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The history of vaccine and vaccination against influenza in Poland

Historia szczepionki i szczepień przeciwko grypie w Polsce

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Abstract

The influenza virus is an important cause of morbidity, complications and mortality worldwide. Anyone can be infected, regardless of latitude or age. The paper describes the history of obtaining a modern influenza vaccine that does not deviate from current World Health Organization standards in Poland. Dozens of studies assessing the post-vaccination humoral response for different types of influenza vaccine, measuring levels of anti-haemagglutinin and anti-neuraminidase antibodies (although not in all of the studies) have been presented. The research was conducted mainly in high-risk populations, regardless of the age of vaccine recipients. What is noteworthy, the paper presents specific examples that may help promote prevention and encourage healthcare personnel to protect not only patients, but also their relatives. Prophylaxis in the form of vaccination is the cheapest and most effective form of preventing both dangerous complications and mortality. Infection caused by the influenza virus should be viewed not only in the context of exacerbation of a pre-existing disease or causing a new disease, but also in terms of measurable public costs. There are many types of imported influenza vaccines available on the Polish pharmaceutical market, from the inactivated intramuscular split or subunit vaccine to the intranasal live vaccine obtained from strains adapted to lower replication temperatures. Currently, quadrivalent influenza vaccines, i.e. containing two influenza A virus subtypes (A/H1N1/pdm09, A/H3N2) and two influenza B virus lineages (Victoria and Yamagata), are used. Depending on the type of vaccine, immunisation is recommended from the age of 6 months, whereas the upper age limit is not specified. The composition of vaccines is updated every epidemic season.

Keywords: influenza, vaccine, humoral response, pharmacoeconomics

Streszczenie

Wirus grypy jest istotną przyczyną zachorowań, powikłań i zgonów na całym świecie. Zakaża populację ludzką bez względu na szerokość geograficzną i niezależnie od wieku pacjenta. W pracy opisano historię otrzymania w Polsce nowoczesnej szczepionki przeciwgrypowej, nieodbiegającej od obecnych norm Światowej Organizacji Zdrowia. Przedstawiono dziesiątki badań oceniających odpowiedź humoralną po szczepieniu różnymi rodzajami szczepionki przeciwko grypie poprzez oznaczenie poziomu przeciwciał antyhemaglutyninowych i antyneuraminidazowych (chociaż nie we wszystkich badaniach). Badania prowadzono głównie w grupach podwyższonego ryzyka, bez względu na wiek osób szczepionych. Co warte podkreślenia, w tekście zaprezentowano konkretne przykłady – mogą być one pomocne w krzewieniu profilaktyki, powinny też zachęcić pracowników opieki zdrowotnej do ochrony nie tylko pacjentów, ale również ich bliskich. Profilaktyka w postaci szczepienia to najtańsza i najskuteczniejsza forma zapobiegania zarówno groźnym powikłaniom, jak i zgonom. Infekcję spowodowaną przez wirus grypy należy rozpatrywać nie tylko w kontekście zaostrzenia choroby, względnie – wywołania nowej choroby, ale także wymiernych kosztów finansowych ponoszonych ze środków publicznych. Na polskim rynku farmaceutycznym dostępnych jest wiele rodzajów importowanych szczepionek przeciwko grypie: od inaktywowanej szczepionki typu *split czy subunit*, podawanej domięśniowo, po szczepionkę żywą, otrzymaną ze szczepów zaadaptowanych do obniżonej temperatury replikacji, podawaną donosowo. Obecne szczepionki przeciwko grypie są czteroskładnikowe, zawierają dwa subtypy wirusa grypy typu A (A/H1N1/pdm09, A/H3N2) oraz dwie linie wirusa grypy typu B (linia Victoria i linia Yamagata). Szczepienia rekomenduje się – w zależności od typu szczepionki – od 6. miesiąca życia; górnej granicy wieku nie określono. Skład szczepionek jest uaktualniany co sezon epidemiczny.

Słowa kluczowe: grypa, szczepionka, odpowiedź humoralna, farmakoekonomika

INTRODUCTION

Influenza has decimated the human population since ancient times. Historical records by Hippocrates and Livius referring to influenza epidemics date back to 412 BC. Despite the high pathogenicity of the influenza virus, which is highly variable and very common in the animal world, the infection still tends to be ignored.

