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Influenza vaccine efficacy in patients aged 60–75 years in the 2016/2017 season

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** From among the available and scientifically verified methods, vaccination every flu season is one of the most effective methods that aim at preventing flu, post-influenza complications and deaths. Its efficacy in preventing hospitalisation in patients over 65 years of age is 50–60%, and in preventing death from influenza and its complications, even up to 80%.
Objectives. The aim of the study was the assessment of influenza vaccine efficacy in patients aged 60–75 years in the 2016/2017 season.
Material and methods. The study included 96 patients aged 60–75 years. BMI, as well as the initial level of haemagglutinin H1, H3, HB antibodies, were determined for all patients. All subjects were vaccinated with trivalent seasonal vaccine (Vaxigrip). In the period of 4–5 weeks after vaccination, the level of haemagglutinin H1, H3, HB antibodies was measured again in all patients.
Results. GMTs for all anti-haemagglutinins before and after vaccination differ significantly ($p < 0.00001$). The protection rate is higher after the vaccination than before for all anti-haemagglutinins, and these differences are statistically significant ($p < 0.00001$). In respect of each anti-haemagglutinin, the protection rate significantly exceeds the 60% threshold. The study showed proper immunogenicity of the influenza vaccine in the group of elderly people.
Conclusions. The influenza vaccination induces a proper immune response in patients aged 60–75, and therefore, it should be recommended in such patients as a form of effective protection against influenza and its complications.
Key words: influenza, human, vaccination, aged, immunization.

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Background

Influenza is a contagious disease occurring seasonally, which is a global public health problem. The most effective preventive behaviour, both in the general population and in risk groups, is vaccination against influenza [1]. Recommendations indicate the elderly as a group which should, in particular, be covered by a preventive programme of vaccination against influenza. Age-related deterioration of the immune system results in a higher risk of complications, including death, in these patients than in the general population. In 2003 in the United States, Thompson et al. estimated that the mortality rate e.g. from flu or pneumonia in the years 1990–1999 was the largest in the population of people over the age of 65, and regardless of the strain of influenza virus, this amounted to 22.1/100 thousand people/year [2]. The rate of hospitalisation due to influenza is even higher in this group. Statistics strongly suggest the deterioration every subsequent 5 years of life and achieve up to 628.6/100 thousand people/year in people aged over 85. The number of days that older people spend in hospital due to complications caused by influenza also increases with age [3]. Importantly, the higher incidence of hospitalisation and mortality from flu in this group of patients does not result from a greater incidence of influenza and *influenza like illnesses* (ILIs). Age and related illnesses constitute the risk factor. Moreover, Barker et al. observed that the occurrence of influenza significantly deteriorates the overall functioning of the elderly in terms of such activities as mobility, getting dressing or taking a bath during 3–4 months after infection [4].

In accordance with the recommendations of the World Health Organization (WHO) and Advisory Committee on Immunization Practices (ACIP), the elderly are one of the risk groups due to age-related deterioration of the immune system, which makes the risk of complications, including death, much higher than in the general population. Moreover, the efficacy of vaccination in the elderly is estimated as only 17–53%, depending on the type of virus circulating in the given season, while in the younger group, the efficiency is 70% [5].

Epidemiological reports of the National Institute of Public Health – National Institute of Hygiene (NIPH–NIH) indicate a greater incidence of influenza and influenza-like illnesses: in the 2015/2016 and 2016/2017 seasons, more than 4 million cases of these diseases were observed. The number of hospitalisations due to influenza also increased by 16% [6].

Throughout the world, the influenza vaccination rate remains relatively high, although it is widely varied. The international study of the Vaccine European New Integrated Collaboration Effort (VENICE) showed that from 2% to 80% of people

aged over 65 were vaccinated in Europe in the 2006/2007 influenza season [7]. Traditionally, in the group of people aged over 65, the percentage of vaccinated people remains much higher than in younger age groups. Unfortunately, the efficacy of these vaccinations, resulting from a weaker immune response in the elderly, reduces the effect expected on the basis of favourable statistics [8].

The deterioration of the immune system equals a reduction of reactivity due to changes in the number and activity of individual cell populations: a reduction of about 30% of the total number of the main cells of a specific immune system is observed in persons aged over 60, in comparison to persons under 35 years of age, as well as weaker expression of the receptors and surface molecules regulating the immune response. Hence, the efficacy of the vaccine in the given season in terms of immune response in patients aged over 65 is only assessed as 30–40% [9]. Unfortunately, in Poland, the vaccination rate for the entire population has remained at a very low level for many years. In the 2016/2017 season, only 3.3% of Poles were vaccinated against influenza [6, 10]. Nevertheless, elderly patients are among the biggest beneficiaries of seasonal influenza vaccinations. Many years of research in this area and critical meta-analyses have provided solid evidence that the actual efficacy of vaccination is very high, namely in preventing hospitalisation in this group of patients. In general, it amounts to 50–60%, and in preventing death from influenza and its complications, up to 70–80% [9].

