OCCURRENCE OF ADVERSE EVENTS FOLLOWING VACCINATION IN PATIENTS WITH ALLERGIES: A PROSPECTIVE STUDY

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SUMMARY

Objectives: Allergic patients may be concerned about more frequent and/or more severe adverse events following vaccination, which may lead to the refusal of vaccines among these patients. The aim of this study is to assess whether allergic patients have more frequent adverse events (AEs) after vaccination than healthy individuals.

Methods: Study participants (N = 591) underwent vaccination of their choice at a selected Vaccination and Travel Medicine Centre. At a 10 to 14-day interval, they were contacted for a telephone questionnaire survey on the occurrence of AEs after vaccination. A group of allergic patients (n = 188) and healthy controls (n = 403) were followed in the study.

Results: No significant difference was found in the occurrence of AEs between study and control group. Only in redness and swelling, which was more common in allergic patients, but only in a few individuals. All side effects were minor, such as pain at the injection site or fatigue. No participant experienced a serious or life-threatening adverse event. In the studied group, no statistically significant differences were found even in the occurrence of AEs after singular vs. simultaneous administration of vaccines (p = 0.094), nor after vaccination with inactivated vs. attenuated vaccines (p = 0.655), or after vaccination against bacterial vs. viral infections (p = 0.140).

Conclusions: Vaccination of allergic patients did not cause more frequent and/or more serious adverse events in our study compared to healthy people. If general contraindications are observed, then vaccination of allergic patients is considered safe.

Key words: vaccination, allergy, adverse events, adverse event following vaccination, prevention

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INTRODUCTION

Vaccination is an important method to prevent infectious diseases in the population. The application of the vaccine may be associated with adverse events, which means any medical event that is temporally related to the administration of the vaccine. Adverse reactions after vaccination can be classified according to frequency (very common ≥ 10%; common ≥ 1 and < 10%; uncommon ≥ 0.10 and < 1%; rare ≥ 0.01 and < 0.10%; very rare < 0 .01%), extent (local or systemic) and severity. The safety of vaccines is monitored for a long period of time, and most side effects are minor and resolve spontaneously in a few hours or days. Serious or life-threatening effects, such as anaphylactic shock, are very rare (1, 2). Most often, in up to 80% of vaccines administered, local adverse events appear within a few hours after the vaccine is administered. These AEs are usually mild and self-limiting. Systemic AEs (such as fever, rash, headache, joint or muscle pain) usually occur a few days after vaccination and are also mild in most cases (1, 3). A warning about the possible occurrence of adverse events, typically pain at the injection site and subfebrile/febrile, should be part of the patient's instruction when administering the vaccine. Some possible side effects caused by an administration error can be avoided by following appropriate vaccine administration procedures. The pre-vaccine checklist should include the question of whether the patient has had a serious adverse reaction to the vaccine in the past or is allergic to any component of the vaccine (1, 4, 5).

An allergy is an inadequate reaction of the organism to an antigenic stimulus, which is mostly a natural part of the environment, but it can also be a component of the vaccine. The most common allergens in vaccines are neomycin, gentamicin, formaldehyde, gelatin, and egg and chicken proteins. The most immediate reactions are type I hypersensitivity reactions, which are mediated by the interaction of IgE antibodies with a specific component of the vaccine and appear primarily within a few minutes, up to 4 hours at most. Delayed type IV hypersensitivity reactions occur approximately 48 hours after vaccination and peak at 72–96 hours and are generally considered harmless. Most delayed reactions are classified as type III hypersensitivity, and the most common manifestation is exanthema (2, 6, 7). People who have experienced an adverse reaction after vaccination may have reduced confidence and be hesitant to undergo further vaccinations, resulting in avoidance of all vaccinations and underimmunization of these individuals even with vaccines to which they are not allergic. Allergic individuals may have similar unfounded fears

about vaccination in general, as they may assume that vaccination will cause an inadequate response and adverse events (6–8). The aim of the study was to determine whether people with allergies have a higher risk of adverse effects after vaccination compared to people without allergies and other chronic diseases.

MATERIALS AND METHODS

The purpose of the research was to prospectively monitor the occurrence of adverse events following vaccination in patients with allergies (study group) compared to healthy individuals (control group). All subjects gave their informed consent to be included before participating in the study. The study was carried out in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Faculty of Medicine of the University of Ostrava (No. 04/2022).

