

# Preface

It would be difficult to find a person who has never experienced mild or severe influenza symptoms. Influenza infection is a very contagious affliction and it concerns all of us as it propagates by air. Flu transmission becomes evident after only a few hours in individuals infected not only by family members, but also by people met on a sidewalk, in a store, etc. The only protection can be furnished by a vaccine against the influenza virus. It begins to have a protective effect already seven days after vaccination, with its potency increasing with time and lasting for about a year. Influenza vaccine prevents flu and, in case of illness, makes its course milder, with significant reduction in possible complications. The most serious course of influenza has been observed in elderly patients, children below 5 years of age and other groups of high risk patients.

Flu appearance was noted for the first time in Poland in November 1729, during a flu epidemic of 1729–1730. However, the influenza virus was identified by Wilson Smith, Christopher Andrewes and Patrick Laidlaw at the National Institute for Medical Research in London only in 1933. They prepared homogenates from the lungs of infected mice that they used for patient vaccination. However, such preparations were not suitable for human use, and this line of experimentation was abandoned as the vaccine triggered dangerous side effects. It was not until the introduction of virus propagation in fertilized eggs in 1937 (still in use today) that the production of vaccine could occur on a large scale. Thomas Francis and Jonas Salk at the University of Michigan made the first modern vaccine against flu in 1937. This vaccine, prepared from the formalin-killed virus obtained from the allantoic fluid of infected chicken embryos, was used in 1941 for soldiers' vaccination and showed 70% protection against the coming influenza A epidemic. Vaccine production for general public was allowed in 1945. The split (1968) and subunit (1976) types of vaccine appeared after many years of research and the use of subunit influenza vaccine was first approved for people in 1980. The first modern adjuvant was approved in 1999 in Italy, and it consisted of aqueous squalen emulsion stabilized with Tween 80 and Span 65. The function of this adjuvant named MF59 was to activate macrophages for release of cytokines, which should reinforce the immune response.

Both live and inactivated viruses can be used in vaccine preparations. Live, attenuated influenza vaccines have been based on temperature-sensitive variant vaccine virus strains that replicate well in the nasopharynx but poorly in the lower respiratory tract<sup>1</sup>. Inactivated influenza vaccines exist in three types: the whole virus vaccines, split virus vaccines, and subunit vaccines. In the whole virus vaccine, the virus is inactivated by a formalin treatment. In split virus vaccines, the formalin-inactivated virus has been disrupted by a detergent. In first generation subunit vaccines, hemagglutinin (HA) and neuraminidase (NA) have been further chromatographically purified after removal of other viral components by ultracentrifugation. These vaccine preparations start with a virus multiplied in the embryonated eggs or in the MDCK or Vero cell cultures ([www.who.int](http://www.who.int)). Recently, vaccines have appeared that contain the influenza antigens prepared with molecular biology techniques. One of such vaccines, Flublok, is approved for use in people 18 through 49 years of age, does not contain preservatives, antibiotics or adjuvants and contains three times more HA than most other flu vaccines. The application of the latest molecular biology techniques means that influenza strains used for manufacturing of the influenza vaccine are almost 100% matched with those that appear in the next influenza season ([www.who.int](http://www.who.int)).

In Poland, starting in 1951, production of an influenza vaccine was carried out by Biomed in Krakow. This vaccine contained two Polish influenza strains propagated in chicken embryos and inactivated by formalin. It contained aluminium hydroxide and merthiolate. Feliks Przesmycki, Leon Sawicki and Halina Dobrowolska at the State Institute of Hygiene in Warsaw performed a vaccination trial of healthy volunteers, in the period of 1951–1957<sup>2</sup>. This trial on intranasal vaccine induced 2–4 fold decrease in the influenza incidence among the study group. About 25% of examined individuals had in their blood sera cross-reacting antibodies against an influenza B strain that was not included in the vaccine. Another team from the same Institute did the second trial in 1973<sup>3</sup> with the inactivated vaccine further purified by zonal ultracentrifugation. It gave only a weak rise of antibodies in vaccinated individuals. At this step production of the Polish influenza vaccine was terminated.

One possible argument for production cessation might be a high cost of vaccine production. It appears that the traditional egg-produced flu vaccine with 100 million doses a year might cost 150 million US dollars, while 50 million doses of vaccine obtained from the mammalian cell culture might cost 600 million US dollars<sup>4</sup>. Additionally, influenza vaccines are really only used from September through January and so a certain amount of the produced vaccine will be destroyed if unused (*“This year, companies have produced about 145 million doses. Only about 129 million have been distributed. Last year, companies lost even more on the flu vaccine because it was such a light flu season and fewer people decided to get the shot. Only about 42% of the U.S. population got an influenza vaccine last year, which meant that about 30 million doses were never used and had to be destroyed — A. Semuels, Los Angeles Time, January 21, 2013*). The same article points out that the flu vaccine is rather inexpensive — in the US, the flu vaccines are provided for \$10 to \$16 per dose, while the tetanus vaccine costs a provider \$38, HPV vaccine — \$130, Hepatitis B — \$52, but these other vaccines can be used for several years. Interestingly, the province of Ontario, Canada, in 2000 tried giving away the flu vaccine for free and found that it reduced influenza cases by 61% and decreased the cost of healthcare services by 52%<sup>5</sup>. This clearly indicates that economically sensible production of the influenza vaccine has to fulfil two requirements. First — the production has to be cheap, and second — its scale has to be easily adjustable according to the real needs of the health system. Both conditions are satisfied by the second generation subunit vaccines overproduced in yeast and bacteria or by DNA vaccines that could be a much safer alternative to inactivated viruses. Such approach is proposed in frame of the Polish Vaccine Consortium. However, validation and industrial

<sup>1</sup>Douglas RG Jr, Betts RF (1978) Studies with live attenuated influenza vaccines. *Am J Clin Pathol* **70**: 153–158.

<sup>2</sup>Przesmycki F, Sawicki L, Dobrowolska H (1959) Vaccination against influenza in Poland, 1953/56. *Bull World Health Organ* **20**: 333–353.

<sup>3</sup>Filczak K, Semkow R, Wrzos H, Zakrzewski K, Zgorzelska K (1973) Influenza vaccines purified by zonal ultracentrifugation. *Acta Microbiol Pol A* **5**: 261–270.

<sup>4</sup>Robinson J, Bader B (2008) Economics of influenza vaccine production using virus-like particles in insect cell culture. [[www.novavax.com/download/file/interphex.pdf](http://www.novavax.com/download/file/interphex.pdf)]

<sup>5</sup>Sander B, Kwong JC, Bauch CT, Maetzel A, McGeer A, Raboud JM, Krahn M (2010) Economic appraisal of Ontario's Universal Influenza Immunization Program: a cost-utility analysis. *PLoS Med* **7**: e1000256.

production of such anti-influenza vaccines can be only achieved through the common efforts of scientists, pharmaceutical industry and the Polish Government.

This issue of *Acta Biochimica Polonica* contains a series of reviews and experimental papers covering various clinical and veterinary aspects related to influenza. The papers are divided into three major groups: (i) describing biology and variability of the virus and the host, (ii) focusing on influenza virus surveillance, monitoring and detection methods and (iii) covering problems related to the prevention of virus spread and to vaccination, from a clinical and veterinary perspective.

Last but not least, we are proud to emphasize that many of the papers in this issue are written from the national perspective and refer to the circumstances encountered in Poland. The Editorial Board thanks all the authors, contributors and the reviewers, whose hard work made this issue possible.

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