Objectives

The aim of the study was the assessment of influenza vaccine efficacy in patients aged 60–75 years in the 2016/2017 season.

Material and methods

The study protocol was approved by the Bioethics Committee of the Wroclaw Medical University. The study included 96 consecutive patients who came to the GP practice to see a general practitioner in the period from September to November 2016. Inclusion criteria included: age: 60–75 years of age and written consent to participate in the study. Exclusion criteria included: presence of malignant disease, autoimmune disease, contraindication to vaccination against influenza, or a situation requiring special caution (as recommended by ACIP) [11], severe renal or hepatic insufficiency, primary hyperparathyroidism. The average age in the study group was 66.67, and 63.5% of the respondents were female.

In the first stage of the study, a blood sample was taken from each patient in order to determine the starting haemagglutinin antibody titres.

All subjects were vaccinated against influenza with the trivalent vaccine (Vaxigrip®, Sanofi Pasteur), valid in the 2016/2017 season. A single dose of the vaccine (0.5 ml) contained: 15 µg of haemagglutinin from the strain of influenza virus A/H3N2/, /15 µg of haemagglutinin from the strain of influenza virus A/H1N1/, 15 µg of haemagglutinin from the strain of influenza B virus. After approx. 4 weeks after the vaccination, a 5 ml blood sample was taken from each patient in order to obtain serum for the determination of haemagglutinin antibody titres.

To evaluate the serological response to the vaccination, anti-haemagglutinin antibody titration (anti-HA) was carried out. This part of the study was conducted in the Department of Research on Influenza Virus – National Centre for Influenza (*Zakład Badania Wirusów Grypy – Krajowy Ośrodek ds. Grypy*) of the National Institute of Public Health – National Institute of Hygiene in Warsaw. Anti-HA antibody titration was conducted for the following antigens contained in the vaccine:

- H1: A/California/7/2009(A/H1N1/pdm09),
- H3: A/HongKong/4801/2014(A/H3N2/),
- HB: B/Brisbane/60/2008/.

The anti-HA titre was determined by means of the haemagglutination inhibition test. The anti-HA titre of the given strain of the virus is assumed to be the highest serum dilution in which haemagglutination inhibition occurred. The following parameters were analysed:

- Geometric Mean Titres (GMT) – before and after influenza vaccination.
- Mean Fold Increase (MFI) – after the influenza vaccination, calculated as the ratio of GMT before and after vaccination.
- Protection Rate (PROT) – the percentage of subjects with antibody titres ≥ 1:40 before and after vaccination against influenza.
- Response Rate (RESP) – the percentage of subjects who had at least a fourfold increase in antibody titres after vaccination.

According to the CPMP guidelines for the evaluation of the serological reaction to vaccination against influenza, the following values suggest an efficient response to vaccination in patients aged over 60 [1]:

- MFI ≥ 2.0,
- PROT ≥ 60%,
- RESP ≥ 30%.

Analyses were performed using the R statistical programme (version 3.1.3). All features, except for age, had distributions different than normal, which was proven with the use of the Shapiro–Wilk test of normality. In all tests, the level of statistical significance was $p < 0.05$.

Results

The immune response to vaccination was evaluated.

The data presented in Table 1 show that GMTs for all anti-haemagglutinins before and after vaccination differ significantly ($p < 0.00001$).

Table 2 shows that the protection rate is higher after vaccination than before vaccination for all anti-haemagglutinins, and these differences are statistically significant ($p < 0.00001$). In respect of each anti-haemagglutinin, the protection rate significantly exceeds the 60% threshold.

