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Influenza vaccines and vaccinations in Poland – past, present and future

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Summary

Influenza causes seasonal infections worldwide that can lead to complications and deaths in every age group. The most effective and cheapest way to combat influenza is through vaccination. In many countries, including Poland, for each age group, the rate of vaccination against influenza is still at a very low level, which generates high social costs, not infrequently family tragedies in the case of irreversible complications of influenza, or death of a loved one. Regular vaccination should be part of good medical practice, as well as an individual's engagement in their own health and in that of their family. Based on numerous studies, it is estimated that the effectiveness of current inactivated influenza vaccine in reducing morbidity and mortality in high-risk groups ranges from 50–70%. According to data from the National Institute of Public Health-National Institute of Hygiene, the rate of vaccination in children in 2008 in Poland was very low. In the group of children aged from 6 months to 14 years, only 1.1–1.6% were vaccinated. Although influenza vaccination for people aged over 65 years was free of charge in many provinces in this group, only 13.4% of this population was immunized, while in the case of people with chronic diseases, only 11.1% were immunized. The vaccination rate among health care employees is an embarrassing 6.4%. More educational activities addressed to both medical professionals and patients are required in order to increase influenza vaccine coverage in Poland.

key words: **influenza • vaccination • vaccines • Poland**

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Background

Influenza causes seasonal infections worldwide that can lead to complications and deaths in every age group [1]. According to information from the WHO, between 330 million and 1.575 billion individuals suffer from influenza and influenza-like virus every year throughout the world, with deaths of between 0.5 and 1 million individuals [2]. In many countries, including Poland, for each age group, the rate of vaccination against influenza is still at a very low level, which generates high social costs, not infrequently family tragedies in the case of irreversible complications of influenza, or death of a loved one. The most effective and cheapest way to combat influenza is through vaccination [1–3].

Three pandemics caused by 3 different subtypes of the influenza virus occurred in the twentieth century [1]. The pandemic of 1918–1919, referred to as the *Spanish flu,* was caused by the A/H1N1/ virus; the pandemic 1957–1958, known as *Asian flu,* was caused by the A/H2N2/ (1–4 million of deaths); and the pandemic known as *Hong Kong flu* was caused by the A/H3N2/ (1–4 million of deaths) [2]. According to the present data, the 1918–1919 pandemic resulted in 50–100 million deaths [1]. People who had lived during the pandemic and who had survived, and remembered the spectre of death caused by influenza, did not challenge the validity of vaccination when the 1957–1958 *Asian flu* pandemic occurred and were eager to undergo vaccination, notwithstanding the lesser quality of vaccines at that time compared with the present [1,4]. During the *Spanish* pandemic, the highest incidence was recorded in individuals aged 5–14 years, while the highest mortality rate was recorded in the population aged from 24–40 years [4]. Therefore, in order to avoid complications from influenza, and to ensure the appropriate development of children and young people, preventive measures, including regular vaccination against influenza, should be in place [5]. This does not mean that other age groups should be omitted from vaccination. The high variability of the influenza virus is a characteristic feature that has been known for many years [6]. In each successive seasonal epidemic, the circulation of influenza virus strains can be expected within a population. These strains are genetically and antigenically different from those which caused illness in the past or even in a number of recent epidemics, not only because of mutations, but also due to changes of reassortment resulting from the segmented genome [7]. This may in turn, have health and economic impacts associated with the occurrence of epidemic and pandemic influenza. Therefore, regular vaccination is one of the few steps that may be taken to protect people, especially in high-risk groups, from the potential, serious complications of influenza [1].

Vaccination Against Influenza

Regular vaccination should be part of good medical practice, as well as people's engagement in their own health and in that of their family [1,4,7]. Based on numerous studies, it is estimated that the effectiveness of current inactivated influenza vaccine in reducing morbidity and mortality in high-risk groups ranges from 50–70% [8–12]. We should realize that the flu is a disease in which the continuous evolution of the virus is essential for the occurrence of seasonal epidemics in the human population and, from time to time, as pandemic influenza.

