Dubaj Maciej, Słomczyńska Katarzyna, Karczmarczyk Marta. Influenza season - is there anything to worry about? Journal of Education, Health and Sport. 2021;11(9):781-797. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2021.11.09.094
https://apcz.umk.pl/JEHS/article/view/JEHS.2021.11.09.094
https://zenodo.org/record/5544053

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 15.09.2021. Revised: 20.09.2021. Accepted: 30.09.2021.

INFLUENZA SEASON - IS THERE ANYTHING TO WORRY ABOUT?

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SUMMARY

Influenza (the flu) is an acute infectious disease caused by viruses of the *Orthomyxoviridae* family, causing a wide variety of symptoms in humans, ranging from mildly disturbing daily activities to life-threatening pneumonia, depending on the state of their immune system. The annual increase in the incidence of this disease is called "the flu season", which is a periodic epidemic that affects people all around the world. Despite the individual, economic and epidemiological risks associated with infection with the influenza virus, the disease is often underestimated by people. The aim of this study was to present influenza as a threat to the health of individuals and society by describing the pathomechanisms of its formation and spread, available diagnostic and therapeutic options, as well as annual vaccinations as the most effective method of disease prevention. The current publications available in online scientific databases from many countries around the world were reviewed. Despite the large number of widely available research results on influenza, it is necessary to update them every year, as well as vaccines against this disease, to popularize knowledge about it, which will enable more effective epidemiological control of influenza.

Key words: influenza, flu season, vaccinations, influenza virus, infectious diseases

1. INTRODUCTION AND PURPOSE

The “flu season” is a period each year, lasting from the beginning of autumn to early spring, when this disease is much more common than in the rest of the year and is epidemic - it affects a very large group of society, regardless of the individual condition or health of a

given person [1]. In the era of the SARS-CoV-2 coronavirus pandemic, thanks to greater awareness of people, concern for health and compliance with sanitary requirements, including isolation and wearing protective masks in public spaces, the "flu season" last year was milder compared to previous years, but cases of this disease are constantly recorded around the world. Influenza is currently one of the most common and potentially lethal diseases in the world [2]. It seems that every person has had the flu, knows its symptoms and basic treatment. Unfortunately, few people are aware of the real threat it is, especially for the youngest patients, pregnant women, the elderly or those suffering from chronic diseases. In addition to the extremely high incidence, it is also characterized by a significant mortality, and the influenza virus has one of the highest pandemic nature among pathogens known to man [2,3]. Every year, influenza causes the death of millions of people around the world, and paradoxically, its symptoms are very often overlooked or only attempts are made to treat them using popular over-the-counter pharmaceutical products, available even in grocery stores or gas stations [2]. The public's attitude to influenza is measurably expressed in the percentage of people receiving vaccination against this disease. In Poland, where flu vaccines are not compulsory, but widely available for a fee, in the last few years it has been only a few percent, and a worrying fact is its continuous decline [4].

The aim of this work was to present influenza as a serious health, economic and epidemiological problem of the world society on the eve of the beginning of „the flu season" by presenting the pathomechanisms of the emergence and spread of this disease, its basic clinical manifestations, available diagnostic and therapeutic methods, as well as disease prevention in all its phases. In addition, attention was paid to the differential diagnosis of influenza, with particular emphasis on SARS-Cov-2 coronavirus infection due to the significant difficulty in effectively distinguishing between both diseases.

Current publications were analyzed, which were available in the online medical databases of scientific articles: PubMed, Google Scholar and medRxiv, with the use of terms contained in the MeSH. The articles came from 2005-2021, from many countries around the world, which allowed for universal reflection on the topic.