Table 1. Geometric mean titres (GMT) and mean fold increase (MFI) in the study group

	Variables	*n*	GMT	Mean	SD	Median	Min	Max	Shapiro–Wilk test *p*	MFI 95% CI	W test *p*
H1	H1 before vaccination	96	9.54	35.83	52.63	10.00	0.00	320.00	0	6.79 3.02; 9.12	0
	H1 after vaccination	96	64.78	176.50	209.81	80.00	0.00	640.00	0		
H3	H3 before vaccination	96	6.45	38.44	85.50	0.00	0.00	640.00	0	13.28 5.89; 18.01	0
	H3 after vaccination	96	85.65	244.90	244.95	160.00	0.00	640.00	0		
HB	HB before vaccination	96	16.83	23.02	14.15	20.00	0.00	80.00	0	5.51 3.81; 7.76	0
	HB after vaccination	96	92.67	162.29	188.71	80.00	0.00	640.00	0		

In the case of H1, the chance that the titre will have a value of at least 1:40 is 4.3 times higher after vaccination than before it. In the case of H3, the chance that the titre will have a value of at least 1:40 is 6.3 times higher after vaccination than before it. In the case of HB, the chance that the titre will have a value of at least 1:40 is 41 times higher after vaccination than before it.

Table 2. Protection rate (PR) in the study group

PR	Titres	Before vaccination		After vaccination		OR 95% CI	F test
		n	%	*n*	%		*p*
H1	< 1:40 ≥ 1:40	58 38	60.4 39.6	25 71	26.0 74.0	4.30 2.25; 8.39	0
H3	< 1:40 ≥ 1:40	65 31	67.7 32.3	23 73	24.0 76.0	6.58 3.37; 13.22	0
HB	< 1:40 ≥ 1:40	67 29	69.8 30.2	5 91	5.2 94.8	40.98 14.79; 142.77	0

As shown in Table 3, the response rate for each anti-haemagglutinin is higher than 30%. For H3 and HB anti-haemagglutinins, the response rate is significantly higher than 50%. The highest response rate is 64.6% for HB, and the lowest value is 56.2% for H1.

Table 3. Response rate (RR) in the study group

RR	Titres	*n*	%	95% CI for fractions	P test *p*
H1	< 4x ≥ 4x	42 54	43.8 56.2	47.3 100	0.13080
H3	< 4x ≥ 4x	35 61	36.5 63.5	54.7 100	0.00536
HB	< 4x ≥ 4x	34 62	35.4 64.6	55.7 100	0.00293

Obtaining the results exceeding the values of parameters for people aged over 60 suggests that the vaccination against influenza caused an immune response in the study group.

Discussion

The process of population ageing generates rising costs in the area of public health. The percentage of people aged over 60 is constantly growing. In 1950, it was calculated that this group of people constituted 8% of the population, whereas in 2000 – as much as 10%. It is estimated that in 2050, this will be as much as up to 21% of the population. The immune response to the influenza vaccination is weaker in the elderly than among younger people, and this is the group that is most vulnerable to severe influenza infections and their complications. The key to understanding the differences and lower efficiency of vaccines in the elderly resulting from these differences is *immunosenescence* – i.e. a gradual deterioration of the immune system caused by the ageing process [12, 13]. This includes both the ability of the organism to respond to infections and tumours, as well as the development of long-term immunological memory, in particular through the vaccination, which results in far-reaching implications for specific and non-specific immune responses. Some authors suggest that this phenomenon can be partly explained by the intensification of "antigenic stress" and chronic inflammation occurring in the ageing body [14]. Immune cells isolated from the elderly present higher levels of pro-inflammatory cytokines, which results from the abnormal regulation of *toll like receptors* (TLR). This leads to permanent subclinical inflammation in the ageing organism, which causes difficulties in identifying the real inflammation and in responding to the pathogen. Studies carried out on mice suggest that the result of the chronic inflammation can be increased susceptibility to infections and worse response to vaccines [15, 16].

The study assessed the immune response to the vaccine in a study group aged 60–75. As the analysis of the data obtained shows, GMTs before and after the vaccination differ significantly for all anti-haemagglutinins ($p < 0.00001$), which means that patients in the 60–75 age group respond to the influenza vaccination.

The presented conclusions of the study coincide with the results obtained by prof. Lidia B. Brydak et al. in 1999 on the basis of a study carried out on a group of 45 people aged 62–93 [17]. Equally good immunogenicity in the elderly was observed by Zhu et al., who assessed the safety and immunogenicity of two different TIVs in different age groups. The group of people aged over 60 consisted of 240 people [18]. On the other hand, researchers in France analysed the humoral immune response to the influenza vaccination in elderly residents of long-term care facilities for 9 consecutive years of having regular vaccinations against seasonal influenza, and they also observed a good response to the vaccination, as in this study [19].

Conclusions

The results suggest that people aged between 60 and 75 have a normal immune response to the influenza vaccine, and therefore, it should be advised to use the influenza vaccination in these patients as a form of effective protection against influenza and its complications.

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Tables: 3
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References: 19

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