preventing severe illness, hospitalization, and death associated with the virus. According to the WHO, there are eight COVID-19 vaccines on the Emergency Use Authorization list. These vaccines utilize different mechanisms, including mRNA technology and viral vector-based platforms, to elicit an immune response against the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) [9].

COVID-19 vaccines proved to have high effectiveness in the elderly, demonstrating the importance of immunization in this age group [10, 11]. While the immune system may naturally weaken with age, studies have indicated that older adults still mount a substantial immune response following vaccination [12–14]. Vaccines are effective in preventing severe illness, reducing the risk of hospitalization, and decreasing the likelihood of death among the elderly population [15–17].

In addition to the direct benefits of vaccination, COVID-19 vaccines also play a crucial role in protecting the elderly by contributing to herd immunity. Herd immunity occurs when a significant portion of the population is immune to a disease, making it difficult for the virus to spread and protecting those who cannot receive the vaccine due to medical conditions or other reasons. By vaccinating the elderly, we reduce their individual risk and create a protective barrier for the entire community [18].

To ensure equitable access to vaccines for the elderly, many countries have implemented prioritization strategies and vaccination campaigns specifically tailored to this population [19]. Vaccination efforts often involve mobile clinics, outreach programs, and partnerships with healthcare providers to reach elderly individuals in nursing homes, long-term care facilities, and homebound settings [20]. These initiatives aim to overcome barriers such as limited mobility, transportation issues, and access to healthcare, ensuring that vulnerable elderly individuals can receive the COVID-19 vaccine.

As the global fight against COVID-19 continues, ongoing research and monitoring are essential to evaluate the long-term effectiveness and safety of the vaccines in the elderly population. Continued surveillance will provide valuable data on the duration of protection, the potential need for booster doses, and any rare adverse events that may emerge over time.

The elderly are a heterogeneous group with many ailments, using various pharmacotherapy. They often use drugs with complex mechanisms of action that may influence the vaccination-related adverse effects. The present paper presents the initial results of the analysis of adverse effects after the Pfizer BioNTech vaccine against SARS-CoV-2 in the group of older people and the relationship between the occurrence of adverse reactions and the pharmacotherapy used by the participants.

Material and methods

The research was a retrospective study on 200 people aged 60 or older who received two doses of the COVID-19 mRNA vaccine (Pfizer). Information was collected via the analysis of medical documentation concerning:

— adverse effects observed after vaccination,

— COVID-19 in the past,

— pharmacotherapy used by the participants.

The population was divided into two groups based on the presence (group 1) or absence (group 2) of vaccination adverse effects. Drugs used by participants were grouped according to the Anatomical Therapeutic Chemical (ATC) Classification. Statistical analysis was performed using StatSoft Statistica 13.1 software. The Shapiro-Wilk test was used to assess the normality of the distribution of numeric variables. The Mann-Whitney U test was used to calculate the significance concerning the age of participants. Pearson's chi-square was used to calculate differences concerning categorical variables (participants' sex, occurrence of COVID-19, and pharmacotherapy). Yates correction was applied if the expected frequencies were lower than 5. Phi coefficient was calculated to assess the strength of the association between variables.

The study is a retrospective analysis of data from medical documentation. According to Poznan Medical University Bioethics Committee regulations, no ethics-committee approval is necessary in such a situation. No data allowing for the identification of patients was included in the publication.

Results

Twenty-three people reported adverse effects after vaccination (group 1), while 177 (group 2) did not. The most common adverse effects included fatigue, fever, and pain at the injection site (Table 1).

The participants' ages ranged from 60 to 92 (average 70.37 ± 6,44) and had abnormal distribution, revealed by the Shapiro-Wilk test ($p = 0.000$). The average age was significantly higher in group 2 (70.88 *vs*. 66.43 years; $p = 0,002$; Fig. 1). Drug groups that were most frequently taken by participants included agents acting on the renin-angiotensin system, diuretics, lipid modifying agents, antithrombotic agents and calcium channel blockers (Table 2). Patients most commonly took such drugs or supplements as amlodipine, ASA (acetylsalicylic acid), indapamide, magnesium, and vitamin D3 (Table 2).

