INFLUENZA PROPHYLAXIS: CURRENT APPROACHES

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ABSTRACT

Influenza is an acute respiratory disease. It holds a top position among infectious pathologies due to its high morbidity and mortality, but also due to its socio-economic implications.

Apart from personal prevention measures, the prevention of influenza also includes vaccination and prophylaxis with antivirals. The aim is to present the current methods aimed at preventing seasonal influenza epidemics.

We have reviewed the specific literature, the influenza guidelines and recommendations.

The influenza vaccination is the most effective way to prevent the disease; until the development of universal influenza vaccine, the efforts of physicians, researchers and policy-makers should focus on increasing vaccination coverage, especially among high-risk groups, improving existing vaccines stocks, vaccines formulation and delivery, as well as on the training of medical professionals and population.

For preventing influenza illnesses, pre-exposure or post-exposure prophylaxis with antivirals can be considered but it depends on several factors such as costs, compliance, side effects and the most important thing, the risk of emerging antiviral-resistant strains.

Nowadays, neuraminidase inhibitors such as oseltamivir and zanamivir are used for influenza chemoprophylaxis. In some countries, new antiviral agents (Baloxavir marboxil and Laninamivir) are available.

The antiviral agents mustn't replace the influenza vaccine and mustn't decrease the acceptability rate of influenza vaccination.

Keywords: influenza, prophylaxis, antivirals, vaccination

Influenza is an acute respiratory infection that recurs annually to the attention of medical specialists due to its increased morbidity, complications, excess mortality, but also due to its socio-economic implications [1,2].

Annually, the World Health Organization (WHO) reports 3-5 million flu illnesses and 290,000-650,000 deaths. Children, elderly, pregnant women, chronic and immunodepressed patients are the most severely affected [1,3].

Influenza generates significant yearly economic costs due to workplace absenteeism, socio-economic disruption, medical care costs [1].

Influenza can be prevented or controlled through general measures to prevent respiratory infections, the use of antiviral medication and vaccination, the latter being by far the most effective measure available today [1,4].

a) **<u>Chemoprophylaxis with antiviral drugs</u>**

When opting for influenza chemoprophylaxis, the following factors are taken into account: cost, compliance, adverse reactions and especially the possibility of emerging resistant strains.

Chemoprophylaxis is recommended for people who are not vaccinated against the influenza virus, especially those who are at risk (healthcare professionals or their entourage, immunosuppressed patients or patients with associated chronic diseases) [5,6].

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Currently, for the chemoprophylaxis of influenza, neuraminidase inhibitors are primarily used, notably oseltamivir and zanamivir.

They are not substitutes for the influenza vaccine and should not decrease the influenza vaccination acceptance rate [5,6].

In the past, prior to the emergence of amantadine resistant strains, inhibitors of influenza type A viruses' uncoating (M2 protein inhibition, which is a proton channel), Amantadine and Rimantadine , were used [6] *(Table 1)*.

	Amantadine*	Rimantadine*	Zanamivir	Oseltamivir
Target protein	M2	M2	Neuraminidase	Neuraminidase
Activity	Only type A	Only type A	A and B	A and B
Adverse effects	CNS (13%) GI (3%)	GI (6%) GI (3%)	Bronchospasm	GI (9%)
Metabolization	-	Multiple (hepatic)	-	Hepatic
Excretion	Renal	Renal+others	Renal	Renal (tubular secretion)
Drugs interactions	Antihistamines, anticolinergics	None	None	Probenecid (high doses of oseltamivir)
Dosage adjustments	Age ≥ 65 y.o. Cr cl < 50 ml/min	Age ≥ 65 y.o. Cr cl < 10 ml/min	None	Cr cl < 30 ml/min Severe hepatic failure

Table 1: Antiviral agents used for the influenza treatment prophylaxis [6]

**Currently the influenza viruses are resistant to amantadine and rimantadine;*

** CNS – Central Nervous System; Cr cl – Creatinine Clearance; GI – Gastrointestinal.*

All 4 antiviral agents are effective for influenza prophylaxis, given that the drugs are administered continuously throughout the exposure period. For this prophylaxis several schemes have been evaluated, including seasonal prophylaxis, when medication is administered throughout the whole influenza epidemic period (generally from 4 to 6 weeks), family prophylaxis, when the medication is administered over a short period of time to family members of a confirmed influenza patient, and prophylaxis initiated within the institutional framework during an epidemic, which could be considered a different variant of family prophylaxis. In addition, short-term prophylaxis may be considered for people in the at-risk groups who are vaccinated during the influenza season, until the appearance of the post-vaccine immune response [6].