2. DESCRIPTION OF THE STATE OF KNOWLEDGE

2.1. CAUSES OF INFLUENZA

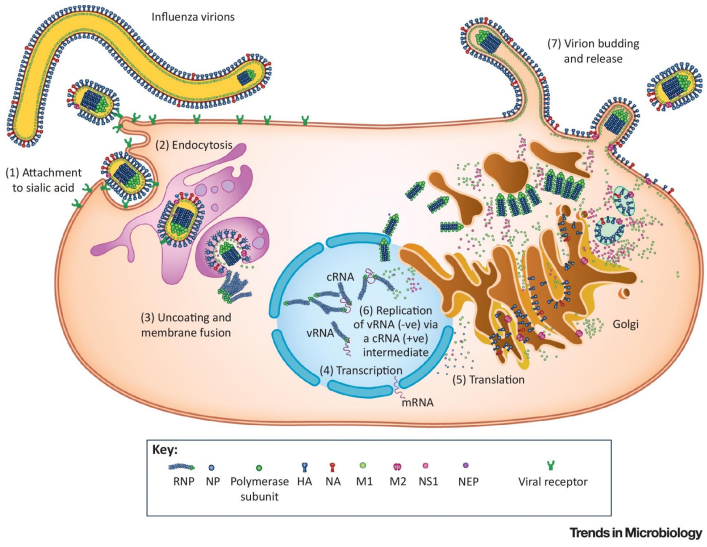
Influenza is caused by viruses of the *Orthomyxoviridae* family, the most important representatives of which are influenza viruses types A (*Alphainfluenzavirus*), B (*Betainfluenzavirus*) and C. Type A (in case of seasonal influenza these are mostly subtypes H1N1 and H3N2) and B viruses are responsible for morbidity in people of more severe and epidemic character, whereas type C usually causes disease of milder symptoms, not causing an epidemic [5]. Type D is also distinguished, but it occurs only in animals and does not cause infections in humans [8]. The presence of a segmented genome in viruses of the *Orthomyxoviridae* family predisposes them to easy creation of new strains as a result of mutations and gene exchange. These phenomena result in annual influenza epidemics. The type with particular antigenic variability is the type A virus, which, combined with its short incubation period, creates the possibility of yearly outbreaks and thus updated influenza vaccines.

Influenza virions are pleomorphic spherical or cylindrical structures ranging in size from 80 to 120 nm. The previously mentioned segmented genome consists of 8 segments containing negative-strand RNA, a nucleoprotein and an RNA polymerase with proteins PB1, PB2 and PA (polymerase complex proteins). Two surface proteins are present in the lipid coat

- haemagglutinins, which enable connection with the target cell, and neuraminidases, which break down sialic acid and its derivatives present in the mucus of the upper respiratory tract. Specific antibodies produced in the human body upon infection are also directed against the antigenic determinants of these glycoproteins. Matrix proteins (M1 - facilitating virion assembly), nucleoproteins (NP) and membrane proteins (M2 - forming ion channels in the cell membrane) are type-specific proteins and therefore serve to identify and distinguish types of influenza viruses from each other [6].

The influenza virus first attacks and disrupts the function of mucus-producing cells in the upper respiratory tract, as well as ciliary and epithelial cells - they bind to them through surface haemagglutinins. This leads to disturbances in the mechanisms of the first line of immunity and, as a result, easier adherence of bacteria to tissues and their drainage from the area of the nose and mouth to lungs, which may result in the development of pneumonia. The replication cycle of the influenza virus is shown in Scheme 1.

People and animals, such as horses, pigs, and birds are reservoirs for the pathogen. Usually, infection occurs through droplets or contact with infected objects. Factors increasing the risk of infection include direct contact with an ill or infected person, staying at a distance of less than 1.5 m with the ill person for a longer time without covering the mouth and nose with a mask, and too infrequent washing and disinfection of hands [5].



Scheme 1. The replication cycle and pathogenesis of influenza virus infection. Source: [7].

2.2. EPIDEMIOLOGY

Influenza is a seasonal disease that is a global threat and affects all countries. According to the World Health Organization (WHO), there are between 3 and 5 million cases and 290 000-650 000 influenza-related respiratory deaths worldwide each year [9,10]. According to the data of the European Center for Disease Prevention and Control (ECDC), there are 15 000-70 000 deaths in Europe per year due to the seasonal flu [11]. Furthermore, in Poland, according to the data of the National Institute of Hygiene, about 2 million Polish suffer from influenza each year and about 1000 people die [12].