Table 3 presents the results of the statistical analysis of categorical variables. The groups did not differ concerning the sex and COVID-19 course in the past. A statistically significant difference was found for the following drug groups: agents acting on the renin-angiotensin system (weak negative association), analgesics and anti-inflammatory drugs (weak negative association), antithrombotic agents (moderate negative association), calcium

channel blockers (weak negative association), diuretics (moderate negative association), drugs for acid-related disorders (weak negative association), lipid modifying agents (weak negative association), mineral supplements (weak negative association), psychoanaleptics (negligible negative association), psycholeptics (weak negative association), and vitamins (negligible negative association). The participants taking drugs from these groups were less likely to experience adverse effects post-vaccination.

We decided to check if particular drugs from these significant groups were associated with a decreased frequency of post-vaccination adverse effects. The results are presented in Table 4. Seven such drugs were identified: amlodipine (weak negative association), ASA (moderate negative association), atorvastatin (negligible negative association), indapamide (negligible negative association), magnesium (weak negative association), ramipril (negligible negative association), and vitamin D3 (negligible negative association).

Discussion

According to WHO data, 15% of patients with COVID-19 develop severe disease, and 5% require intensive care [21]. The risk of severe COVID-19 increases with age. Therefore, adults aged 65 and older were among the first to receive the vaccination. Pfizer-BioNTech mRNA vaccine was the first COVID-19 vaccine registered for use in individuals aged 16 years and older [22]. Currently, in Poland, the number of fully vaccinated people exceeds 22 million. Almost 42% of vaccines were administered to people aged 60+ years [23]. According to the data from clinical trials, the effectiveness of Pfizer-BioNTech mRNA vaccines in patients aged 65 years and older is over 95% [10]. Another important aspect is the vaccine's safety, as many adverse effects (such as increased blood pressure, pain, and gastrointestinal disturbances) may be falsely interpreted as a symptom of a new disease of the patient and, therefore, cause the introduction of new unnecessary pharmacotherapy.

Like any vaccine, the Pfizer-BioNTech vaccine can cause temporary adverse effects, which are generally mild and resolve on their own within a few days. Common adverse effects reported in the elderly include pain at the injection site, fatigue, headache, muscle pain, chills, fever, and joint pain [10]. These adverse effects generally indicate the body’s immune response to the vaccine and are expected as the immune system is stimulated. Serious adverse effects, although rare, have been reported in some individuals, including the elderly. These include severe allergic reactions (anaphylaxis), myocarditis (heart muscle inflammation), and blood clotting disorders. However, it is crucial to note that these severe adverse effects are infrequent, and the benefits of vaccination in preventing COVID-19 outweigh the risks [24,

25]. Healthcare professionals closely monitor vaccine safety and continue to assess and investigate any reported adverse events to ensure the ongoing safety of the vaccine, particularly in vulnerable populations such as the elderly. It is vital for individuals, including the elderly, to consult their healthcare provider if they have any concerns or experience any unexpected or persistent symptoms after receiving the Pfizer-BioNTech COVID-19 vaccine.

Our results confirmed that adverse effects after vaccination affect a relatively small number of patients and are mild. It is consistent with results obtained in other studies [13, 26, 27]. Moreover, older people tend to have less frequent adverse effects than younger populations [13, 26, 27]. The present data indicated that such diversity could be observed even within the group of older patients: the group with no adverse effects was older than those who developed adverse effects after the vaccine. Biological ageing is known to negatively impact the immune system's functioning (immunosenescence) [28]. The inflammation state, associated with immunosenescence, is a pathomechanism responsible for many age-related disorders (e.g., cardiovascular diseases, rheumatologic diseases, and chronic pain) [29–31]. It can be characterized by redness, swelling, heat, pain, and loss of tissue function resulting from local immune, vascular, and inflammatory cell responses.[32] Moreover, inflammation plays a significant role in severe COVID-19 course [33]. Immunosenescence also significantly reduces naïve T cells that can respond to a vaccine, decreasing the effectiveness of vaccination in older people [2].