Dosage

The indications, route of administration and doses used for each antiviral agent are summarized in *Table 2*.

	Drug	Route of administration	Dosage
Influenza type A and B prophylaxis	Oseltamivir	Oral	Adults: 75 mg/day Children aged 1 or more: 30-75 mg/day depending on weight
	Zanamivir	Oral inhalation	Adults and children aged 5 or more: 10 mg/day
Influenza type A prophylaxis	Amantadine* or Rimantadine*	Oral	Adults: 200mg/day Children aged 1-9: 5 mg/kg/day (maximum 150mg/day)

Table 2: Chemoprophylaxis in influenza [6]

**Amantadine and rimantadine are no longer used in influenza prophylaxis due to the resistance of circulating viral strains. Still, they could be taken into acount if the influenza virus will regain its sensibility to these drugs.*

Post-exposure chemoprophylaxis

Neuraminidase inhibitors prophylaxis can be assured pre or post exposure. It must be administred as soon as possible given the short incubation period of the disease (1-4 days, 2 days average). Post-exposure prophylaxis is typically used for up to 10 days after the most recent close contact with a confirmed influenza patient [7].

Studies on prophylaxis show that in addition to the presence of nausea and vomiting, the use of oseltamivir has been associated with the onset of headache and of various "neurologic events". In the same study, the use of zanamivir was not associated with an increase in the frequency of adverse reactions [8].

Studies have shown that post-exposure prophylaxis with zanamivir or oseltamivir has been associated with an 8% decrease in the risk of developing influenza after being in contact with a confirmed case, and that individual pre and post exposure usage of oseltamivir decreases the risk of confirmed cases of type A (H1N1) [8,9].

Following a randomized trial to evaluate the efficacy of oseltamivir prophylaxis in which 405 participants were included, a 13.6% decrease in the risk of developing symptomatic flu forms among family members who received oseltamivir compared to those who had received placebo was observed, the results of this study being confirmed by other studies [7,10].

Pre-exposure chemoprophylaxis

Pre-exposure prophylaxis can be administered for a short period of time if exposure is anticipated, or can be administered throughout the influenza season. There is still no consensus on the duration of prophylaxis during the influenza season. 28-days prophylaxis regimens for zanamivir and 16 weeks for oseltamivir have been studied and were found to be well tolerated. The failure of long-term administration of these drugs is more common in children due to adverse reactions (nausea and gastrointestinal discomfort) [7].

Studies have shown that in healthy adults pre-exposure prophylaxis with oseltamivir during the whole influenza season is associated with a reduction in the risk of developing clinical manifest influenza. Prophylactic administration of oseltamivir was not associated with a reduction in the risk of bronchitis or hospitalization rates.

Also, following a randomized controlled placebo study of vaccinated elderly subjects that received pre-exposure prophylaxis with oseltamivir for 6 days, there was a 92% decrease in the incidence of confirmed influenza cases compared to placebo [11].

A recently published study provides evidence that recommends seasonal prophylaxis for immunocompromised individuals. This study revealed a statistically significant decrease in the frequency of positivity of cultures (0.4% versus 3.8%; 88% protection efficacy) or RT-PCR (1.7% versus 8.4%; 74.9% protection efficacy) from recipients of renal, hepatic and hematopoietic stem cell transplant who received oseltamivir for 12 days for influenza prophylaxis [12].ECDC recommendations on influenza prophylaxis with neuraminidase inhibitors are summarized in *Table 3*.

	Pre – and post – exposure chemoprophylaxis in asymptomatic patients
Healthy adults aged 18 to 65 years	Prophylaxis during seasonal influenza epidemics must be individualized – for example, for family members of persons who are in a risk group, particularly in the case of unvaccinated or immunocompromised persons not responding to vaccination in those years where vaccine efficacy is expected to be low because of the mismatch of vaccine strains with circulating ones. The effectiveness of prophylaxis is probably higher than of treatment. Prophylaxis for emerging influenza or pandemic outbreaks should be considered based on the estimated risk, eg susceptibility to antivirals, transmissibility, virulence, complication frequency, hospitalization and fatality. The effectiveness of prophylaxis is probably better than of treatment.
Healthy adults aged over 65 years	Prophylaxis during seasonal influenza epidemics must be individualized – for example, for family members of persons who are in a risk group, particularly in the case of unvaccinated or immunocompromised persons not responding to vaccination in those years where vaccine efficacy is expected to be low because of the mismatch of vaccine strains with circulating ones. The effectiveness of prophylaxis is probably higher than of treatment. Prophylaxis for emerging influenza or pandemic outbreaks should be considered based on each individual case or on the estimated risk, eg susceptibility to antivirals, transmissibility, virulence, complication frequency, hospitalization and fatality.