Research Design

Multicentric data collection took place at 11 Vaccination and Travel Medicine Centres in the Czech Republic. These centres provide vaccinations at the clients' own request, e.g., for reasons of travel or protection against seasonal infections, they do not provide vaccinations according to the national immunization schedule. Participants were approached by a centre staff member with an offer to participate in the research; if they agreed, they received information about the course of the study and an informed consent to sign. The research group consists of persons who have undergone vaccination, understand and speak Czech and have expressed their consent to the research. The healthcare worker in the vaccination centre wrote the client's identification, including personal anamnesis and data on health status, including allergies, which are updated at each client visit to the centres so that possible contraindications can be assessed and health fitness verified before vaccination, contact details, and information about the vaccine/vaccines administered. Subsequently, approximately 10 to 14 days after vaccination, a telephone questionnaire survey was conducted with the participant to determine the occurrence of adverse events after vaccination application. They were asked to report any other health problems that appeared in the following days that could be related to vaccination. All patient data was processed in anonymised form based on a unique code assigned to the participant by the person conducting the telephone questionnaire survey. Processing of personal data was carried out in accordance with the requirements of GDPR Regulation No. 2016/679 and Act No. 110/2019 Coll., on the processing of personal data.

Inclusion criteria were consent to enter the study and application of the selected vaccine. Exclusion criteria were failure to perform or non-cooperation with the telephone questionnaire survey, age below 16 years, presence of a disease other than allergies in anamnesis. The monitored data included sex, age, health and allergy history, date of vaccine administration, administered vaccines, and subsequently the presence and duration of adverse events.

Statistical Analysis

Basic descriptive statistics (arithmetic mean ± standard deviation (SD), frequency and %) were used to describe the data. Quantitative data were tested for normality using the Shapiro-Wilk test. Statistical tests were used to evaluate the differences between the observed group and the control group and other factors.

Statistical tests, such as two-sample t test with equal variances, Pearson's chi-squared test and Mann-Whitney test, were evaluated at a significance level of 5%. To evaluate the influence of monitored factors on AEs between the monitored and control groups, a fully adjusted binary logistic regression model was used, the results were expressed as odds ratio (OR) with 95% confidence intervals (CI).

Stata software version 17 was used for statistical analysis.

RESULTS

Sample Characteristics

In total, 962 people agreed to participate in the study and 785 people were able to complete the subsequent telephone questionnaire survey. After excluding persons under the age of 16 (due to the validity of the questionnaire survey) and patients with a diagnosis other than allergies in anamnesis, the research group consisted of a total of 591 persons, of which 188 with a history of allergies and 403 completely healthy persons (Fig. 1).

Allergies were mainly caused by pollen, dust, mites, fur, but also drugs (mostly antibiotics) and/or wasps/bee stings. According to the type of allergy (Table 1), it was not possible to perform an analysis because pollen allergy prevailed (39.36%) and its combination (pollen, drugs, dust, fur) was reported by 41.50% of patients. A single drug allergy was reported in 9.57% (n = 18), but it was a combination of drugs. Study participants were administered various vaccines, most often against tick-borne encephalitis, typhoid, rabies, or type A or A+B hepatitis. Vaccines against covid-19 were not included in the study. List of all vaccines is presented in Table 2. Due to simultaneous applications, the total number of 673 vaccines were administered to our 591 participants (514 of them received one vaccine, 72 received two vaccines and 5 of them received three vaccines).