The isolation of the virus in 1933 by C. Andrews, W. Smith and P. Laidlaw at the National Institute for Medical Research (NIMR) in London became the cornerstone of extensive influenza research[1]. These studies took place at NIMR, which, until 2016, also housed the International Collaborating Center for Reference and Research on Influenza Virus. Currently, the centre is still located in London at the Francis Crick Institute. The institute was officially opened by Queen Elizabeth II in November 2016 and was fully operational in spring 2017. It is worth noting that all national influenza centres in Europe are required to cooperate[2].

The first authorisation for influenza vaccine, which was sponsored by the United States Armed Forces, was given in 1941[2]. It was also at that time that the manufacture of the vaccine for the civilian population began. Despite multiple adverse vaccine reactions, societies that experienced the first influenza pandemic in the 20th century (1918–1919) were willing to undergo immunisation. Scientific progress has led to improvement in production technologies, giving rise to many types of influenza vaccines, ranging from various inactivated to live vaccines derived from viruses that are able to replicate at lower temperatures[2].

HISTORICAL OUTLINE OF INFLUENZA VACCINE IN POLAND

In the early 1950s, an influenza vaccine was produced in Poland and the immunisation process began. Manufacture was handled by the Serum and Vaccine Production Plant in Cracow (Wytwórnia Surowic i Szczepionek w Krakowie). According to the data of the Department of Epidemiology of the National Institute of Public Health of the National Institute of Hygiene – National Research Institute (NIZP PZH-PIB), the vaccination coverage was low, within a few, a dozen, rarely slightly more than twenty thousand per season. Starting from the 1985/1986 epidemic season, binary vaccines containing the influenza type A virus, subtypes A/H1N1/ and A/H3N2/, were used.

It was also in the 1985/1986 epidemic season that the first research on influenza vaccination was conducted in Poland in the elderly population (with binary vaccines from the above-mentioned factory)[3]. The levels of anti-haemagglutinin and anti-neuraminidase antibodies were measured and vaccine adverse events (VAEs) were monitored. The results for post-vaccination humoral response indicated a high increase in antibody titres in elderly people, who are clinically considered a high-risk group[3].

In the years 1983–1984, first technology for the production of inactivated influenza vaccine with chromatographic purity was developed in Poland in the National Influenza Centre at the Department of Virology, National Institute of Hygiene in Warsaw by Lidia B. Brydak, Romuald Semkow in cooperation with the Military Institute of Epidemiology by Wiesław Gall[4]. These were first and third generation vaccines. One was an inactivated, whole-virion, chromatographically pure vaccine, while the other was also chromatographically pure, subunit vaccine containing only haemagglutinin (HA) and neuraminidase (NA). The vaccines were developed on a laboratory scale. Animal experiments and controlled human trials have shown superior quality and efficacy compared to the conventional inactivated vaccine produced in Cracow. The vaccine obtained had the so-called state control and was tested by the Department of Serum and Vaccines of the NIZP PZH-PIB. A total of 1,215 soldiers from three army divisions classified into three groups were vaccinated. The soldiers were immunised with vaccines against influenza A (inactivated, whole-virion highly purified), B (inactivated, subunit, containing highly purified haemagglutinin and neuraminidase) or C (conventional, commercial, partially purified by Sharples centrifugation). The group receiving the influenza A and B vaccine was further divided into two subgroups receiving vaccines with different protein content per dose. The first and the second batch contained 0.5 mg/mL and 1.0 mg/mL protein/dose, respectively. Blood was collected for tests four times – on the day of vaccination, as well as at months 1, 2 and 4 after the first vaccination. Humoral response was measured by determining the levels of anti-haemagglutinin and anti-neuraminidase antibodies using a method recommended by World Health Organization (WHO)[5,6]. VAEs were monitored. The study demonstrated a significant superiority of inactivated purified and subunit vaccines as well as whole-virion vaccines over conventional vaccine manufactured by the Serum and Vaccine Production Plant in Cracow. No differences were found in serological response between the first vs. the second batch. The results of the study suggested the possibility of producing a vaccine that did not deviate from WHO standards. Unfortunately, despite having access to modern technology, Poland did not undertake the production of influenza vaccine. Since 1989, no influenza vaccine has been made in our country.