	Pre – and post – exposure chemoprophylaxis in asymptomatic patients
Adults in risk groups, including immunocompromised adults and pregnant women, aged 18 or more	During seasonal influenza epidemics, prophylaxis should be considered for vulnerable populations, particularly in the case of unvaccinated or immunocompromised persons not responding to vaccination, given the safety profile, the pathogenicity of circulating influenza virus strain and comorbidities. This is particularly important during the years when a mismatch between vaccine strains and circulating virus strains is anticipated. The effectiveness of prophylaxis is probably better than of treatment. The safe use of zanamivir during pregnancy has not been established. Zanamivir should not be used during pregnancy unless the expected benefit to the mother exceeds any possible risk to the fetus.
Medical staff	Prophylaxis should be considered during seasonal influenza epidemics to protect vulnerable patients, particularly those who are unvaccinated or immunocompromised, who are not responding to vaccination. This is particularly important during the years when a mismatch between vaccine strains and circulating virus strains is anticipated. The effectiveness of prophylaxis is probably better than of treatment. Prophylaxis for emerging influenza or pandemic outbreaks should be considered based on the estimated risk, eg susceptibility to antivirals, transmissibility, virulence, complication frequency, hospitalization and fatality.
Workers who come into contact with birds or pigs / laboratory staff working with the influenza virus	See recommendations for healthy adults during seasonal flu. Prophylaxis should be considered for workers coming into contact with birds or pigs during epizootic diseases. Prophylaxis in laboratory personnel handling emerging influenza viruses or known influenza viruses with potential for the induction of severe human disease should be considered in the case of lower biosecurity levels than those recommended for these viruses. The effectiveness of prophylaxis is probably better than of treatment.
Healthy children under the age of 18 years	Prophylaxis during seasonal influenza epidemics should be considered on a case-by-case basis, for example for family members of persons who are in a risk groups, particularly in the case of unvaccinated or immunocompromised persons not responding to vaccination. This is especially important in those years where vaccine efficacy is expected to be low because of the mismatch between vaccine and circulating virus strains. The effectiveness of prophylaxis is probably better than of treatment. Prophylaxis for emerging influenza or pandemic outbreaks should be considered based on the estimated risk, eg susceptibility to antivirals, transmissibility, virulence, complication frequency, hospitalization and fatality. The effectiveness of prophylaxis is probably better than of treatment.
Children in risk groups, including immunocompromised children	During seasonal influenza epidemics, prophylaxis should be considered for vulnerable population groups, particularly in the case of unvaccinated or immunocompromised persons not responding to vaccination. This is especially important in those years where vaccine efficacy is expected to be low because of the mismatch between vaccine and circulating virus strains. The effectiveness of prophylaxis is probably better than of treatment.
Patients of any age admitted to hospital, institutionalized persons	During seasonal influenza epidemics, prophylaxis should be considered especially for unvaccinated or immunocompromised persons who are not responding to vaccination. This is especially important in those years where vaccine efficacy is expected to be low because of the mismatch between vaccine and circulating virus strains. Although the evidence comes only from observational studies, the prophylaxis of admitted patients (or residents) during emerging influenza epidemics and pandemics should be considered based on the estimated risk, eg susceptibility to antivirals, transmissibility, virulence, complications, hospitalizations and fatality.

Table 3: ECDC recommendations on influenza prophylaxis with neuraminidase inhibitors [7]

New agents used for influenza prophylaxis

Laninamivir has been approved for use in Japan but remains an experimental drug in other countries of the world. It is a long-acting neuraminidase inhibitor administered by inhalation that has been reported to be effective for the prophylaxis of influenza infections in persons who had contact with patients with influenza within the family. In a randomized

study in Japan, family members of patients diagnosed with influenza (most of them infected with influenza virus type AH3N2) who came into contact with them within the first 48 hours of symptoms onset were randomly assigned to receive a single dose of 40 mg of laninamivir, two doses of 20 mg of laninamivir given daily for 2 days or placebo. The proportion of participants who developed laboratory-confirmed influenza was significantly lower in the case of laninamivir compared to the placebo group (4.5% in the group receiving a single dose of laninamivir, 4.5% in the group receiving two doses of laninamivir and 12.1% in the placebo group) [13].

