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Prevention of influenza infection – a Polish perspective

Zapobieganie zachorowaniom na grypę – z polskiej perspektywy

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Summary

Influenza is a viral respiratory illness that causes high morbidity and significant mortality in humans. Costs associated with influenza in terms of human suffering are immeasurable and the economic costs are very high. Every year, according to the World Health Organization (WHO), 5-25% of the global population suffers from infection with influenza and influenza-like viruses and between 500 thousand and one million individuals of all ages die from multiple organ complications, irrespective of the geographic location. Influenza vaccination is still neglected and the percentage of the global population vaccinated remains low. The first authorization for the use of influenza vaccines in humans was issued in 1941. Currently, many varieties of influenza vaccine are available, containing either fragments of inactivated influenza virus or live vaccine which consists of attenuated virus. The influenza vaccine is most often developed in chick embryos or less frequently in tissue culture such as MDCK and Vero. A variety of inactivated vaccines are registered in Poland. Due to the mutability of the virus, it is not yet possible to develop a universal vaccine, nor can the disease be eradicated; however, prevention is possible by inoculating the greatest percentage of the global population. According to the WHO, Poland is in the penultimate position in Europe in terms of the percentage of the population vaccinated. In the last epidemic season of 2012/2013 only 3.75% of the Polish population was immunized.

Key words: **influenza • prevention • vaccination**

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A brief history of influenza vaccines

In the history of influenza, 1933 was a crucial year, marking the discovery and isolation of the influenza virus from humans by three British researchers, Wilson Smith, Christopher Andrews, and Patrick Laidlaw from the National Institute for Medical Research in London [7]. It is noteworthy that the institute is also currently a WHO Collaborating Centre for Reference and Research on Influenza in Europe [39]. The first attempts to develop an influenza vaccine used animals and infected mouse cells homogenates, but these were not suitable for use in humans. In 1937, the introduction of viral propagation in chick embryos enabled the production of the vaccine on a large scale and this method is still used today. The first authorization for the administration of influenza vaccines in humans was issued in 1941 based on studies sponsored by the Armed Forces of the United States [7,37].

Intensive research on the splitting of the virus occurred in the 1960s and '70s using ether, tri-n-butyl phosphate, polysorbate 80. The first authorization for the clinical use of a vaccine with split virions, the so-called split vaccine, was issued in 1968 and it is still in use in many countries. A different type of vaccine was introduced in 1976. This vaccine contains only the hemagglutinin and neuraminidase subunit, and is known as the subunit vaccine. Both the split and subunit vaccines are chromatographically pure. Improved purification by zonal centrifugation and column chromatography allows for the disposal of most of the chicken protein contaminants, resulting in a significant reduction in the number of side effects [5,37,39]. The introduction of a recombinant virus from a wild-type strain produced in conjunction with a laboratory strain A/PR/8/34/H1N1/, with good propagation characteristics in the chick embryo, significantly increased the efficiency of vaccine production [39].