Data from clinical trials indicated that adverse effects most commonly observed after the BoNTech mRNA COVID-19 vaccine are typical for acute and chronic inflammation [26]. The results of the present study confirm this observation. The elderly usually take many drugs for chronic disorders typical for this population, such as pain, cardiovascular diseases, CNS (central nervous system) disorders, and diabetes, with some of them having an anti-inflammatory effect [34–47]. ACE (angiotensin-converting enzyme) inhibitors (ACEIs) like ramipril reduce inflammatory markers such as CRP (C-reactive protein), IL-6 (interleukin 6), and TNF-α (tumor necrosis factor-alpha), also enhancing nitric oxide and vasoactive prostaglandins levels by preventing bradykinin degradation [35]. Moreover, Ramipril was shown to decrease pain threshold levels [36]. Calcium channel blockers (CCBs) suppress immune cell activation and reduce inflammatory markers such as NF-κB (nuclear factor kappa B) and COX-2 (cyclooxygenase 2) [37, 38]. Statins modulate immune responses by interfering with endothelial adhesion and leukocyte migration, reducing vascular inflammation and circulating CRP levels [39–41]. Indapamide decreases monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1alpha (MIP-1

alpha) and was shown to reduce oxidative stress and inflammation of the renal cortex in animal models [42]. Metformin also exerts anti-inflammatory effects, beneficial for cardiovascular health in diabetic patients by suppressing NF-κB activation via AMPK (5’ adenosine monophosphate-activated protein kinase)-mediated pathways [43–45]The anti-inflammatory effects of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are mediated through multiple mechanisms. SSRIs such as sertraline and escitalopram reduce pro-inflammatory cytokines like IL-1β (interleukin-1 beta), TNF-α, and IL-6, and modulate neurotoxic metabolites of the kynurenine pathway. They also impact gene expression related to inflammation and endothelial dysfunction, such as ICAM1 (intercellular adhesion molecule 1), VCAM1 (vascular cell adhesion molecule 1), COX2 (cyclooxygenase 2), and iNOS (inducible nitric oxide synthase). SNRIs, including venlafaxine, regulate the immune system by modulating stress responses and reducing oxidative and nitrosative stress, thereby protecting against cognitive deficits and inflammation. Both SSRIs and SNRIs influence the balance of neurotransmitters and mitigate inflammatory processes, which may contribute to their therapeutic efficacy in treating depression [46]. Proton pump inhibitors (PPIs), commonly used to treat acid-peptic disorders, also exhibit significant anti-inflammatory effects independent of gastric acid suppression. Key mechanisms include prevention of oxidative damage in tissues by PPIs like omeprazole, lansoprazole, and esomeprazole, reduction of neutrophil functions like ROS (reactive oxygen species) release and chemotaxis and their adhesion, lowering the production of pro-inflammatory cytokines such as IL-8 (interleukin 8) and TNF-α, likely by interfering with the NF-κB pathway and modulation of gut microflora [47].

Such ongoing pharmacotherapy may influence the risk of the most common adverse effects associated with inflammation (pain, fever). Indeed, the present data indicated that the use of drugs with anti-inflammatory and analgesic effects was higher in the group of participants who did not report adverse effects after vaccination. Chronic anti-inflammatory therapy may affect the immune response to the vaccine [48]. However, no recommendations suggest withholding NSAIDs (non-steroidal anti-inflammatory drugs) or other anti-inflammatories before receiving the COVID-19 vaccine [49].

Our study has some limitations concerning a relatively small number of participants and high disproportion between studied groups. Moreover, it would be worth considering the assessment of SARS-Cov-2 antibodies to estimate the immune response of the participants. Therefore, the research has been continued to provide more valuable data.

Conclusions

The results of the present study confirm that adverse effects in the elderly population are rare and do not pose a threat to the health and life of the patient. Moreover, chronic pharmacotherapy may influence the risk of experiencing adverse effects, likely due to the potential analgesic and anti-inflammatory effects of certain drug groups.