Baloxavir marboxil was approved for use in Japan (February 2018) and US (October 2018) for patients over 12 years of age, whose symptoms started less than 48 hours earlier.

It is a selective cap-dependent endonuclease inhibitor, it has shown its therapeutic activity against influenza A and B viruses, including strains resistant to current antiviral medication.

It has a unique mechanism of action compared to existing antiviral drugs today: by selective inhibition of cap-dependent endonuclease it inhibits the polymerase activity and implicitly the replication of viral RNA.

Regarding the administration during pregnancy and lactation and the interaction with the live attenuated vaccine, current studies are insufficient in order to accurately state the possible side effects that may arise [14,15].

b) **Prophylaxis by vaccination**

Vaccination is the most effective available method to control influenza infections. Influenza vaccines are unique among the viral vaccines currently approved by the fact that, due to the constant antigenic changes of the flu viruses (by antigenic drift or by antigenic shift), it is necessary to periodically update the vaccine composition so that they are effective against viral strains circulating in a particular influenza season [2].

Composition of influenza vaccines

The antigenic composition is established annually by World Health Organization specialists in February-March for the Northern Hemisphere, respectively August-September for the Southern one. For the determination of the vaccine composition, the clinical, virological and epidemiological surveillance data provided by the World Health Organization's global influenza surveillance network are being used [2].

The consensus about the vaccine composition should be reached out several months before the onset of the influenza season so that the producers have sufficient time to produce and distribute the influenza vaccines.

Flu vaccination should be performed before the onset of influenza in the community. Children aged 6 months to 8 years who are vaccinated for the first time should receive two doses of the vaccine, one as soon as the vaccine is available and the second dose at least four weeks after the first administration. Most adults develop a protective response approximately 2 weeks after the immunization [2].

Due to the phenomenon of antigenic drift or the change of phylogenetic descendance of the influenza B virus, the viruses included in the vaccine may be different from the circulating influenza viruses in some seasons.

Furthermore, antigenic differences between vaccine viruses and circulating viruses could also be attributed to the adaptive mutations that vaccine viruses suffer during the embryonic egg development stage during production.

These may lead to a decrease in influenza vaccine efficacy, recent studies highlighting that the influenza A (H3N2) candidate vaccine strain undergoes mutations in ovo that affect its immunogenicity. This is particularly problematic for the elderly who are most vulnerable to the severe consequences of infection with A(H3N2) [2,16].

The composition of the influenza vaccine used in the influenza season 2018-2019 was as follows:

A/Michigan/45/2015 (H1N1)pdm09-like virus;

A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus;

B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)-for the trivalent vaccine;

B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) [17].

The composition of the influenza vaccine recommended by the WHO for the influenza season 2019-2020 is:

A/Brisbane/02/2018 (H1N1)pdm09-like virus;

B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage);

B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)– for the trivalent vaccine;

A/Kansas/14/2017(H3N2);

Component A (H3N2) was announced after the February WHO meeting in Beijing, the specialists noting that recent antigenic changes required a longer time to select this component [17].

Following the studies and results of the virological surveillance, it was found that the effectiveness of the current influenza vaccine was lower compared to the circulating A (H3N2) strain. For the 2019-2020 influenza season, the WHO specialists decided to keep both B virus strains contained in the vaccine composition of the influenza vaccine in the 2018-2019 season because in the 2018-2019 influenza season there was no evidence of an increased number of infections caused by the influenza B viruses [17].

In the influenza season 2018-2019, according to preliminary study results, the vaccine efficacy for A (H1N1) pdm09 was 72%, 78% in Canada and Australia respectively [18].

Influenza vaccines have undergone continuous qualitative improvement, the viral composition evolving from whole virus vaccines, which induced a very good immunological response but exhibited a high reactogenicity, to split or subunit vaccines, having an immune response identical to that of whole virus vaccines but with lower reactogenicity and that can be administered to children older than 6 months[2].

Current influenza vaccines are trivalent and tetravalent. During pandemics, monovalent vaccines containing the vaccine strain responsible for the pandemic are used, as was the case during the 2009 pandemic. The vaccine composition of the vaccine used at that time was A/California/7/2007(H1N1) [2].

