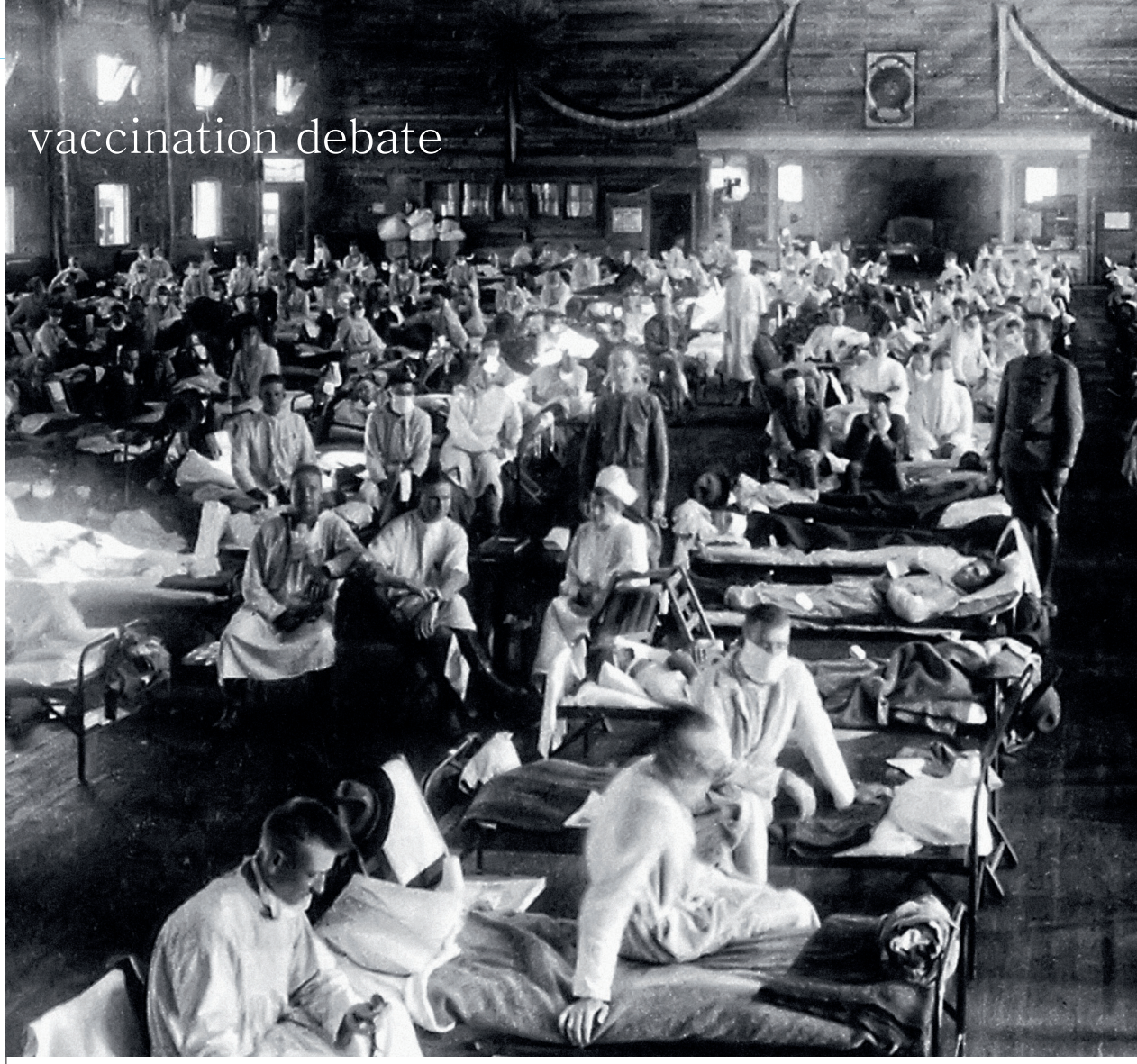

The 1918 pandemic of the "Spanish flu" caused around 50 to 100 million deaths, in other words about 5 to 11 times more lives than were claimed by WWI

Influenza – A Master of Metamorphosis

"The influenza virus behaves just as it seems to have done for five hundred or a thousand years, and we are no more capable of stopping epidemics or pandemics than our ancestors were," wrote Charles Cockburn from the World Health Organization back in 1973. Is his remark still just as apt today?