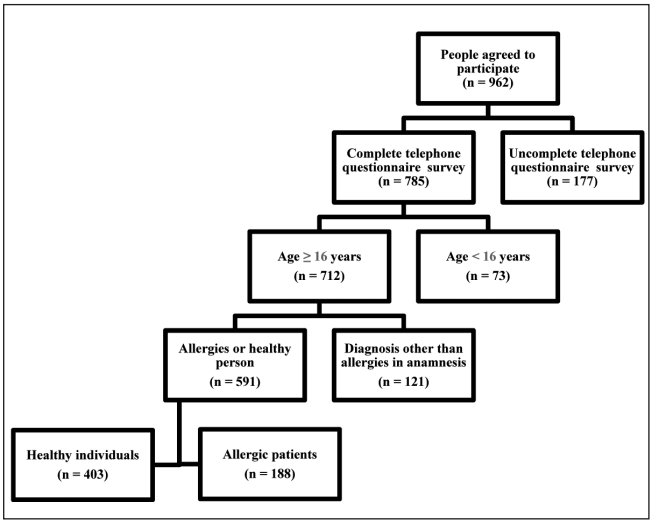

Fig. 1. *Flow chart describing study recruitment.*

Table 1. *Description of types of allergies (n = 188)*

Allergies	n	%
Atopic eczema	1	0.53
Cold	1	0.53
Foodstuffs	4	2.13
Iodine	1	0.53
Drugs (including antibiotics)	18	9.57
Mould	1	0.53
Pollen (grasses, trees)	74	39.36
Wasp/bee	6	3.19
Hair	4	2.13
Combination (2–3 allergens: pollen, drugs, dust, fur)	78	41.50

Demographic Characteristics

The average age of allergic patients was 34.97 years (± 10.48), and the average age of healthy people was 36.49 years (± 11.24), so there was no statistically significant age difference between the groups (p = 0.117). In the study, 52.12% of participants were men and 47.88% women, and there were also no statistically significant differences by sex between the studied and control groups (p = 0.111). As can be seen in Table 3, at entry there was no statistically significant difference in the administration of vaccines to the study and control groups, either singular vs. simultaneous (p = 0.359), or vaccines inactivated vs. attenuated (p = 0.381), or vaccines bacterial vs. viral (p = 0.422). To assess the incidence of inactivated vs. attenuated and bacterial vs. viral vaccine administration, simultaneous administrations (n = 77, where inactivated plus attenuated and/or bacterial plus viral vaccines are often combined) were excluded.

Adverse Events Occurrence

The incidence of adverse events (AEs), regardless of severity, was reported by 303 participants (51.27%), while the difference in incidence between the study and control groups in our research sample was not statistically significant (p = 0.321), although AEs were slightly more frequently reported by allergic patients (102, 54.26%) compared to healthy subjects (201, 49.88%). According to age, no significant differences were found in the occurrence of AEs (p = 0.149), although a decreasing trend in the incidence of AEs with increasing age is visible. There was a significant difference in reporting AEs by sex (p = 0.002), indicating that in

Table 2. *List of vaccines administered to participants in this study*

Vaccine	n	Vaccine type	Vaccine against
Adacel	33	Inactivated	Bacterial
Avaxim	27	Inactivated	Viral
Bexsero	6	Inactivated	Bacterial
Boostrix	1	Inactivated	Bacterial
Dukoral	5	Inactivated	Bacterial
Encepur	14	Inactivated	Viral
Engerix-B	7	Inactivated	Viral
FSME Immun	276	Inactivated	Viral
Gardasil 9	33	Inactivated	Viral
Havrix	19	Inactivated	Viral
Imovax Polio	2	Inactivated	Viral
Menveo	10	Inactivated	Bacterial
M-M-RvaxPro	2	Attenuated	Viral
Nimenrix	10	Inactivated	Bacterial
Pneumovax 23	2	Inactivated	Bacterial
Stamaril	22	Attenuated	Viral
Twinrix	32	Inactivated	Viral
Typhim Vi	98	Inactivated	Bacterial
Vacteta	1	Inactivated	Bacterial
Vaqta	11	Inactivated	Viral
Varilrix	22	Attenuated	Viral
Verorab	40	Inactivated	Viral

Table 3. *Characteristics of a sample and differences between study and control group*

Variable	Category	Patients with allergies (n = 188) n (%)	Healthy individuals (n = 403) n (%)	p-value
Age (years), mean (SD)		34.97 (10.48)	36.49 (11.24)	0.117[b]
Sex	Men	107 (56.91)	201 (49.88)	0.111[c]
	Women	81 (43.09)	202 (50.12)	
Adverse events	None	86 (45.74)	202 (50.12)	0.321[c]
	Appeared	102 (54.26)	201 (49.88)	
Administration	Singular	167 (88.83)	347 (86.10)	0.359[c]
	Simultaneous	21 (11.17)	56 (13.90)	
Vaccine type[a]	Inactivated	154 (92.22)	327 (96.18)	0.381[c]
	Attenuated	13 (7.78)	13 (3.82)	
Vaccine against[a]	Bacterial	26 (15.57)	64 (17.51)	0.422[c]
	Viral	141 (84.43)	283 (81.49)	