Currently there are three types of vaccine, live attenuated vaccines (LAIV – live-attenuated influenza vaccine), inactivated (IIV – inactivated influenza vaccine) and recombinant (RIV – recombinant influenza vaccine) [2,19]. Each type of vaccine has a number of advantages and limitations [18].

Inactivated influenza vaccines IIV are obtained by growing the viruses in embryonated eggs followed by the purifying of the viral haemagglutinin, the only viral antigenic component. They may contain three or four different antigens and may be administered intramuscularly or intradermally [2].

Live attenuated influenza vaccines LAIV are trivalent or tetravalent and are obtained by the cold adaptation of viral strains followed by heat sensitization and attenuation. These are administered intranasally to immunocompetent individuals aged 2 to 49. Live attenuated viral strains multiply in the nasopharyngeal mucosa, inducing lower levels of serum antibodies but a more efficient cellular and local immune response [2].

If the person receiving LAIV sneezes, the dose does not have to be re-administered. If the person who should receive LAIV has nasal congestion that prevents the administration of the vaccine, the administration of LAIV should be postponed and the administration of IIV should be taken into account. LAIV is not recommended in the first 48 hours after discontinuation of antiviral medication [2,20].

The recombinant influenza vaccine RIV was approved in 2013 in the US and is recommended for people over the age of 18. It is administered intramuscularly and has the advantage of being safe to administer to people with egg allergy because the purified HA proteins are produced on cell cultures (vaccinated insects) [2,20].

In the influenza season 2017-2018, US military personnel was immunized with a new type of recombinant vaccine that was produced by growing the influenza virus on dog renal cells. The efficacy of this vaccine is currently being estimated [14].

In Romania the inactivated trivalent or tetravalent influenza vaccine is available on the market; a live attenuated influenza vaccine will also be available starting with the 2019-2020 influenza season.

Vaccination recommendations

In Romania, according to the influenza surveillance methodology developed by the National Center for Control and Surveillance of the Infectious Diseases, influenza vaccination is recommended for population groups considered at risk [4]:

- Individuals aged 6 months to 64 years with chronic medical conditions such as pulmonary, cardiovascular, metabolic, renal, hepatic or neurological diseases, diabetes,

obesity, asthma or human immunodeficiency virus infection;
- Pregnant women;
- Physicians, nurses and auxiliary staff in healthcare establishments including employees of care facilities (for children or for the elderly) and of chronic illness units who, by their nature, come in respiratory contact with patients;
- Persons, adults and children residing in social care institutions, as well as persons providing health care, social care and home care for high risk patients;
- Children aged 6 to 59 months;
- All persons over the age of 65.

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination particularly in population groups who are at risk to develop severe influenza or who can contribute to the spread of influenza viruses [2,20]:
- Children aged 6 to 59 months;
- All persons over the age of 50;
- Persons with chronic lung disease (including asthma), cardiovascular (except isolated hypertension), kidney, liver, neurological, hematological or metabolic (including diabetes mellitus) diseases;
- Immunocompromised individuals;
- Pregnant women;
- Children and adolescents (6 months to 18 years of age) receiving aspirin or salicylate containing medicines that may be at risk of developing the Reye syndrome;
- Institutionalized people;
- People with extreme obesity (BMI ≥40);
- Contacts of high-risk individuals;
- Medical staff;
- People taking care of children aged 0 to 59 months (ie <5 years), especially children 0-6 months and adults over 50 years old;
- Hospital employees who provide outpatient or home care (doctors, nurses, stretcher-bearers, etc.)

Contacts and caregivers of patients with medical conditions are at increased risk for severe complications of influenza.

So much has been insisted on vaccinating groups that are at risk that it has come to the conclusion that influenza vaccination is not necessary in other segments of the population. In the case of the influenza vaccine, it must be noted the important effect of a high vaccine coverage that considerably diminishes the infection rate in the receptive population. Considerable vaccine coverage among the general population reduces the risk of influenza among people who have contraindications to vaccination (eg children less than 6 months of age) [19].

Contraindications and precautions

Inactivated influenza vaccines are contraindicated to:
- Children aged 0 – 6 months;
- Persons who have experienced a severe, life-threatening adverse reaction to a previous vaccination or to one of the vaccine components;
- Patients with allergies to the vaccine components;

Influenza vaccines may be administered to patients with egg allergy but either a recombinant vaccine (if available and if the patient is older than 18 years) or a live attenuated vaccine should be used, under close supervision of a physician [21].