BE&W

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Influenza has decimated human populations over and over, since times immemorial. The first written mentions describing epidemics, by Hippocrates and Livy, date from 412 BCE. It has been and remains the cause of great tragedy. According to the latest research, the 1918 pandemic of the so-called "Spanish flu" caused around 50 to 100 million deaths, in other words about 5 to 11 times more lives than were claimed by WWI (around 9 million). The Spanish flu is considered the most devastating influenza pandemic in history in view of this huge number of lethal cases, but also because of the vast social and economic losses that it wrought. However, it did trigger significant advances in research aiming to identify the etiology of the disease. Deciphering the genome of the virus causing the Spanish flu more recently became possible through the development of molecular biology techniques and thanks to scientific expeditions that collected lung tissue samples from the bodies of individuals known to have died of influenza, which still remain preserved in frozen state today (in places like Alaska).

A changing, silent killer

Influenza is an acute infectious disease. Under the case definitions adopted in the European Union, the clinical criteria for influenza include sudden onset of cough, fever >38°C, muscle pain and/or headache, etc. The clinical criteria, in turn, may be confirmed by means of various molecular biology techniques at specialist labs throughout Poland. Such confirmation is important to be able to curtail the development of the disease through the application of the latest generation of anti-influenza drugs (neuraminidase inhibitors). Such drugs cannot take the place of vaccination, but they are crucial for treatment.

We should stress that after penetrating the respiratory system, the influenza virus damages the epithelium and thereby opens up a pathway for bacterial pathogens and possibly causing a host of post-influenza complications. Influenza infection may cause complications in multiple systems of organs, including pulmonary, cardiological, neurological, laryngological, nephrological, obstetrical-gynecological, and psychiatric complications, the intensification or exacerbation of chronic illnesses, organ rejection, and others.

Heraclitus' famous aphorism *Natura abhorret vacuum* (nature abhors a vacuum) certainly applies very aptly to influenza, as the structure of the virus exhibits a very extensive capacity for antigen change. Newer and newer strains continually appear, triggering outbreaks of an epidemic, pandemic, or inter-epidemic nature. We should also stress that the influenza virus occurs not only in people, but also in water fowl, chickens, turkeys, and especially pigs, horses, and marine mammals (such as seals). It was also recently attested in herbivorous bats.

The constant evolution of the influenza virus is an important cause of the yearly epidemic outbreaks that occur in the human population (the result of point mutations, or antigen *drift*), and from time to time also pandemic outbreaks (the result of genetic reassortment, or antigen *shift*).

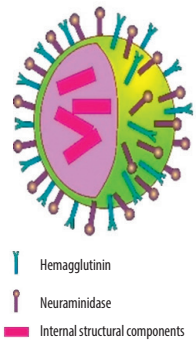
After R.W. Shope managed to isolate the influenza virus from pigs in 1931, in a landmark achievement, intensive work led three researchers – Ch. Andrews, W. Smith and P. Laidlaw – to successfully isolate the influenza virus in humans in London (where the WHO Collaborating Centre for Reference and Research on Influenza at the Francis Crick Institute is now situated) shortly thereafter, in 1933. These discoveries laid the foundation for today's multifaceted research on influenza.