Since 1968, influenza vaccines have been ternary. In accordance with WHO recommendations, seasonal split or subunit inactivated influenza vaccines contain 15 μg of hemagglutinin subtype A/H1N1/, 15 μg of subtype A/H3N2/, and 15 μg of type B 1 [1,2,3,28]. Companies that manufacture influenza vaccine receive these strains from the WHO [7,39]. Due to the antigenic drift, resulting from point mutations that occur during replication that generate new variants of influenza virus, it is currently difficult to develop a universal vaccine against influenza [37,39]. The application of the latest molecular biology techniques means that influenza virus strains used for current influenza vaccines seem to be almost 100% compatible with those that appear in the next epidemic season [1,2,3,28]. The 1983–1984 Polish study by Lidia Brydak, Wiesław Gall and the now deceased Romuald Semkow on inactivated influenza vaccine bears mentioning [7,12]. The National Center for Influenza at the Department of Virology, National Institute of Hygiene in Warsaw in cooperation with the Military Institute of Epidemiology in Warsaw, obtained first and third generation inactivated influenza vaccines [7,12]. One was a chromatographically pure inactivated vaccine containing whole virions. The other, also chromatographically pure, was a subunit vaccine containing only the hemagglutinin and neuraminidase components [12]. These vaccines were developed on a laboratory scale. Evaluation of the results of their application in animal and controlled human studies showed improved quality and effectiveness in comparison with conventional inactivated vaccine that was manufactured by the Serum and Vaccine Manufacturing Plant in Krakow [7,12]. A total of 1,215 people were vaccinated, with four comparative groups of subjects vaccinated with a three-component vaccine against influenza with varying levels of purity. Anti-neuraminidase and anti-hemagglutinin antibody levels were measured. The resulting vaccine was subject to state regulation. It was tested by the Department of Sera and Vaccines at the National Institute of Hygiene in Warsaw. The results of these studies indicated the possibility of the manufacture of a modern vaccine that would be consistent with WHO standards. Regrettably, the results of this pioneering study were not implemented in large-scale production [7,12]. Poland has not manufactured an influenza vaccine since 1989; influenza vaccines available on the Polish market are imported.

After the first experiments performed in the 1930s, it seemed as if it would be impossible to obtain an effective vaccine. Vaccines developed for one epidemic were ineffective against the next and research revealed the existence of different strains of the virus. Ineffectiveness of vaccines was associated with the constant changes in the circulating virus, which in this way gained the potential to infect individuals who had been resistant during the previous epidemic season.

Current influenza vaccines

Two types of vaccine are currently used in the prevention of influenza:
- live attenuated vaccine;
- various forms of inactivated vaccine: a vaccine containing the whole virus,
- split virion vaccine, and highly purified subunit preparations, containing surface hemagglutinin and neuraminidase [4,12,39].

Inactivated split or subunit vaccines are the most frequently manufactured. Influenza vaccine does not contain thimerosal [1,2,3,4,7,28,39]. Inactivated influenza vaccine is produced mostly in chick embryos and less often in MDCK (Madin Darby canine kidney – a cell line derived from canine kidney for culturing influenza virus) and Vero (green monkey kidney cells) tissue culture. In addition, inactivated adjuvanted oil, virosomal, and MF59 vaccines are also available. These are used in some countries (for example, in Germany, Italy, Switzerland, England and Russia) even though the American Committee on Immunization Practices (ACIP) does not recommend them [1,2,3,4,27,28,39]. The decision on vaccine choice is made by the national health authorities. Beyond the ef-

forts aimed at a more satisfactory use and distribution of currently available vaccines, a number of strategies are in place. These are focused on increasing the immunogenicity of vaccines that have already received regulatory approval; the aim is to improve the overall quantity and quality of available doses.