[a]Singular applications only; [b]two-sample t test with equal variances; [c]Pearson's chi-squared test

Table 4. *Occurrence of adverse events according to various variables*

Variable	Category	Without AEs (n = 288) n (%)	AEs appeared (n = 303) n (%)	p-value[b]
Age	16–30 years	86 (29.86)	112 (36.96)	0.149
	31–45 years	144 (50.00)	142 (46.87)	
	>45 years	58 (20.14)	49 (16.17)	
Sex	Men	169 (58.68)	139 (45.87)	0.002
	Women	119 (41.32)	164 (54.13)	
Administration	Singular	256 (88.89)	258 (85.15)	0.177
	Simultaneous	32 (11.11)	45 (14.85)	
Vaccine type[a]	Inactivated	237 (92.58)	244 (94.57)	0.356
	Attenuated	19 (7.42)	14 (5.43)	
Vaccine against[a]	Bacterial	35 (13.67)	55 (21.32)	0.023
	Viral	221 (86.33)	203 (78.68)	

[a]Singular applications only; [b]Pearson's chi-squared test

Table 5. *Occurrence of adverse events in the study group (allergic patients) and control group (healthy individuals) according to different variables*

Group	Variable	Category	Without AEs n (%)	AEs appeared n (%)	p-value[b]
Study (n = 188)	Administration	Singular	80 (47.90)	87 (52.10)	0.094
		Simultaneous	6 (28.57)	15 (71.43)	
	Vaccine type[a]	Inactivated	73 (47.40)	81 (52.60)	0.655
		Attenuated	7 (53.85)	6 (46.15)	
	Vaccine against[a]	Bacterial	9 (34.62)	17 (65.38)	0.140
		Viral	71 (50.35)	70 (49.65)	
Control (n = 403)	Administration	Singular	176 (50.72)	171 (49.28)	0.551
		Simultaneous	26 (46.43)	30 (53.57)	
	Vaccine type[a]	Inactivated	164 (50.15)	163 (49.85)	0.393
		Attenuated	12 (60.00)	8 (40.00)	
	Vaccine against[a]	Bacterial	26 (40.63)	38 (59.38)	0.074
		Viral	150 (53.00)	133 (47.00)	

[a]Singular applications only; [b]Pearson's chi-squared test

our study, AEs were reported more often by women (Table 4). Most of the participants (514, 86.97%) received one vaccine, 77 participants (13.03%) received simultaneous administration. After simultaneous administration, no statistically significant differences were observed in our research sample in the occurrence of AEs compared to administration of a single vaccine ($p = 0.177$), however, AEs were a little bit more frequently reported by patients after simultaneous administration (Table 4). Live attenuated vaccines were applied to 33 (7.78%) participants, while even the administration of live attenuated vaccine did not increase the incidence of AEs ($p = 0.356$). AEs occurred statistically significantly more ($p = 0.023$) in vaccination with bacterial vaccines: 35 (13.67%) patients without AEs vs. 55 (21.32) reporting AEs compared to viral ones: 221 (86.33%) patients without AEs vs. 203 (78.68%) reporting AEs.

The difference in occurrence of AEs in our study and control groups according to administration, vaccine type or vaccine against bacterial or viral diseases were not significant (Table 5). The most obvious difference in occurrence of AEs were found in simultaneous administration in the study group where AEs appeared in 15 (71.43%) patients of 21 with simultaneous administration and in 87 (52.10%) of 167 patients with singular administration, however, the difference is not significant ($p = 0.094$).

In the vast majority of cases, it was an AE in the form of pain at the injection site which was reported by 232 (76.56%) patients of all 303 reported AEs, lasting an average of 1.97 days after administration (Table 6). The second most common AE was excessive fatigue in 111 (36.63%) patients of all AEs lasting an average of 1.80 days after administration. Other AEs occurred to a lesser extent (Table 5). Among other AEs, the most frequently reported were nausea (8 times) or chills (8 times). No significant differences were found between the study group and the control group in the appearance of pain at the injection site ($p = 0.193$), nor in the occurrence of excessive fatigue ($p = 0.289$). A statistically