Currently, the influenza virus strains that are used for vaccine production are almost 100% compatible with those that will appear in the coming epidemic season, which is owing to the participation of 149 national centres for influenza (including the Polish centre) in the Global Influenza Surveillance and Response System and the use of the latest molecular biology technologies along with sequence analysis of influenza viruses circulating in a given epidemic season[7].

In 1935, many scientific studies confirmed that the influenza virus replicates in domestic poultry embryos, where vaccines are still produced today[8]. Progress in research on the

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viral structure and an influenza vaccine that would cause as few VAEs as possible gave rise to a subunit inactivated vaccine in 1968, and a split-virus (or simply split) inactivated vaccine in 1976[2]. In June 2003, the Food and Drugs Administration (FDA) approved a live attenuated influenza vaccine obtained from the so-called cold-adapted influenza viruses[9].

Between 1980 and 1990, the National Influenza Centre of the NIZP PZH-PIB in Warsaw conducted research on the adaptation of A/H3N2/ influenza viruses to replicate at lower temperatures, and subsequently established the antigenic and biochemical properties necessary to determine the possibility of using these viruses as gene donors for recombinant vaccine strains. Genetic markers for both baseline and cold-adapted strains were also determined[10]. As a result of these studies, two Polish mutants, A/Pol/71/H3N2/ and A/Pol/79/85, that can be used as gene donors for the above-mentioned method were obtained, as confirmed by Professor L. Döhner from the University of Greifswald in Germany[10].

In the 1990/1991 and 1991/1992 epidemic seasons, Poland received a gift of 100,000 and 50,000 doses of Wyeth's subunit vaccine, respectively, from the US foundation Project HOPE[11,12]. Following WHO recommendations, the vaccine contained 15 μg of HA of A/Taiwan/1/86 (H1N1), A/Shanghai/16/89 (H3N2) and B/Yamagata/16/89/ in each dose (0.5 mL) in the 1990/1991 epidemic season.

The vaccine was delivered to 49 voivodships proportionally to the number of inhabitants in each voivodship. Vaccinations were carried out in nine age groups: 6–35 months, 3–8 years, 9–12 years, 13–20 years, 21–30 years, 31–40 years, 41–50 years, 51–64 years, and ≥65 years[11,12]. The following groups were vaccinated:

- children, adolescents and teachers (nurseries, schools, orphanages, boarding schools, educational centres);
- elderly people with chronic diseases (retirement homes, nursing homes);
- healthcare workers;
- employees of wards for the chronically ill;
- employees of transport, trade, construction, police.

A total of 39,356 people were vaccinated in the 1990–1991 epidemic season, while 75,638 people aged 6 months to over 65 years were vaccinated in the 1991–1992 season[11,12]. Blood samples were collected from some of the vaccinated patients on the day of vaccination and about 3 weeks later. Antibody levels for influenza A/H1N1/, A/H2N3/ and B strains were measured during both collections using the haemagglutination inhibition reaction and the neuraminidase inhibition reaction. During the study, humoral response was assessed by determining the levels of haemagglutinin-inhibiting and neuraminidase-inhibiting antibodies using a method recommended by the WHO[5,6]. Geometric mean antibody titres were assessed for influenza haemagglutinins and neuraminidases before and after vaccination. High seroconversion was found, indicating immunological activity of the vaccine used. The increase in the level of both anti-haemagglutinin and anti-neuraminidase antibodies was statistically significant[11,12]. The project was carried out as part of scientific collaboration with the Centers for Disease Control and Prevention (CDC) in Atlanta (USA) and the HOPE Project (USA) as well as epidemiology departments and virology laboratories of voivodship sanitary and epidemiological stations. Similar VAEs were reported for 1990/1991 and 1991/1992 epidemiological seasons. Systemic reactions, such as fever, malaise, muscle pain, chills occurred in 0.4% of the vaccinated subjects, while local reactions such as soreness and swelling ranged from 0.4 to 0.7%[11,12].