The production cycle of split and subunit inactivated influenza vaccine in chick embryos takes about 6 months. This indicates the length of time needed for manufacture. Therefore the supply of the vaccine in a timely manner must be preceded by an earlier decision of the amount of vaccine that is needed. Apart from continually enhanced inactivated vaccine, vaccines containing live attenuated virus are also used, because they induce an immune activation process similar to one that occurs in a natural infection. The first trials of the use of vaccines derived from cold-adapted mutants were performed in 1938-1939 by Smorodincev [36]. They contained a virus that had lost its pathogenicity for humans due to multiple replication in the lung cells of white mice. The mass vaccination with cold adapted virus vaccine of schoolchildren in the Soviet Union showed a significant reduction in the incidence of infection. At this point it is worth mentioning Polish studies concerning cold adapted virus [6,7]. During 1980–1990 the National Center for Influenza, National Institute of Hygiene in Warsaw, conducted research on the adaptation of influenza viruses A/H3N2/ antigen to low temperature for replication, with analysis of the antigenic and biochemical properties necessary to determine their potential as donor genes for obtaining recombinant vaccine strains [6,7]. Indicators were designated as genetic markers necessary for this type of research on emergent and cold-adapted strains that are adapted to low temperatures. As a result of these studies there were developed two Polish mutants, A/Pol/L/71/ H3N2/ and A/Pol/79/85, that can be used as donors of genes for recombinant influenza vaccine strains, which was confirmed by Professor Dr. L. Döhner of the University of Greifswald in Germany [6,7]. It was not until 2003 that ACIP and the Centers for Disease Control and Prevention (CDC) in Atlanta issued a supplement for the first time, for use of the ternary attenuated intranasal influenza vaccine FluMist, manufactured by MedImmune, which was authorized for use in the United States in June 2003 [39]. A live attenuated influenza vaccine is not registered in Poland [7,8,9]. Although it has been known for decades that the vaccine has saved many lives, and its use currently reduces morbidity and mortality associated with influenza, the need to develop a universal vaccine and more efficient products remains the dream of virologists. Inactivated influenza vaccine has been in use since the 1940s and has had good safety and efficacy records over many years.

Pandemic influenza vaccines

Intensive research to improve inactivated vaccines is still being undertaken with special emphasis on the ability to respond to pandemic influenza. During the past decade, significant progress occurred in technology of vaccine production; this helped either in terms of vaccine manufacture or the improvement of vaccine immunogenicity. New routes of administration have also been tested and implemented. One proposal was to increase the immunogenicity of the vaccine by adding an effective and safe adjuvant, which may also allow a reduction in the amount of antigen needed to produce an effective immune response. Several different adjuvants have been tested for their ability to increase the immunogenicity of protein vaccines for a number of different diseases. In the preventive use of currently available inactivated vaccines in individuals who have had previous infection with influenza, a dose of 15 μg of HA of each strain stimulates the required level of antibodies (≥ 1:40).

Provisions harmonizing the vaccines used in the Member States entered into force on 1 January 1992, although they are not entirely in line with ACIP recommendations. In the European Union, a vaccine manufactured and with regulatory authorization in one Member State must be accepted by the other Members [7,28,39]. However, in accordance with European Union directives (the European Directorate for the Quality of Medicines), a vaccine registered in the European Union, having OCABR approval (the Office of Consumer Affairs and Business Regulation), does not require re-examination in EU Member States [7,28,39].

Recommendations for influenza vaccination

Inactivated split or subunit influenza vaccines can be used and should be recommended for all age groups, starting from 6 months of age. The latest recommendations from the WHO and ACIP [1,2,3,4,7,39] define the clinical indications for vaccination and identify the high-risk groups particularly vulnerable to the occurrence of influenza complications. These include, among others, individuals who have undergone organ transplantation, healthy children from the age of 6 months to 18 years, patients in high-risk groups from the age of 6 months onwards, patients with any disease that can cause impairment of respiratory function including asthma and chronic obturative pulmonary disease (COPD), children and adults with chronic cardiovascular or respiratory disease, metabolic diseases, renal failure, hemoglobinopathies, immunodeficiency, pregnant women, residents of homes for the elderly, health care workers and chronic care facility workers and residents [1,2,3,4,28,39]. However, other indications include individuals who can act as carriers of influenza to participants of high-risk groups and those healthy individuals who could become a source of infection for these persons, for example medical professionals and care givers of children aged less than 6 months, and public servants. Over the course of many epidemic seasons the Influenza Virus Research Institute, National Center for Influenza NIPH-NIH, provided and disseminated information to the public that the vaccine should be offered throughout the epidemic season, even if there is information that the influenza virus is circulating in