List of abbreviations:

ACE — angiotensin-converting enzyme
ACEIs — ACE inhibitors
AMPK — 5’ adenosine monophosphate-activated protein kinase
CCBs — calcium channel blockers
CDC — Centers for Disease Control and Prevention
CNS — central nervous system
COVID-19 — coronavirus disease 2019
COX2 — cyclooxygenase 2
CRP — C-reactive protein
ICAM1 — intercellular adhesion molecule 1
IL-1β — interleukin-1 beta
IL-6 — interleukin 6
IL-8 — interleukin 8
iNOS — inducible nitric oxide synthase
MCP-1 — monocyte chemoattractant protein-1
MIP-1 — alpha macrophage inflammatory protein-1alpha
NF-κB — nuclear factor kappa B
NSAIDs — non-steroidal anti-inflammatory drugs
PPIs — proton pump inhibitors
ROS — reactive oxygen species
SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2
SNRIs — serotonin-norepinephrine reuptake inhibitors
SSRIs — selective serotonin reuptake inhibitors
TNF-α — tumor necrosis factor-alpha
VCAM1 — vascular cell adhesion molecule 1
WHO — World Health Organization

Article information

Data availability statement: *Data available on demand after contacting the authors.*
Ethics statement: *The study is a retrospective analysis of data from medical documentation. According to Poznan Medical University Bioethics Committee regulations, no ethics-committee approval is necessary in such a situation. No data allowing for the identification of patients was included in the publication.*
Author contributions: *Katarzyna Korzeniowska — conceptualization, investigation, writing — review and editing, methodology; Artur Cieślewicz — conceptualization, investigation, writing — original draft, writing — review and editing, formal analysis, validation; Katarzyna Grabańska-Martyńska — conceptualization, investigation, writing — review and editing; Anna Jabłecka — supervision, writing — review and editing, project administration.*
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Table 1. The most common adverse effects observed in the studied population after vaccination with the Pfizer COVID-19 mRNA vaccine

Adverse effect	Number of cases	%
Fatigue	12	52.17%
Fever	11	47.83%
Pain at injection site	9	39.13%
Pain (muscle, joint, head)	7	30.43%
Increased bp (blood pressure) and pulse	4	17.39%
Chills	4	17.39%
Local edema at injection site	3	13.04%
Nausea	2	8.70%
Impaired concentration and memory	2	8.70%
Tinnitus, hearing impairment	1	4.35%

Table 2. List of drugs taken by patients in the study population. Drugs were divided into functional groups based on the ATC

Drug group	Drug name	Number of patients		
		Total	**With adverse effects after COVID-19 vaccine**	**Without adverse effects after COVID-19 vaccine**
Agents acting on the renin-angiotensin system		129	8	121
	Candesartan	4	0	4
	Captopril	1	1	0
	Cetirizine	1	1	0
	Enalapril	4	0	4
	Lisinopril	7	0	7
	Losartan	4	0	4
	Perindopril	27	4	23
	Quinapril	2	0	2
	Ramipril	52	2	50
	Telmisartan	14	0	14
	Valsartan	16	1	15
Analgesics and anti-inflammatory drugs		62	1	61
	Aceclofenac	5	0	5
	Buprenorphine	3	0	3
	Diclofenac	3	0	3
	Ibuprofen	2	0	2
	Meloxicam	6	0	6
	Naproxen	11	0	11
	Paracetamol	35	1	34
	Tramadol	17	1	16
Antianemic preparations		4	1	3
	Folic acid	2	1	1
	Iron	3	0	3
Antiepileptics		12	0	12
	Carbamazepine	2	0	2
	Clonazepam	3	0	3
	Moxonidine	1	0	1
	Pregabalin	2	0	2

	Valproic acid	4	0	4
Antigout preparations		9	0	9
	Allopurinol	9	0	9
Antihypertensives		7	0	7
	Doxazosin	7	0	7
Antithrombotic agents		91	0	91
	Acenocoumarol	2	0	2
	Asa (acetylsalicylic acid)	84	0	84
	Cilazapril	2	0	2
	Clopidogrel	4	0	4
	Dabigatran	2	0	2
	Rivaroxaban	5	0	5
Beta blocking agents		72	7	65
	Bisoprolol	26	5	21
	Carvedilol	6	0	6
	Metoprolol	13	1	12
	Nebivolol	25	1	24
	Propranolol	1	0	1
	Sotalol	2	0	2
Calcium channel blockers		90	3	87
	Amlodipine	74	2	72
	Lacidipine	1	1	0
	Lercanidipine	15	0	15
	Verapamil	4	0	4
Cardiac therapy		10	0	10
	Amiodarone	1	0	1
	Digoxin	2	0	2
	Propafenone	2	0	2
	Propafenone	3	0	3
	Trimetazidine	2	0	2
Corticosteroids, dermatological preparations		1	0	1
	Methylprednisolone	1	0	1
Cough and cold preparations		1	0	1
	Ambroxol	1	0	1
Diuretics		122	3	119
	Amiloride	4	0	4