Recommendations from international medical societies concerning influenza vaccinations:

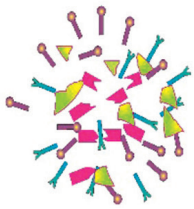
- Advisory Committee on Immunization Practices (ACIP)
- American Academy of Pediatrics (AAP)
- American Academy of Family Practice (AAFP)
- American Academy of Family Physicians (AAFP)
- US Preventative Services Task Force (USPSTF)
- American College of Physicians (ACP)
- American Society of Internal Medicine (ASIM)
- Infectious Diseases Society of America (IDSA)
- Canadian Task Force on Preventative Health Care (CTFPHC)
- American Society of Clinical Oncology (ASCO)
- American College of Obstetrics and Gynecology (ACOG)
- Director General of the UK Department of Health
- American Heart Association / American College of Cardiology
- Global Initiative for Chronic Obstructive Lung Disease (GOLD)
- Global Strategy for Asthma Management and Prevention (GINA guidelines)

For a review, see: Brydak LB., 2007

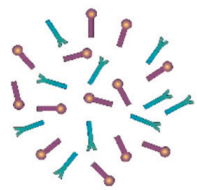
Whole-virus vaccines



Split viron vaccines



Subunit vaccines



BRYDAK L.B., 2008

The rapid expansion of the disease is made possible on the one hand by the modern capacity for humans to travel quickly from place to place, leading to constant growth in the number of international voyages, and on the other by the existence of animal reservoirs. At the 4th International Congress of Microbiology in Copenhagen in 1947, the WSI proposed a worldwide system of epidemiological and virusological study to keep a close eye on influenza. This monitoring system, now known as the WHO Global Influenza System Surveillance and Response System (GISRS), operates at a set of six international WHO Collaborating Centers for Reference and Research on Influenza situated in London, Atlanta, Tokyo, Beijing, Melbourne, and Memphis. Moreover, the WSI collaborates with 142 National Influenza Centers (NIC). One such center functions in Poland at the National Institute of Public Health – National Institute of Hygiene. The surveillance maintained by the WHO aims to identify the antigen changes occurring in viruses in current circulation as well as to report the appearance of new types and subtypes, then to recommend the seasonal composition of the influenza vaccine.

It should be borne in mind that the virus infects people regardless of age, geographical location, or the time of year. According to WHO data, around 5–10% of all adults and 20–30% of children contract influenza annually. Each year, 3–5 million acute cases are recorded, with 250,000–500,000 individuals dying, including 28,000–111,500 children below age 5. The world was made aware of the threat posed by pandemics and the huge potential economic losses they can entail by the incident of 9 May 1997 involving a virus crossing the species barrier, taking on the form of Highly Pathogenic Avian Influenza (HPAI), which is still in circulation in many countries, causing around 53% of all influenza deaths.

Bringing many weapons to bear

However, influenza can be prevented. We can prepare various types of vaccines against it, develop new anti-influenza substances, and continually synthesize more effective drugs – such as neuraminidase inhibitors for the influenza virus, such as zanamivir, oseltamivir, and peramivir, active against both type A and type B influenza.

The first permission allowing influenza vaccinations to be administered to humans was granted in 1941. Those shots caused numerous side effects, but even so the people who then faced the prospect of dying in the Spanish flu epidemic did not challenge the sense of such vaccination – as paradoxically occurs today, when medicine has developed vaccinations of chromatographic purity.

The blessing of influenza vaccinations bore fruit during the next pandemics of the 20th century: the

Humoral response to influenza vaccination in groups of heightened risk

Children	Adults
age groups 6–35 months, 3–8 years, 9–12 years, 13–20 years	age groups 21–30 years, 31–40 years, 41–50 years, 51–64 years, above 64 years *(two PhD theses)*
with acute lymphoblastic leukemia, vaccinated at various periods after completion of treatment	barracked students of the Military Medical Academy
with severe and mild hemophilia	chronically ill patients
with chronic lung disease	patients with acute lymphoblastic leukemia
with glomerular nephritis	patients with chronic kidney failure (part of a DSc thesis)
with chronic kidney failure, treated by continuous ambulatory peritoneal dialysis, hemodialysis, and with chronic kidney failure vaccinated once and twice	allogenic kidney transplant patients
infected with HIV	patients infected with HIV with differing levels of CD4, with AIDS symptoms and without
after splenectomy, vaccinated in age groups 0–5 years, 6–10 years, 11–15 years, above 16 years *(PhD thesis)*	breast cancer patients
with plastic anemia	thyroid cancer patients
with asthma	asthma patients *(part of a PhD thesis)*
with inflammatory bowel disease	patients with chronic obstructive lung disease (COLD) *(part of a PhD thesis)*
	younger and senior patients *(PhD thesis)*
	patients with acute cardiovascular incidents *(part of DSc thesis)**
	patients with non-Hodgkin lymphomas *(PhD thesis)*
	lupus patients *(PhD thesis)*
	patients with primary systemic vasculitis: Wegener's granulomatosis *(part of a DSc thesis)*