the population, refuting one of the myths that vaccination can only take place in October [34,39]. According to the Polish vaccination procedures, it is the doctor who decides if vaccination can take place at any given time. The following vaccines are available in Poland for the 2012/2013 influenza epidemic season: Vaxigrip, Fluarix, Influvac and IDflu, which is administered intradermally (inactivated vaccines should be administered intramuscularly) [34]. IDflu contains a total of 27 µg HA/0.1 mL for individuals aged 18–59 years, and 45 µg HA/0.1 mL for those ≥ 60 years [27]. World Health Organization experts provide the influenza strains to manufacturers for vaccine production. It should be noted that in the 2012/2013 epidemic season, two components of the trivalent influenza vaccine, namely the subtype A/H3N2/ and type B, have been changed, which rarely happens [4,39]. In accordance with the recommendations of the WHO, the influenza vaccine for the current season for the northern hemisphere contains:

- A / California / 7/2009 (H1N1) pdm 09-like virus
- A/Victoria/361/2011 (H3N2)-like virus
- B/Wisconsin/1/2010-like virus (which is similar to the Yamagata line B) [27].

Future for influenza vaccines

Since 1968, as mentioned above, influenza vaccine has had a ternary composition [4,37]. Currently, studies are devoted to the construction of a quadrivalent inactivated influenza vaccine [4,36]. The new vaccine will contain two lines of influenza B virus, because two lines of type B influenza viruses are antigenically different: B/Victoria and B/Yamagata. Vaccination against one type of influenza B virus gives limited crossover protection against the other type B virus. It is important to take into account the difficulty in predicting which subtype of the B virus will be circulating in a given epidemic season [4]. The widespread use of a future ACIP-recommended quaternary inactivated influenza vaccine would help to evaluate its impact and enable the formulation of evidence-based conclusions concerning the change from the trivalent to the quadrivalent vaccine. It is clear, however, that this would depend on many factors such as the availability of the vaccine, the percentage of the population vaccinated, the effectiveness, and of course on the frequency of influenza caused by the type B virus lines. Moreover, it should be noted that in February 2012, the US Food and Drug Administration approved the intranasal quadrivalent live vaccine (LAIV) FluMist Quadrivalent from MedImmune; however, this vaccine will only be available in the 2013/2014 epidemiological season [27].

Effectiveness of influenza vaccines

It is believed that 70-80% of the population must be vaccinated to ensure the necessary herd immunity [1,30,39]. The efficacy of vaccination in the elderly is lower than that in younger subjects. An anti-hemagglutinin antibody titer ³ 1:40 is assumed to be protective [1,7,30,39]. Most cases of influenza-associated health complications or even death occur in elderly individuals. Therefore, it is recommended that they undergo protective seasonal vaccination. Individuals aged over 65 years and those suffering from chronic respiratory and cardiovascular diseases, residents of homes for the elderly and care homes and for those with chronic disease and similar institutions are at risk of complications from influenza and should be included in the special vaccination programs [39]. The proportion of individuals at high risk increases with age, particularly in the elderly (tenfold increase). Prospective studies, critical reviews of existing studies and meta-analyses of the available data provide solid scientific evidence for a policy of seasonal vaccination of patients in high-risk groups [27,37, 39]. Based on numerous tests it is estimated that the efficiency of inactivated influenza vaccine currently in use in reducing morbidity and mortality in high-risk groups ranges from 50% to 70% [7,34,39]. Clinical and economic data accumulated over the years have contributed to a more harmonized influenza prevention policy in European countries and coherent recommendations from several prestigious scientific immunization societies [7, 34,39].