	Furosemide	16	0	16
	Hydrochlorothiazide	21	0	21
	Indapamide	65	3	62
	Spironolactone	9	0	9
	Torasemide	20	0	20
Drugs for acid-related disorders		63	0	63
	Dexlansoprazole	3	0	3
	Esomeprazole	5	0	5
	Famotidine	3	0	3
	Omeprazole	29	0	29
	Pantoprazole	23	0	23
Drugs for functional gastrointestinal disorders		4	0	4
	Mebeverine	4	0	4
Drugs for obstructive airway diseases		25	1	24
	Beclometasone	2	0	2
	Budesonide	4	0	4
	Ciclesonide	2	0	2
	Fenoterol	2	0	2
	Formoterol	10	1	9
	Glycopyrronium	1	0	1
	Ipratropium	2	0	2
	Salbutamol	4	0	4
	Salmeterol	3	0	3
Drugs used in diabetes		55	4	51
	Acarbose	2	2	0
	Gliclazide	3	0	3
	Glimepiride	1	0	1
	Glipizide	1	0	1
	Insulin	14	0	14
	Metformin	48	2	46
Lipid modifying agents		112	4	108
	Atorvastatin	58	2	56
	Ezetimibe	4	0	4
	Fenofibrate	10	0	10

	Rosuvastatin	39	2	37
	Simvastatin	8	0	8
Mineral supplements		88	2	86
	Magnesium	86	2	84
	Potassium	5	1	4
Ophthalmologicals		14	1	13
	Brimonidine	4	1	3
	Dorzolamide	11	0	11
	Timolol	4	0	4
Other nervous system drugs		5	0	5
	Betahistine	5	0	5
Psychoanaleptics		43	1	42
	Agomelatine	1	1	0
	Amitriptyline	2	0	2
	Citalopram	6	0	6
	Donepezil	2	0	2
	Escitalopram	2	0	2
	Memantine	1	0	1
	Mianserin	6	0	6
	Opipramol	3	0	3
	Paroxetine	3	0	3
	Piracetam	2	0	2
	Rivastigmine	2	0	2
	Sertraline	6	0	6
	Trazodone	2	0	2
	Venlafaxine	1	0	1
	Vinpocetine	6	0	6
Psycholeptics		74	2	72
	Alprazolam	6	0	6
	Bromazepam	3	0	3
	Clozapine	1	0	1
	Diazepam	2	1	1
	Estazolam	12	0	12
	Hydroxyzine	19	1	18
	Lorazepam	3	0	3
	Oxazepam	4	0	4
	Perazine	1	0	1
	Promazine	1	0	1
	Quetiapine	4	0	4
	Sulpiride	4	0	4
	Thiethylperazine	1	0	1
	Tiapride	1	0	1

	Zolpidem	13	0	13
	Zopiclone	8	0	8
Thyroid therapy		20	0	20
	Levothyroxine	18	0	18
	Thiamazole	2	0	2
Urologicals		20	0	20
	Finasteride	14	0	14
	Oxybutynin	1	0	1
	Tamsulosin	14	0	14
	Tolterodine	1	0	1
Vitamins		73	4	69
	Vitamin b6	1	1	0
	Vitamin c	13	3	10
	Vitamin d3	72	4	68

Table 3. Statistical analysis of categorical variables in the studied population. The statistical significance threshold is $p < 0.05$