It is known that since 9 May 1997 the A/H5N1/HPAI influenza virus subtype is circulating within the population, creating more and more new mutants, which has resulted in the registration of an approximate mortality of 56.7% among infected individuals [13]. The reassortment of the 2 strains of viruses – A/H5N1/ (HPAI), which is very infectious, but does not have the ability of human to human transmission; and A(H1N1)pdm09, a pandemic virus which does have this ability – must be feared. Reassortment could result in the creation of a virus with all of the characteristics of the pandemic virus [3]. For example, during the 2010/2011 epidemic season more people died than during the previous year's influenza pandemic, even though a vaccine was available from 5 different companies, in pharmacies, from the family doctor, or from private medical centres [14,15].

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Influenza Vaccine Coverage in Poland

According to data from the National Institute of Public Health-National Institute of Hygiene (NIPH-NIH), the rate of vaccination in children in 2008 was very low [16]. In the group of children aged 6 months to 14 years, only 1.1–1.6% were vaccinated. Although influenza vaccination for people aged over 65 years was free of charge in many provinces in this group, only 13.4% of this population was immunized, according to the European Centre for Disease Control (ECDC) and the VENICE Network New Integrated Collaboration Effort; while in the case of people with chronic diseases, only 11.1% were immunized (data VENICE ECDC and Network) [17,18]. The vaccination rate among health care employees is an embarrassing at 6.4% (data VENICE ECDC and Network) [17,18]. According to the latest data from WHO, the uptake of vaccine places Poland in the penultimate place in Europe (2010) [2]. The situation is no better in terms of individuals with different types of insurance within private medical centers. There are over 30 ways to increase of rate of vaccination in Poland [1].

Pandemic Influenza Caused by a (H1N1)pdm09 Virus in Poland

The pandemic announced by WHO on 11 June 2009 was caused by the influenza virus subtype A/H1N1/v, which proved to be a reassortment [2]. According to data from WHO and ECDC, the mean number of deaths worldwide was about 18,000, which is incomparably less than for seasonal influenza [2]. We must not forget that 1 million people throughout the world die from seasonal influenza and influenza-like viruses [2]. The global hysteria unleashed because of the purchase of pandemic flu vaccine did not fail to affect Poland. Statements were also made by individuals who had no substantive grounds for doing so. With regard to the issue of vaccination against the pandemic influenza virus A(H1N1)pdm09, the decision taken in Poland should be considered as appropriate when taking into account the type of restrictions imposed on Poland by pandemic vaccine manufacturers, who placed the entire burden of responsibility for vaccine safety onto the state, which is not the practice for seasonal vaccines. Furthermore, in accordance with manufacturers' requirements, the vaccine could not be made available in pharmacies.

With regard to the Polish position adopted by the Minister of Health, Ewa Kopacz, the Council of Europe voiced its marked appreciation repeatedly. In effect, throughout the

Table 1. Recommendations for vaccination against influenza (ACIP, 2011) [19].

The Advisory Committee on Immunization (ACIP – Advisory Committee on Immunization Practices), together with WHO, each year make recommendations regarding vaccination against influenza. According to them, the indications for the use of inactivated vaccines with *split virion* and *subunit vaccines* are as follows.
Clinical indications for influenza vaccination High-risk groups particularly vulnerable to the occurrence of complications of influenza
Currently, it is recommended influenza vaccination for **all persons, from 6 months old**. Particular attention is, however, that vaccination should be extended to particular groups as follows:
• organ transplant individuals
• all children aged 6 months – 4 years (59 months)
• all persons aged ≥50 years, because in this group greatly increases the number of people belonging to high risk groups
• adults and children who have chronic pulmonary(including asthma), or cardiovascular (except isolated hypertension), renal, hepatic, neurological, hematologic or metabolic disorders (including diabetes mellitus);
• persons who have immunosuppression (including immunosuppression caused by medications or by HIV)
• women who are or will be pregnant during the influenza season
• children and adolescents (aged 6 months old - 18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
• residents of nursing homes, and other long-term- health care facilities
•persons who are morbidly obese (BMI ≥40)
Epidemiological indications for influenza vaccination
Persons who live with or care for person at higher risk for influenza-related complication (persons who can transmit influenza to persons at high risk and healthy people could be a source of infection for these persons):
• HCP
• household contacts and caregivers of children aged ≥5 years and adults aged ≥50 years, with particular emphasis on vaccinating of children aged ≥6 months;
• household contacts and caregivers of person with medical conditions that put them at higher risk for severe complications from influenza
• All health professionals; doctors, nurses and other staff of hospitals and outpatient centers, emergency services,
• employees of nursing homes and care facilities who have contact with inmates or patients (including children), as well as persons providing home care to patients with high-risk groups
• family members of persons belonging to high risk groups
• cashiers, policemen, soldiers, teachers, kindergarten, journalists, construction workers, shop assistants shops and stores, craft service, etc.
• people caring for children under the age of 5 years,
• public service employees, such as conductors, workers, shop and stores, craft service etc