INFLUENZA PREVENTION WITH A FOCUS ON POLAND

Seventeenth-century theologian Thomas Adams once wrote "Prevention is so much better than healing because it saves the labour of being sick". Undoubtedly, these words can also be applied to influenza, which, along with other infections, takes priority among the multiple respiratory conditions[13]. Growing data points to the involvement of influenza viruses in the aetiology of not only respiratory diseases, but also those involving other systems. These include e.g. otitis media, auditory receptor dysfunction and, consequently, partial hearing loss or even deafness in 25–67% of cases, exacerbation of asthma, chronic obstructive pulmonary disease, exacerbation of cystic fibrosis, myocarditis and pericarditis, febrile seizures, myositis and myoglobinuria (which may lead to renal failure), neurological complications (including Guillain–Barré syndrome, transverse myelitis, encephalomyelitis), higher incidence of schizophrenia in cases of intrauterine infection[13]. These complications occur in all age groups and are fatal in many cases. Healthy young children under 5 years of age and all high-risk groups are most exposed. Complications of influenza in the elderly population, where about 80% of all deaths occur, are a clear example. However, fatal outcomes are also observed among young people, especially those with chronic diseases. To prevent mortality, it is necessary to vaccinate not only as many at-risk individuals as possible, but also healthy children up to school age; from the epidemiological point of view, it is this group that determines the course of the epidemic[13].

Influenza prevention is the goal of all public health organisations[14–42]. In addition to international and national scientific societies that recommend influenza vaccination, there are also groups of experts dealing with this issue, e.g. appointed by the WHO, CDC, European Centre for Disease Prevention and Control (ECDC) and the European Union. These actions aim to reduce the impact of epidemic and pandemic influenza in Europe by optimising methods for combating the disease[15–17].

For many years, the National Influenza Centre has been deeply involved in the WHO Global Influenza Surveillance Network, the European Influenza Surveillance Network

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Children:
• aged 6–35 months, 3–8 months, 9–12 years, and persons aged 13–20 years • with acute lymphoblastic leukaemia, vaccinated at different time points from the end of treatment • with mild and severe haemophilia • with bronchopulmonary dysplasia • with chronic renal failure, undergoing continuous outpatient peritoneal dialysis and with chronic renal failure, vaccinated once or twice • HIV-positive • after splenectomy, vaccinated in age groups: 0–5 years, 6–10 years, 11–15 years, over 16 years (*doctoral dissertation*)* • with aplastic anaemia • with asthma • with inflammatory bowel disease
Adults:
• adults aged 21–30, 31–40, 41–50, 51–64, and over 64 years (*2 doctoral dissertations*) • barracked students of Military Medical Academy • chronically ill patients, • with acute lymphoblastic leukaemia • with chronic renal failure (*part of the habilitation thesis*) • with chronic renal failure treated with haemodialysis • after allogeneic kidney transplantation • HIV-positive patients with varying levels of CD4, with and without symptoms of AIDS • with breast cancer, thyroid cancer • with asthma (*part of the doctoral dissertation*) • with chronic obstructive pulmonary disease (*part of the doctoral dissertation*) • from a group of young people and seniors (*doctoral dissertation*) • with acute cardiovascular events (*part of the habilitation thesis; results included in ESC***) • with lupus (*doctoral dissertation*) • with non-Hodgkin's malignant lymphomas (*doctoral dissertation*) • with primary systemic polyangiitis, Wegener's granulomatosis • an elite group of athletes receiving influenza vaccine in the Northern and Southern Hemispheres (2015/2016) • with chronic diseases, healthy and ill patients undergoing haemodialysis (*part of the habilitation thesis*) • people over 55 years of age vaccinated with the quadrivalent influenza vaccine in the 2018/2019 epidemic season (*doctoral dissertation*) • overweight patients (*doctoral dissertation*) • patients from the senior group with a certain level of vitamin D (*doctoral dissertation*)
* The study protocol was changed due to the clinical data. ** The results of Polish studies in patients with acute cardiovascular events (Ciszewski et al., 2006[39]) were highly evaluated and included in the European cardiological recommendations for influenza vaccine (Task Force Members, Eur Heart J 2013[43]).