Variable	Adverse effects after vaccination		p	Phi coefficient
	Group 1 yes (%)	Group 2 no (%)		
Sex			0.232	–0.084
Male	7 (30.43)	77 (43.50)		
Female	16 (69.57)	100 (56.50)		
Covid19 in the past			0.798	–0.005
Yes	3 (13.04)	24 (13.56)		
No	20 (86.96)	153 (86.44)		
Agents acting on the renin–angiotensin system			0.002	–0.224
Yes	8 (34.78)	121 (68.36)		
No	15 (65.22)	56 (31.64)		
Analgesics and anti–inflammatory drugs			0.003	–0.208
Yes	1 (4.35)	61 (34.46)		
No	22 (95.65)	116 (65.54)		
Antianemic preparations			0.950	0.060
Yes	1 (4.35)	3 (1.69)		
No	22 (95.65)	174 (98.31)		
Antiepileptics			0.411	–0.091
Yes	0 (0.00)	12 (6.78)		
No	23 (100.00)	165 (93.22)		
Antigout preparations			0.567	–0.078
Yes	0 (0.00)	9 (5.08)		
No	23 (100.00)	168 (94.92)		
Antihypertensives			0.713	–0.069
Yes	0 (0.00)	7 (3.95)		
No	23 (100.00)	170 (96.05)		
Antithrombotic agents			0.000	–0.329
Yes	0 (0.00)	91 (51.41)		
No	23 (100.00)	86 (48.59)		
Beta blocking agents			0.554	–0.042
Yes	7 (30.43)	65 (36.72)		
No	16 (69.57)	112 (63.28)		
Calcium channel blockers			0.001	–0.232
Yes	3 (13.04)	87 (49.15)		
No	20 (86.96)	90 (50.85)		
Cardiac therapy			0.509	–0.083
Yes	0 (0.00)	10 (5.65)		
No	23 (100.00)	167 (94.35)		
Corticosteroids. Dermatological preparations			0.226	–0.026

Yes	0 (0.00)	1 (0.56)		
No	23 (100.00)	176 (99.44)		
Cough and cold preparations			0.226	–0.026
Yes	0 (0.00)	1 (0.56)		
No	23 (100.00)	176 (99.44)		
Diuretics			0.000	–0.354
Yes	3 (13.04)	119 (67.23)		
No	20 (86.96)	58 (32.77)		
Drugs for acid–related disorders			0.001	–0.244
Yes	0 (0.00)	63 (35.59)		
No	23 (100.00)	114 (64.41)		
Drugs for functional gastrointestinal disorders			0.950	–0.051
Yes	0 (0.00)	4 (2.26)		
No	23 (100.00)	173 (97.74)		
Drugs for obstructive airway diseases			0.357	–0.089
Yes	1 (4.35)	24 (13.56)		
No	22 (95.65)	153 (86.44)		
Drugs used in diabetes			0.248	–0.082
Yes	4 (17.39)	51 (28.81)		
No	19 (82.61)	126 (71.19)		
Lipid modifying agents			0.000	–0.280
Yes	4 (17.39)	108 (61.02)		
No	19 (82.61)	69 (38.98)		
Mineral supplements			0.000	–0.256
Yes	2 (8.70)	86 (48.59)		
No	21 (91.30)	91 (51.41)		
Ophthalmologicals			0.924	–0.037
Yes	1 (4.35)	13 (7.34)		
No	22 (95.65)	164 (92.66)		
Other nervous system drugs			0.915	–0.058
Yes	0 (0.00)	5 (2.82)		
No	23 (100.00)	172 (97.18)		
Psychoanaleptics			0.033	–0.151
Yes	1 (4.35)	42 (23.73)		
No	22 (95.65)	135 (76.27)		
Psycholeptics			0.003	–0.211
Yes	2 (8.70)	72 (40.68)		
No	21 (91.30)	105 (59.32)		
Thyroid therapy			0.184	–0.120
Yes	0 (0.00)	20 (11.30)		
No	23 (100.00)	157 (88.70)		
Urologicals			0.184	–0.120
Yes	0 (0.00)	20 (11.30)		
No	23 (100.00)	157 (88.70)		
Vitamins			0.043	–0.143
Yes	4 (17.39)	69 (38.98)		