Live attenuated influenza vaccines are contraindicated to [20]:
- children under 2 years and adults over 50 years;
- children aged 2 to 7 years following aspirin treatment, due to the development risk of Reye's syndrome;
- children aged 2 to 4 years who have asthma or who have experienced a wheezing episode in the last 12 months (medically recorded or reported by the family)
- pregnant women;
- immunocompromised persons or caregivers of immunocompromised persons (avoid contact with them within 7 days of vaccination).

Influenza vaccines are administered with caution to people who have developed Guillain-Barre Syndrome less than six weeks after a previous administration, to persons with moderate or severe

infections, with or without fever, or to patients who have recently been hospitalized [21].

Live attenuated vaccines should also be administered with caution to children with asthma aged over 5 years or to individuals who have associated medical conditions that give them an increased risk of developing severe influenza complications such as [20,21]:

- Chronic pulmonary and cardiovascular diseases, except for hypertension;
- Neurological or neuromuscular diseases;
- Metabolic diseases, such as diabetes;
- Liver or kidney failure;
- Hematological conditions, such as hemoglobinopathies.

Side effects

Severe side effects are rare. The most commonly reported were inoculation site pain, erythema at the site of administration, headache, asthenia, myalgia and general malaise [20].

Efficacy and vaccine coverage

The effectiveness of influenza vaccines (the proportional reduction in flu cases among vaccinated individuals compared to unvaccinated ones) depends on the antigenic mutations of the vaccine during its development on embryonic eggs, depends on the circulating strains, patient age and immune status (in the elderly, due to immunosenescence, and in the patients who have undergone a solid organ transplant, it is necessary to administer vaccines with a higher amount of viral proteins or containing various adjuvants to increase the vaccine efficacy), on the concomitant medication (treatment with statins decreases the effectiveness of the influenza vaccine) [16].

A vaccine coverage of 35% in the general population may be sufficient to control a seasonal flu epidemic, provided that other epidemiological measures are applied consistently. The ECDC target is to provide a vaccine coverage of at least 75% of the population at risk, with none of the European countries reaching this target [2].

In the influenza season 2017-2018, vaccine coverage in the USA was 37% and in Romania 5.2% [14,22].

To overcome the limitations of the current influenza vaccines, the goal of the researchers in the field is to create a universal influenza vaccine that is effective against all A subtypes, can be administered to all age groups, and has a vaccine efficacy of at least 75%. If the current vaccine preparations contain the distal portion of the haemagglutinin molecule, that frequently undergoes antigenic mutations, it is desired that the universal influenza vaccine would contain the strain of the antigenically stable molecule, this aim being to improve the quality of current influenza vaccines [14].

The main obstacles in the creation of a universal influenza vaccine are [21,23]:

- the evaluation of effectiveness requires numerous and complex studies:
  - the need to include children in these studies to diminish the effects of preexisting immunity;
  - comparing the effectiveness of these vaccines with existing vaccines can be complicated;
  - the results depend on the synchronization with major strains suffering minor or major antigen mutations.
- many of the strategies behind the creation of the Universal Influenza Vaccine are too complex to implement in the real world:
  - difficult to produce at low cost, on a large scale;
  - still at the experimental stage.

However, until the creation of a universal vaccine, the efforts of doctors, researchers, decision-makers should focus on [14,21,23]:

- improving existing stocks of vaccines;
- improving the way the vaccine is administered to make it easier for the population to accept;
- creating improved formulas (thermostable, providing immunity for a longer period of time);
- training of medical professionals and of population.

References:

1. Ivan A. Tratat de epidemiologie a bolilor transmisibile. Ed. Polirom București 2002

2. Miron VD, Drăgănescu AC, Luminos ML, Streinu-Cercel A, Săndulescu O. (coord.). Epidemiologia și etiopatogenia gripei și a colonizării pneumococice la copil-aspecte clinice, paraclinice și microbiologice. Ed. Sigma București 2018

3. World Health Organisation. A Manual for Estimating Disease Burden Associated With Seasonal Influenza, accesat 12.12.2018, disponibil online https://apps.who.int/iris/bitstream/handle/10665/178801/9789241549301_eng.pdf;jsessionid=446CE7BA34EDD9A10B18E3590E3E7034?sequence=1