Table 6. *Occurrence and duration (days) of adverse events (n = 303) in the study and control groups*

Adverse event	Total occurrence	Patients with allergies (n = 188)		Healthy individuals (n = 403)		p-value[a] occurrence	p-value[b] duration
		Occurrence n (%)	Duration (days)	Occurrence n (%)	Duration (days)		
Injection pain	232	81 (43.09)	1.94	151 (37.47)	1.98	0.193	0.960
Redness/swelling	12	7 (3.72)	3.43	5 (1.24)	3.40	0.046	0.734
Excessive fatigue	111	40 (21.28)	1.78	71 (17.62)	1.82	0.289	0.901
Subfebrile	16	3 (1.60)	1.67	13 (3.23)	1.69	0.255	1.000
Febrile	6	3 (1.60)	1.67	3 (0.74)	1.67	0.336	0.814
Headache	39	13 (6.91)	1.83	26 (6.45)	2.54	0.833	0.274
Joint/muscle pain	19	6 (3.19)	1.83	13 (3.23)	2.54	0.982	0.274
Others	26	8 (4.26)	–	18 (4.47)	–	0.907	–

[a]Pearson's chi-squared test; [b]Mann-Whitney test

Table 7. *Fully adjusted binary logistic regression model evaluating influence of monitored factors on AEs between study and control group*

Variables	Categories	OR_{crude} (95% CI)	p-value	$OR_{adjusted}$ (95% CI)	p-value
Allergy	No	1+			
	Yes	1.19 (0.84–1.69)	0.321	1.26 (0.88–1.80)	0.203
Sex	Men	1+			
	Women	1.68 (1.21–2.32)	**0.002**	1.66 (1.19–2.31)	**0.003**
Age	16–30 years	1+			
	31–45 years	0.76 (0.53–1.09)	0.135	0.88 (0.60–1.28)	0.492
	>45 years	0.65 (0.40–1.04)	0.073	0.72 (0.44–1.17)	0.182
Vaccine	Singular, viral, inactivated	1+			
	Singular, viral, attenuated	0.79 (0.38–1.62)	0.515	0.81 (0.39–1.67)	0.562
	Singular, bacterial	1.68 (1.05–2.68)	**0.030**	1.60 (0.99–2.59)	0.053
	Simultaneous	1.50 (0.92–2.46)	0.106	1.51 (0.91–2.51)	0.108

$OR_{adjusted}$ – fully adjusted model (p = 0.005); 1+ reference category; OR – odds ratio; CI – confidence interval

significant difference (p = 0.046) was found only in the case of redness/swelling at the injection site, which occurred in 7 allergic patients (3.72%) and 5 (1.24%) healthy subjects. No one in our research sample had a systemic allergic reaction in the form of shortness of breath, urticaria, eczema, generalised swelling, or any other serious or life-threatening AE.

Estimation of Adverse Events Risk

The estimate of the risk of AEs in patients with allergies in our research sample in the fully adjusted model is 1.26 times higher than in people without allergies, but the relationship is not significant (Table 7). A statistically significant value of OR was found only in gender, women have a 1.7 times higher risk of AEs compared to men.

With increasing age, the OR value decreased, but there was no significant difference. This means that with increasing age there were fewer AEs reported in our study. This trend was evident in Table 4, where adverse effects occurred in 112 subjects in the 16–30 age group, while 86 subjects in this age group did not report AEs. In the 31–45 age group, the incidence of AEs was even (142 subjects reported and 144 did not report AEs). In contrast, in the age group over 45 years 49 persons reported AEs and 58 persons did not report AEs. Depending on the type of vaccines, a higher risk was found for bacterial vaccines compared with inactivated viral vaccine, but after adjustment, this relationship was close to the statistical significance (OR = 1.66).

DISCUSSION

This study focused on the prospective follow-up of adverse events after vaccination in allergic patients and in healthy controls. In patients with a history of allergy, these were common allergens such as dust, pollen, dust mites, bees/wasp stings, or drugs. Vaccination contraindications were observed for all patients according to supplementary protection certificates (SPCs).

Allergic patients may have concerns about vaccination (6). Fear and uncertainty about allergies can lead to incomplete vaccination coverage (9, 10). These could become major problems

in the field of public health, as according to data, the number of people with allergies in the population has increased in recent years. Currently, the allergy is described in approximately 25–30% of the population (11, 12). Thus, refusal to vaccine by allergic patients could endanger collective immunity (13).