No	19 (82.61)	108 (61.02)

Table 4. List of drugs that differed significantly between groups ($p < 0.05$)

Variable		Adverse effects after vaccination		p	Phi coefficient
Drug	**Drug group**	**Group 1 yes (%)**	**Group 2 no (%)**		
Amlodipine	Calcium channel blockers			0.003	–0.211
Yes		2 (8.70)	72 (40.68)		
No		21 (91.30)	105 (59.32)		
Asa	Antithrombotic agents			0.000	–0.307
Yes		0 (0.00)	84 (47.46)		
No		23 (100.00)	93 (52.54)		
Atorvastatin	Lipid modifying agents			0.023	–0.161
Yes		2 (8.70)	56 (31.64)		
No		21 (91.30)	121 (68.36)		
Indapamide	Diuretics			0.034	–0.150
Yes		3 (13.04)	62 (35.03)		
No		20 (86.96)	115 (64.97)		
Magnesium	Mineral supplements			0.000	–0.250
Yes		2 (8.70)	84 (47.46)		
No		21 (91.30)	93 (52.54)		
Ramipril	Agents acting on the renin–angiotensin system			0.044	–0.142
Yes		2 (8.70)	50 (28.25)		
No		21 (91.30)	127 (71.75)		
Vitamin d3	Vitamins			0.048	–0.140
Yes		4 (17.39)	68 (38.42)		
No		19 (82.61)	109 (61.58)		

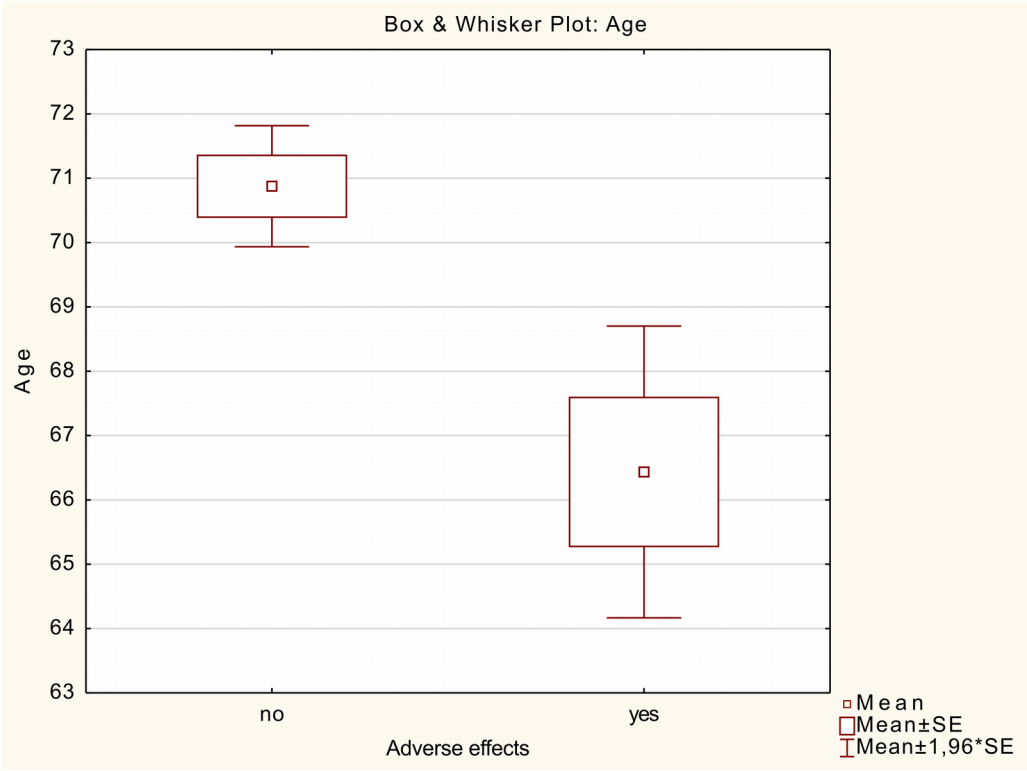

Figure 1. Box and whisper plot showing the mean age of studied groups. The difference is statistically significant (p = 0.001)