4. Centrul Național de Supraveghere și Control al Bolilor Transmisibile. Metodologia de supraveghere a gripei, infecţiilor respiratorii acute (ARI) și a infecţiilor respiratorii acute severe (SARI), accesat 12.02.2019, disponibil online https://www.cnscbt.ro/index.php/metodologii/gripa-infectii-acute-respiratorii-si-sari/765-metodologia-de-supraveghere-gripa-infectii-respiratorii-acute-si-sari-2017-2018/file

5. Ong AK, Hayden FG, John F. Enders lecture 2006: antivirals for influenza. J Infect Dis. 2007;196(2):181-190

6. Bennett JE, Dolin R, Blaser MG. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Eighth Edition. 2015;Vol 2. Elsevier Saunders

7. Robesyn E, Broberg E, Kramarz P. Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza-Review of recent systematic reviews and meta-analyses. European Center for Disease Prevention and Control, Stockholm 2017

8. Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev. 2014;(4)

9. Okoli GN, Otete HE, Beck CR, Nguyen-Van-Tam JS. Use of neuraminidase inhibitors for rapid containment of influenza: a systematic review and meta-analysis of individual and household transmission studies. PLoS One 2014;9(12)

10. Nishiura H, Oshitani H. Household Transmission of Influenza (H1N1-2009) in Japan: Age-Specificity and Reduction of Household Transmission Risk by Zanamivir Treatment. J Int Med Res. 2011;39(2):619-628

11. Peters PH, Gravenstein S, Norwood P, Ward P. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc. 2001;49(8):1025-1031

12. Ison MG, Szakaly P, Shapira MY, Kriván G, Nist A, Dutkowski R. Efficacy and safety of oral oseltamivir for influenza prophylaxis in transplant recipients. Antivir Ther. 2012;17(6):955-964

13. Kashiwagi S, Watanabe A, Ikematsu H, Uemori M, Awamura S. Laninamivir Prophylaxis Study Group. Long-acting Neuraminidase Inhibitor Laninamivir Octanoate as Post-exposure Prophylaxis for Influenza. Clin Infect Dis. 2016;63(3):330-337

14. Mossad SB. Influenza update 2018–2019: 100 years after the great pandemic., Cleve Clin J Med. 2018;85(11):861-869

15. Open Chemistry Database. Baloxavir Marboxil, disponibil online https://pubchem.ncbi.nlm.nih.gov/compound/Baloxavir_marboxil, accesat 17.02.2019

16. Sullivan GS, Price HO, Reagan A. Burden, effectiveness and safety of influenza vaccines in elderly, paediatric and pregnant populations, Ther Adv Vaccines Immunother. 2019;7:1-16

17. European Center for Disease Prevention and Control. WHO recommendations for influenza virus vaccine composition for the 2019–2020 northern hemisphere season, accesat 10.03.2019, disponibil online https://ecdc.europa.eu/en/news-events/who-recommendations-influenza-virus-vaccine-composition-2019-2020-northern-hemisphere

18. Skowronski DM, Leir S, Sabaiduc S, Murti M, Dickinson JA, Olsha R, Gubbay JB, Croxen MA, Charest H, Chan T, Bastien N, Li Y, Krajden M, De Serres G. Interim estimates of 2018/19 vaccine effectiveness against influenza A(H1N1)pdm09, Canada. Euro Surveill. 2019;24(4)

19. Cernescu C. Gripa-studiu critic. Ed. Academiei Române. București 2007

20. Centers for Diseases Control and Prevention, Influenza (Flu), accesat 17.02.2019, disponibil online https://www.cdc.gov/flu/professionals/vaccination/vaccine_safety.htm

21. Navarro-Torne A, Hanrahan F, Kerstiëns B, Aguar P, Matthiessen L. Public Health-Driven Research and Innovation for Next-Generation Influenza Vaccines, European Union. Emerging Infectious Diseases 2019;25(2)

22. Centrul Național de Supraveghere și Control al Bolilor Transmisibile, Sezonul gripal 2016-2017 (prezentare), accesat 10.03.2019, disponibil online http://www.cnscbt.ro/index.php/prezentari/rodica/785-analiza-sezon-gripal-2016-2017/file

23. Barney SG. Universal Influenza Vaccines (prezentare), accesat 25.03.2019, disponibil online https://www.who.int/immunization/research/meetings_workshops/23_Universal_flu.pdf