world many millions of doses of unused vaccine against pandemic influenza are wasted, representing many millions of Euros. Moreover, additional costs arise from the disposal of the vaccine purchased surplus to need, and it was a shame that these sizeable funds could not be devoted to other public health purposes instead. As we have stated and written many times, and what both then and now continues to give us cause for real concern, is the fact that confidence in the WHO has been undermined, the take-up of all vaccines has decreased, and that there will be a further reduction in the already low take-up of the influenza vaccine, particularly in Poland. Therefore, we deplore the fact that all those individuals who expressed themselves so actively in the press, radio and TV did not take action to increase the rate of vaccination against influenza, particularly since the ternary composition of the vaccine for the 2010/2011 season included the A/H1N1/pdm09 pandemic strain.

Let us present the effects of our casual attitude to vaccination. It is worth emphasizing that those individuals who died in the 2010/2011 epidemic season were in high risk groups, were not vaccinated against influenza, and had infection caused by the virus A(H1N1)pdm09 confirmed by use of molecular biology techniques, which was already a component of the vaccine for this season [2,4].

Recommendations for Influenza Vaccination

For many years, since the year 2000, the Advisory Committee on Immunization (ACIP) in the U.S. has recommended the

Table 2. Influenza vaccines registered in Poland [1,3] (Brydak L.B. 2012).

Influenza vaccine received in cultured chick embryos:
Inactivated influenza vaccine split virion with: – VAXIGRIP (Sanofi Pasteur SA, F) – Fluarix (GlaxoSmithKline, B) – Begrivac (Novartis Vaccines and Diagnostics, D) – ID Flu * (Sanofi Pasteur SA, F)
Subunit vaccines containing isolated surface antigens, hemagglutinin and neuraminidase, ie: – Influvac (Abbott, NL) – Agrippal (Novartis Vaccines and Diagnostics SRL, I) *Vaccines wirosomalne:* – Inflexal V (Berna Biotech I, S.r.l.)
Influenza vaccine received in the MDCK cell culture: Inactivated subunit influenza vaccine, containing isolated surface antigens, hemagglutinin and neuraminidase, ie: – Optaflu (Novartis Vaccines and Diagnostics, D)
Influenza vaccine received in the Vero cell culture:
Inactivated influenza vaccine with split virion
Preflucel (Baxter ,A)

* Vaccine administered intradermally.

routine vaccination against influenza of all individuals above the age of 6 months until late old age [19]. Therefore, in the epidemic season, vaccination is recommended for nursing mothers unless they were already vaccinated, and vaccination of household members, caregivers of young children and of individuals who are in close contact with children under the age of 6 months. The recommendations of the Advisory Committee on Immunization (ACIP) are shown in Table 1 [19].

In the 2010/2011 epidemic season, only 5.0% of the population was vaccinated despite the inclusion of the A/H1N1/pdm09 strain in the ternary composition of the vaccine against influenza [14,15]. In Poland in 2009, *split* inactivated or *subunit* vaccines were registered as shown in Table 2.