REVIEW: BRYDAK L.B., 2015

**The results of Polish research on patients with acute cardiovascular incidents have met with strong recognition and have been included into the European cardiological recommendations for influenza vaccination*

JAKUB OSTAŁOWSKI

Prof. Lidia B. Brydak is head of the Department of Virology and of Poland's National Influenza Center (one of 142 in the world)

Asian flu 1957–1958 caused by the virus A/H2N2/ and the Hong-Kong flu in 1968–1969 caused by the virus A/H3N2/. Compared to the Spanish flu, each of these pandemics took a much smaller toll in terms of lives, around 1–4 million each. The Hong Kong pandemic, which reached Poland after a great delay, caused 5,940 deaths in 1971. Continued intensive research on the influenza virus led in 1968 to the development of the inactivated *split viron* type of vaccine, then in 1976 to the *subunit* type, containing just extracted hemagglutinin and neuraminidase.

Each year, 3–5 million acute cases of influenza are recorded, with 250,000–500,000 individuals dying, including 28,000–111,500 children below age 5

At present we have many types of influenza vaccines at our disposal, ranging from various inactivated varieties to attenuated ones created from *cold adapted mutants*. At present, the Advisory Committee on Immunization Practices (ACIP) recommends inactivated split- or subunit-type vaccines (TIV) or live, *cold-adapted* vaccines (LAIV).

In view of the clinical and epidemiological indications, the ACIP recommends for all interested persons to be vaccinated against influenza in each season. The clinical indications include all individuals in the group particularly at risk of influenza-related complications irrespective of their age, including pregnant women and children aged 6 months to 18 years. Under the epidemiological indications, vaccination should be given to individuals who may transmit influenza between individuals in the higher-risk group, which include all staff members at healthcare facilities, old-age homes, hospices, individuals taking care of small children (especially below 6 months) or other individuals in the risk group. In the Polish vaccination schedule, influenza vaccines are listed as recommended (not obligatory).

Imported influenza vaccines have been available in Poland since the 1990/1991 season: inactivated vaccines (which only contain fragments of the flu virus that are not infectious) of the *split* and *subunit* types. Influenza appears every epidemic season, and for that reason is often not treated seriously enough. Yet quite often, contracting influenza may end up putting a patient into the higher-risk group. That is why not only WHO Experts but also many international medical societies recommend vaccination as the most economical and effective route to influenza prevention.

A lesson for just three percent?

Throughout my scientific career, I have tried to act in line with C. P. Scott's famous statement from 1921: "Comment is free, but facts are sacred." To convince not only doctors but also patients, at Poland's National Influenza Center we have evaluated, in conjunction with clinicians, the humoral response to influenza vaccination in groups of heightened risk (see table).

Recognizing the fact that influenza seasonally causes numerous people to fall ill, and given the potential post-influenza complications affecting multiple organs (quite often causing irreparable loss of health or even leading to death), the WHO has appealed for the percentage of the world population vaccinated to be increased. Influenza infections should be viewed not only in terms of the health cost of the disease, but also in terms of the tangible economic costs to society. Regular vaccinations are one of the few things that can be done to protect individuals from the potential serious post-influenza complications, and so they should form part not only of well-considered medical practice, but also of all our efforts under the WHO's slogan "Our health is in our hands." Yet in the recent 2014/2015 epidemiological season, the percentage of the Polish population that was vaccinated against influenza was just 3.55%.

Overall, it would seem that the twentieth century should be viewed as a source of lessons humanity has learned. I wonder why an awareness of the tragedies that befell mankind in the past nevertheless fails to motivate us to take responsible action. After all, those successive pandemics came as true shocks to twentieth-century society.

LIDIA B. BRYDAK

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