Significant health benefits associated with influenza vaccination are evident for all age and high-risk groups. In Poland, influenza vaccination has been included in the immunization schedule since 1994, but solely as a recommended vaccination [7]. Since 1990 the National Influenza Center has attempted to raise awareness of the role of influenza prophylaxis through countrywide lectures, educational and scientific articles published in a variety of magazines, radio and television interviews, press releases, information leaflets for doctors and patients, as well as the publication of three books describing the problem of influenza (the only books on the subject available in Polish) [7,10,11,12,13,14,15,16,17,18,19,20,21,22,23]. It must be known, as it has been repeatedly emphasized in chapters of the latest edition (2008) of the book by Lidia B. Brydak *Flu: pandemic flu, myth or real threat?*, that the occurrence of a pandemic that meets all the long-established criteria is inevitable; in fact it is only a matter of time. From 1990 to the present the National Center for Influenza has performed monitoring studies to evaluate the effectiveness of influenza vaccination not only in high-risk groups but also in selected healthy populations, including that of Warsaw. These studies have been and continue to be conducted in collaboration with several medical academic departments, medical universities and medical research institutes in Poland and the Centers for Disease Control and Prevention in Atlanta [7]. The aim of the above study was to present the effectiveness of vaccination against influenza measured both in patients in high-risk groups and in healthy individuals by evaluating the antibody response to the hemagglutinin and neuraminidase antigens using international parameters of serological response [1,10,11,12,13,14,15,16,17,18,19,20,21,22,36,38,40,41]. The presentation of case studies derived from the above work will be helpful in promoting prevention as well as in encouraging health services staff to

Table 1. Experimental studies conducted at the Polish National Influenza Center [7]

Children
Children aged 6-35 months, 3-8 years, 9-12 years, 13-20 years
Children with acute lymphoblastic leukemia (ALL), vaccinated at different times after treatment
Children with severe hemophilia
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, 6-10 years, 11-15 years
Children with aplastic anemia
Children with bronchial asthma
Children with inflammatory bowel disease
Adults
Adults aged 21-30, 31-40, 41-50, 51-64, > 64 years
Billeted students of the Military Medical Academy
Chronically ill patients
Patients with acute lymphoblastic leukemia
Patients with chronic renal failure
Renal allograft recipients
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
Patients with chronic obstructive pulmonary disease (COPD)
Patients in young and elderly groups
Patients with acute cardiovascular events
Patients with malignant lymphomas – Hodgkin's
Patients with lupus
Patients with primary systemic vascular inflammation: Wegener's granulomatosis

protect not only their patients, but also their loved ones, as shown in Table 1.

The study performed by the Influenza Virus Research Institute, National Influenza Center NIPH-NIH, together with the Institute of Cardiology in Anin, Poland, on subjects with acute cardiovascular events who were vaccinated against influenza, informed the European cardiology recommendations for influenza vaccination [25,26]. The benefits of vaccination of individuals in every age group are convincing but even more evident for those in high-risk groups irrespective of age. Moreover, there are also ethical indications for use of the vaccine in these cases.

Influenza vaccine coverage

In 2008 one of the co-authors of this article, as the first one in Poland, provided 30 different options for increasing the percentage of people vaccinated against influenza [7], as presented in Table 2.

The effects of multi-organ complications from influenza should be considered not only in terms of health, the human tragedy in the death of a close relative, which is immeasurable, but also in economic terms. Taking cardiac transplantation as an example, the cost of this procedure is about 140 thousand PLN, excluding the use of immunosuppressive drugs throughout the lifetime of transplant patients.

In 2012 in Poland a working group was established to develop a National Program for Combating Influenza based on a proposal by Prof. Brydak, from 2008 [7].

It is noteworthy that not only family physicians, but physicians of all specialties, have a crucial role to fulfill in promoting vaccination, and that on a mass scale, especially as in the influenza epidemic season of 2012/2013 only 3.75% of the total population was immunized, placing Poland in the penultimate position in Europe in this respect [8,39].