They can be administered either intramuscularly or intradermally, depending on the type. Vaccines against influenza available in Poland are inactivated (containing fragments of *killed* influenza virus), therefore they are not able to multiply in the body and cause disease, but produce a specific immunity directed against the influenza virus. It is worth noting that irrespective of the recommendations of the Advisory Committee on Immunization (ACIP), 14 scientific societies also recommend vaccination against influenza (Table 3) [1].

Increasingly, the problem of vaccination against influenza is considered in terms of its health and economic aspects, of which we often remain unaware. According to data from the U.S., depending on the influenza epidemic season, the cost impact of influenza infection is between 76–167 billion dollars [1]. The humoral immune response to influenza

Table 3. Recommendations of the International Scientific Societies for influenza vaccination [1] (Brydak L.B. 2008).

– Advisory Committee on Immunization (ACIP)
– American Academy of Pediatrics (AAP)
– American Academy of Family Practice (AAFP)
– American Academy of Family Physicians (AAFP)
– Working Party on Preventive Services (USPSTF U.S.)
– American College of Internal Medicine
– American Society of Internal Medicine, U.S.
– American Society for Infectious Diseases (IDSA)
– Canadian Working Group on Periodic Health Research
– American Cancer Society
– American College of Obstetrics and Gynecology
– Executive Director of the Department of Health UK
– American Heart Association / American College of Cardiology
– Global Initiative on Chronic Obstructive Lung Disease (GOLD)
– Global Strategy for Recognition, Treatment and Prevention of Asthma (GINA guidlines)

vaccination in high-risk groups evaluated in studies undertaken by the Influenza Virus Research Department of the National Centre for Influenza NIPH-NIH in collaboration with clinicians is shown in Table 4 [1].

We are convinced that the presentation of specific examples will be helpful in promoting prevention, and will encourage health professionals to protect not only their patients, but also their relatives. Table 5 includes what in our opinion are the main causes of the low prevalence of influenza vaccination.

Current Status of Influenza Diagnosis and Treatment in Poland

Diagnostic methods have been available in Poland for decades, beginning with the gold standard for identification of the pathogen in the chicken embryo or tissue culture, by ELISA, immunofluorescence (IF), serological methods, and ending with studies using different combinations of molecular biology methods [1,3]. Currently, in Poland and only in the Influenza Virus Research Department of the National Influenza Centre at the NIPH-NIH in Warsaw, 12 respiratory viruses – Influenza type A and B, virus RS type A and B, parainfluenza types 1, 2 and 3, human metapneumovirus (hMPV), adenovirus, rhinovirus, coronavirus, 229E/NL63, and OC43/HKU1 – can be detected from a single sample from the patient, applying the methods of molecular biology [3]. However, in the 12 Provincial Sanitary-Epidemiological Stations (PSES) it is possible to diagnose influenza infections using methods of molecular biology, while the remaining 4 PSES perform diagnostics using the immunofluorescence method (IF). The importance of virological diagnosis of respiratory infections, particularly influenza, is high, not only in medical, but also in economic terms. It serves to avoid antibiotics therapy in the absence of indications and also to ensure that appropriate treatment is administered when necessary.

The appropriate use of currently available new influenza virus neuraminidase inhibitors, such as zanamivir (Relenza) and oseltamivir (Tamiflu), and consequently, the simultaneous prevention of appearance of strains resistant to these drugs, reduce the length of hospital stay [1,20–24].

Table 4. Studies conducted in the Research Department of influenza viruses, the National Influenza Center, NIPH in collaboration with clinicians in the groups at risk and evaluated the humoral immune response to influenza vaccination [1] (Brydak L.B. 2008).