Research suggests that allergic patients may not necessarily have more common adverse events following immunization than healthy individuals. McCallum et al. found that the majority of immunizations in allergic patients were uneventful, with only a small percentage experiencing adverse events (14). There are studies showing that people with allergies suffer more often from respiratory infections, which also have a longer course (15), which could be prevented by vaccination in some respiratory diseases. When we describe side effects, it is crucial to specify whether we mean common side effects or serious or life-threatening side effects. Although adverse effects were reported by 51.27% of our study participants, there were no cases of serious or life-threatening adverse reactions. The occurrence of these minor reactions is similar as in the study performed by Cerpa-Cruz et al., where it was present in 49% of patients (16). All adverse reactions in our study were mild and expected, consistent with the reactions listed in the SPCs.

For that reason, it is difficult to discuss whether there have been recent changes in the incidence of reported AEs. Expert societies, whether the Centers for Disease Control and Prevention (CDC) and its Vaccine Adverse Event Reporting System (VAERS) or the World Health Organization (WHO) and their Monitoring of Adverse Events Following Immunization (AEFI), state that serious and life-threatening and/or unexpected adverse events must be reported (17, 18). However, no such AEs occurred in our study. If we were to evaluate the number of reported side effects regardless of severity, it would also be necessary to take into account the number of vaccines administered. In recent years, there has been a significant increase in reported AEs related to covid-19 vaccination. However, this was not the subject of our study. In the Czech Republic, AEs report to the State Institute for Drug Control (Czech acronym SUKL). In the 2023 annual report, SUKL evaluates the number of reported AEs separately for covid-19 vaccines and for other vaccines. This report says: "For other vaccines, there has been a gradual decrease in the number of reports in recent years. For vaccines other than covid-19, mostly reactions have been reported that correspond to the already known safety profile of the vaccines" (19).

It is well known that vaccines are associated with local reactions, such as pain (20). In contrast, serious and life-threatening reactions after vaccination and anaphylaxis are very rare (6, 21). Although pain at the injection site is not a serious AE and usually lasts only for a few hours or days, in our study it lasted on average of less than 2 days, it can be a significant source of anxiety (22).

However, there are evidence-based recommendations on how to prevent pain at the injection site. These vary by age, but generally apply: use neutral words, avoid language that increases anxiety, proper positioning (sitting upright for youth and adults), do not aspirate during intramuscular administration, use some distractions, administer vaccines that cause the most injection site pain after other vaccines. However, warming the vaccines is not recommended, as well as stimulation of the injection site and the use of oral analgesics before vaccination (23).

In our study, the tick-borne encephalitis (TBE) vaccine was administered the most frequently. A study by Garner-Spitzer et al. (24) dealt with the evaluation of the immune response and reactogenicity of allergic patients after vaccination against TBE. This study examined three groups: allergic patients, allergic patients with specific immunotherapy, and healthy controls. The study found that the rate of local and systemic adverse reactions in allergic patients was slightly lower compared to healthy controls. In our study, although the overall incidence of AEs was slightly higher in allergic patients (54.26% reported AEs), the difference in the incidence of AEs compared to healthy controls (49.88% reported AEs) was not statistically significant ($p = 0.321$). Study by Garner-Spitzer et al. also found more frequent AEs in women compared to men in the group of allergic patients as well as in the group of healthy controls (24). In our study, women also reported significantly more AEs in 54.13% compared to men in 45.87% ($p = 0.002$). The fact that women report side effects more often is described in several studies (25–27). Garner-Spitzer et al. found that most of the participants suffered from local pain, redness and swelling on the injection side, headache, fatigue and muscle pain (24). In our study, the most frequent AE was pain at the injection site, which was reported by 43.09% of allergic patients and 37.47% of healthy controls, but the difference is not significant. In a study by Garner-Spitzer et al. the results of the occurrence of specific AEs are presented only in a graph, divided by sex, from which, unfortunately, the exact values cannot be read, however, women experienced pain in approximately 60% of allergic patients and approximately 70% of healthy controls (24).