Tab. 1. Research assessing the humoral response to influenza vaccinations in high-risk groups, conducted at the Department of Influenza Research, National Influenza Centre at NIZP PZH-PIB in collaboration with clinicians

	Age 18–60 years	**Age >60 years**
Conversion rate[1]	>2.5	>2.0
Protection rate[2]	>70%	>60%
Response rate[3]	>40%	>30%
[1] Mean increase in antibody levels post vaccination. [2] Percentage of people with antibody levels ≥1:40. [3] At least a 4-fold increase in antibody levels post vaccination.		

Tab. 2. Requirements of the Commission of the European Communities and Committee for Proprietary Medicinal Products for influenza vaccination

(EISN), and public health activities, also in terms of promoting influenza prophylaxis[2,14].

There is ample evidence that vaccination prophylaxis is the cheapest and most effective method of combating influenza. After approval of the first influenza vaccine, Spanish flu survivors, who remembered their deceased relatives, eagerly had themselves vaccinated.

The clinical efficacy of the vaccine is assessed in studies conducted after an influenza epidemic. For efficacy assessment, it is useful to estimate the incidence of influenza cases confirmed by serology or virus isolation in vaccinated vs. unvaccinated groups[13].

Poland's accession to the European Union compelled both the Ministry of Health and the National Health Fund to change their position. To this date, there is no tradition or obligation to vaccinate, even among those at high risk. Since 1994, vaccinations against this virus have only been included in the Polish vaccination calendar as recommended vaccines[2].

The National Influenza Centre has attempted to make the public aware of the role of influenza prevention as part of a nationwide educational campaign to spread the awareness of influenza prevention and the dangers of infection. To this end, lectures are held, educational and scientific papers are printed in many journals, as well as press interviews are broadcasted in radio and television throughout the country[2,7].

It is important to understand that an influenza pandemic is inevitable and is only a matter of time. Since 1990, monitored studies have been conducted at the National Influenza Centre to assess the efficacy of vaccination against influenza, not only in the high-risk groups, but also in healthy populations (e.g. in Warsaw). These studies have been conducted in cooperation with many medical university teaching hospitals and medical research institutes in Poland, as well as CDC clinicians in Atlanta[11,12,14]. Six hundred doses of

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subunit influenza vaccine donated in 1993 by N.J. Cox from the CDC to the National Influenza Centre enabled a multifaceted study on humoral response, especially in the group of children with lymphoblastic leukaemia[18–32]. Detailed results for the epidemic seasons 1991/1992–2006/2007 are presented in the form of tables in the book entitled *Grypa, pandemia grypy – mit czy realne zagrożenie?*[15–17]. All studies conducted in the 1991/1992–2018/2019 seasons are summarised in Tab. 1.

In line with international requirements, the humoral response for individual types/subtypes of influenza virus haemagglutinin, i.e. haemagglutinin subtypes H1, H3 and haemagglutinin HB, was assessed based on standardised parameters calculated from anti-HA antibody levels. According to the criteria by the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) and the Commission of the European Communities, regarding the harmonisation of requirements for vaccination against influenza, such parameters as the mean fold increase (MFI) of anti-HA antibody titre, protection rate and response rate measured approximately 3 weeks after vaccination should be taken into account when assessing the serological response to influenza vaccination. These values vary depending on the patient's age, as shown in Tab. 2[16,17].

CONCLUSIONS

The effectiveness of influenza vaccination was measured at the National Influenza Centre in both high-risk individuals and healthy people by assessing the humoral response to haemagglutinin and neuraminidase antigens, presented using international serological response parameters. Humoral immune efficacy, which can only be assessed based on studies in vaccinated individuals, is a reliable exponent at this point. Since there are currently no specific criteria for anti-NA antibodies, the values obtained are presented as post-vaccination rise in antibody titres.

Conflict of interest

The author reports no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

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Author contributions

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript; critical review of manuscript; final approval of manuscript: LBB.

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