Despite the fact that both the ACIP and the American Pediatric Society recommend vaccination of children, the percentage of vaccinated children remains low, particularly in Poland [1,2,3,4,7]. For example, the percentage of those aged 6 months to 4 years who are vaccinated, approximately 1.4%, is outrageously low, while in those aged

Table 2. Opportunities to increase the percentage of people vaccinated against influenza [7]

• Greater acceptance of this form of prevention by doctors
• Implementation of a National Program for Prevention of Influenza
• Inclusion of relevant provisions in health insurance policy
• Deduction against income tax of the cost of the vaccine and vaccination against influenza in all age groups
• Creation of a system of motivation for doctors/nurses to overcome their objections to vaccination
• Evaluation of the direct and indirect economic impact, involving both pharmaco-economic studies that prove the positive impact of influenza vaccination on reducing the cost of treatment in the health system, as well as an analysis of the cost of complications from influenza
• Public education with new data on the effectiveness of vaccination, cost, and the safety of influenza vaccines with the help of public broadcasters and newspapers
• Public education on the effects and risks posed by influenza and especially on the associated complications
• Registration of complications associated with influenza
• Shortening of the distance between the patient and vaccination: doctor – prescription – pharmacy – doctor – vaccination
• Reimbursement of the cost of influenza vaccination for certain groups at high risk of complications from influenza – the National Influenza Center in Warsaw has repeatedly called for this
• Offering influenza vaccination to patients throughout the epidemic season, as recommended by the ACIP in 2000-2007
• Increasing the number of vaccines administered by health care providers, and other entities
• Administering the vaccine to patients hospitalized during routine visits
• Vaccination of children in kindergartens and schools, in order to reduce the spread of infection and reduce the incidence of disease in high-risk groups
• Vaccination in the workplace, universities, shopping centers, pharmacies, etc.
• Increasing the proportion of vaccinated individual in residential care facilities such as nursing homes and other chronic care facilities and staff of these establishments
• Compulsory free-of-charge vaccination of health care workers and others in contact with individuals exposed to an increased risk of a severe course of influenza infection, thus avoiding additional visits to the doctor
• Written or telephone invitations from primary care facilities concerning the need for influenza vaccination, especially for individuals at high risk
• Establishing vaccination points at additional venues prior to the influenza season such as at the University of the Third Age
• Development of plans to improve the vaccination availability and infrastructure providing for greater numbers than in the previous epidemic season – Office for Health Policy / 16 City Mayors
• Identification of legal and administrative barriers to the organization of vaccination by healthcare institutions and physicians
• Annual appointment of Influenza Vaccination Task Force at the central, provincial and municipal levels with appropriate legislative regulations for purchasing and distribution of vaccine in accordance with the provisions of the Pharmaceutical Law
• Free-of-charge vaccination for hospitalized patients who are at risk for the complications of influenza infection
• Introduction of influenza vaccination to health programs run by the National Health Fund (such as the programs for prevention of cardiovascular disease, the fight against cancer, smoking cessation)
• Public education and information, with particular emphasis on patients at risk for complications of influenza infection (based on [29])
• Free-of-charge vaccination (e.g. funded by the municipality) for school and kindergarten staff
• Free-of-charge vaccination for certain professional groups (military, police, customs, central government, and other public agency staff of importance for the functioning of the State)
• Long-term education – awareness-building campaigns in schools

5-14 years the percentage of vaccinations reached only 2.4% [9]. It is always forgotten that it is children who are at high risk for severe complications from influenza, and that the universal vaccination of children would generate herd immunity, which would reduce the spread of influenza in the general population. Nor is the situation satisfactory in other age groups, with 3.1% of 15-64 year-olds vaccinated [34]. The largest percentage of vaccinated individuals was reported for the age group > 65 years, with 14% in the given season. For many epidemic seasons now the Office of the Marshal in most Provinces has sponsored influenza vaccination for individuals aged >65 years, although despite this the level is still low. Regular vaccination is therefore one of the few things that can be done to protect individuals against the potential risk of serious complications from influenza and multi-organ complications and consequently it should be part of good medical practice.

Marcus Aurelius, the Roman emperor who lived from 121 to 180, said: A man's worth is no greater than the worth of his ambitions. These words are also valid in the twenty-first century.

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