In our study, no statistically significant difference was found in the occurrence of AEs in allergic patients compared to healthy controls, with the exception of the appearance of redness or swelling, which was statistically significantly more frequent in allergic patients ($p = 0.046$), but it should be noted that this was an AE that appeared in 7 (3.43%) allergic patients and 5 (1.24%) healthy controls, and therefore may have been biased due to the small number.

The difference in the incidence of AEs after administration of a singular or simultaneous vaccine in our study was not statistically significant overall, neither in allergic patients nor in healthy controls. However, in allergic patients, AEs were more frequent after simultaneous administration (71.43% of AEs) compared to the single administration of vaccines (28.57% of AEs). In a study by Falvo et al. (28) that investigated the occurrence of AEs after simultaneous administration of vaccines, the occurrence of local AEs was reported in 58% of patients and the occurrence of systemic AEs in 39.50% of patients. In our study, AEs occurred in 45 (58.44%) participants who received simultaneous vaccine administration. Falvo et al. also found that the number of vaccines did not affect the duration or severity of the problem. According to them, simultaneous vaccination increases the incidence of AEs, but these are mild AEs that should not be a reason not to administer multiple vaccines at once (28). Bauwens et al. in a systematic review investigated the adverse effects of the simultaneous application of vaccines in children and stated that the available studies on the occurrence of AEs after singular vs. simultaneous vaccination in children are ambiguous and further research is needed (29).

An interesting finding is that in our study the incidence of AE was significantly higher after vaccination with a bacterial vac-

cine vs. a viral vaccine in general ($p = 0.023$), but no statistically significant difference was found in the group of healthy controls ($p = 0.074$) or allergic patients ($p = 0.140$). Unfortunately, it was not possible to find studies that dealt with the occurrence of AEs after vaccination with bacterial vs. viral vaccines.

Among the limitations of this study are the smaller sample size and the diversity of administered vaccines, thanks to which, on the other hand, it is possible to evaluate the occurrence of AEs after the application of live attenuated vs. inactivated vaccines, bacterial vs. viral vaccines, and after singular or simultaneous administration of vaccines. Another possible limitation is the set study protocol, when adverse events were detected 10–14 days after the vaccine was administered. This protocol was chosen in order to make the reporting as accurate as possible. According to the available literature, local reactions (which are more common) occur within hours of vaccine administration, and systemic reactions occur most often 3–21 days after vaccine administration (1). If the telephone survey were to take place after a longer period of time, e.g., after one month, the reporting of local AEs could be distorted, as the person interviewed could forget the presence and duration of, e.g., pain at the injection site after such a period of time, as we found out in the pilot survey. However, to distort the systemic AEs that may have appeared after the AEs were investigated, the participants were instructed (as stated in the methodology) that if they had health problems in the following days that could be related to vaccination, they should inform the contacts listed in the protocol to the study. Another limitation may be the fact that antihistamine premedication (or other pre-existing anti-allergic treatments such as corticosteroids, and other systemic or local medications, as well as desensitization therapies) was not investigated, which could influence whether AEs occur or not.

Mainly adverse events that are serious and life-threatening, or unexpected, or associated with new vaccines, or of serious concern in the population are systematically reported (18). The expected local and systemic AEs are described in the SPCs of each vaccine. However, even these expected reactions, such as pain at the injection site, can be unpleasant for vaccinated people and can be a source of anxiety. Therefore, future research should also focus on verifying these expected AEs in different population groups so that confidence in vaccination is not reduced due to the public feeling that the reporting of AEs is underestimated. For further studies, it would be advisable to determine the occurrence of AEs repeatedly, even at a longer time interval (e.g., 30 days), in order to avoid possible underreporting of the occurrence of AEs; and also verifying whether allergic patients have been premedicated with antihistamines or other medications.

CONCLUSIONS

Vaccination of allergic patients in our study did not cause more frequent and/or more severe side effects compared to healthy people, although the mentioned limitations should be taken into account. AEs after vaccination are reported more frequently by women than men in our study. The occurrence of AEs may be more frequent with simultaneous vaccination, but these are not serious or long-lasting AEs, and therefore there is no reason not to provide simultaneous vaccination. Most side effects after vaccination are mild and resolve spontaneously within a few days. The most common AE is pain at the injection site, which, however, can be partially controlled by following the principles of good practice. If general contraindications are observed, then vaccination of allergic patients is considered safe.

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Conflicts of Interest

None declared

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