Children
Children aged 6–35 months, 3–8 years of age, 9–12 years 0.13–20 years of age
Children with acute lymphoblastic leukemia (ALL), vaccinated at different times after treatment.
Children with severe haemophilia and mild.
Children with bronchopulmonary dysplasia.
Children with glomerulonephritis.
Children with chronic renal failure subjected to continuous ambulatory peritoneal dialysis, hemodialysis and chronic renal failure vaccinated once and twice.
Children infected with HIV.
Children vaccinated after splenectomy in age groups 0–5 years of age, 6–10 years of age, 11–15 years of age, (*dissertation*)
Children with aplastic anaemia
Children with asthma
Children with inflammatory bowel disease
Adults
Adults aged 1921–1930 years of age, from 1931 to 1940 years of age, from 1941 to 1950 years of age, from 1951 to 1964 years of age, >64 years (*2 dissertations*)
Billeted students of the Military Medical Academy
Patients chronically ill
Patients with acute lymphoblastic leukemia
Patients with chronic renal failure
Patients after renal allograft resipients
Patients infected with HIV at various levels of CD4, with symptoms of AIDS and asymptomatic
Patients with breast cancer
Patients with cancer of the thyroid
Patients with asthma (*part of PhD thesis*)
Patients with chronic obstructive pulmonary disease (COPD) (*part of PhD thesis*)
Patients with a group of young and elderly (*dissertation*)
Patients with acute cardiovascular events (*some of the habilitation thesis*)
Patients with malignant lymphomas-Hodgkin's (*PhD thesis*)
Patients with lupus (*PhD thesis*)
Patients with primary systemic vascular inflammation: Wegner's granulomatosis (*part of the habilitation thesis*)

Table 5. Reasons for low prevalence of influenza vaccination [1].

- lack of doctors' greater acceptance for this form of prevention
- lack of awareness about the legal obligation of doctors to recommend vaccination
- insufficient knowledge about influenza and its complications cost, not only in individual cases, but in the whole country
- insufficient knowledge about the types of vaccines
- the expectation that vaccination protects against all upper respiratory tract infections (unrealistic, since respiratory viruses are about 200 types)
- confuse influenza with the common cold in this example, *stomach flu* or other respiratory infections
- frequent adverse events after vaccination confusion with influenza complications
- the need to repeat vaccination every epidemiologic season

The taking of appropriate measures to prevent the spread of infection refutes those myths associated with vaccination that lead to its avoidance [1]. One should be aware that, particularly in individuals in high-risk groups (including healthy young children), the effects of influenza in those who are not vaccinated can result in complications, and even death. Therefore, the rapid identification of influenza virus is a priority when considering the possibility of treatment with effective medication.

Currently, 2 influenza antiviral agents have been present on the market for many years – oseltamivir (Tamiflu) and zanamivir (Relenza) – active in the case of infection both with influenza A and B [1–3,20–24]. The effectiveness of these drugs is dependent on several factors. In the case of seasonal influenza infection, the medication should be given after laboratory confirmation, preferably up to 36 hours from the onset of symptoms [1,20–24]. However, in the event of pandemic influenza, it should be administered on the basis of clinical symptoms, without waiting for the laboratory confirmation of infection. The use of these medicines is indicated not solely for treatment of established infection, but also in prevention, including for post-exposure prophylaxis [1,20–24].

It should be noted that the use of oseltamivir during an epidemic of influenza was recommended from the age of 1 year [2]. However, in the situation of a pandemic, both the manufacturer and the European Medicines Agency (EMEA) recommend the use of this medication for those aged less than 1 year, depending on the child's body weight [25].

Oseltamivir (Tamiflu) is available in capsular form, which allows for its use not only in the case of small children, but also in patients who are unable to swallow capsules [1,20–24]. Zanamivir (Relenza) is formulated for inhalation and can be used from the age of 5 years. These drugs are effective for both seasonal influenza infections as well as for subtypes of other influenza type A and B viruses.

According to WHO and Polish data, the new generation of drugs – the neuraminidase inhibitors – have proved effective in infections with the HPAI virus: subtype A/H5N1/, A/H7N7 /, pandemic influenza virus subtype A(H1N1) pdm09, as well as in the case of seasonal influenza infection [1,26]. Currently, clinical trials of a new antiviral agent, peramivir, are in progress. Results of preliminary studies of this drug seem promising [27].

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