The emergence of the SARS-CoV-2 virus at the end of December 2019 and the declaration of the COVID-19 pandemic on 11 March 2020 resulted in extremely low influenza activity for the 2020-2021 season. Strict public health measures were implemented

in Poland, as well as worldwide, including wearing face masks, physical distance, working at home, increased hygiene measures, etc. This has resulted in reduced transmission of other respiratory viruses, including influenza. As a result, this led to a decline in morbidity, hospitalization and deaths from influenza between 2020 and 2021. Flu vaccination may also have contributed to this. Flu vaccination may also have contributed to this.

Based on the data of the National Institute of Public Health - National Institute of Hygiene (included in Table 1.), it can be observed that in the period from September 1, 2020 to August 31, 2021, a total of 2 716 344 cases of the disease, which is 1.3 million less than in the 2019/2020 season. Moreover, no deaths have been recorded. The total number of hospitalized patients was 4 957, which is 63% less than last year, and the most common reason for referral to the hospital was respiratory symptoms (approx. 89%). The second most common cause of hospitalization was cardiovascular symptoms, accounting for 5% of all causes. This is the lowest hospitalization rate recorded since this type of data collection had begun in 2005. The highest incidence of influenza, as in previous seasons, was in the 0-4 age group [12].

Year	Number of cases and suspected cases of influenza	Number of hospitalizations due to influenza	Number of deaths due to influenza
2013/2014	2 664 201	9 374	15
2014/2015	3 666 410	12 227	11
2015/2016	9 936 341	16 156	143
2016/2017	4 684 820	16 970	25
2017/2018	5 279 689	18 555	47
2018/2019	4 491 879	17 610	150
2019/2020	4 007 447	13 540	65
2020/2021	2 716 344	4 957	0

Table 1. Cases and suspected cases of influenza, referred to hospital because of influenza or suspected influenza, and the number of deaths due to influenza in particular flu seasons.
Source: Own elaboration based on: [12].

According to the data contained in Table 2., the highest number of cases and suspected cases of influenza in Poland in the 2020/2021 flu season can be observed in December 2020 (670 477 people), while the lowest incidence was recorded in August 2021. The largest group of hospitalized patients is over 500 people and it was recorded in three months (March 2021, April 2021, June 2021).

Month	Number of cases and suspected cases of influenza	Number of hospitalizations due to influenza	Number of deaths due to influenza
September 2020	191 476	431	0
October 2020	262 508	387	0
November 2020	242 841	428	0
December 2020	670 477	418	0
January 2021	129 041	314	0
February 2021	186 773	325	0
March 2021	249 825	502	0
April 2021	168 317	530	0
May 2021	164 596	421	0
June 2021	188 070	502	0
July 2021	141 117	408	0
August 2021	121 303	291	0
TOTAL	**2 716 344**	**4 957**	**0**

Table 2. Incidence, hospitalizations and deaths due to influenza in Poland, in the 2020/2021 influenza season.
Source: Own elaboration based on: [12].

In Poland, out of 363 samples collected from patients with influenza or influenza-like symptoms tested during the 2020/2021 epidemic season, only 3% were positive (tested positive for infections with viruses: influenza A, influenza B, RSV (Respiratory Syncytial Virus), parainfluenza type 1, parainfluenza type 2, parainfluenza type 3 and for adenoviruses). Of these, 75% of positive samples belonged to adenoviruses and 25% were influenza B viruses [12].

Influenza viruses are constantly modifying as they undergo their characteristic processes. One of these is the antigenic drift - these are small changes (or mutations) in the genes of influenza A and B viruses that can lead to changes in the virus surface proteins: HA (haemagglutinin) and NA (neuraminidase), occurring every 2-3 years [13]. The HA and NA

surface proteins of influenza viruses are recognized by the immune system and are capable of eliciting an immune response, therefore antigenic drift mutations in these proteins prevent an effective action of a vaccine against them. As a result of the antigenic drift, the composition of the influenza vaccine must be updated every year to keep up with the constantly modifying influenza viruses. Antigenic drift is the cause of annual seasonal influenza epidemics in temperate climates and year-round epidemics in tropical climates. Another type of lesion is the antigenic shift, which is a sudden, major change in influenza A, resulting in the emergence of new HA and NA proteins in influenza viruses that infect people. Such a change happened in June 2009, when a strain of the H1N1 flu virus appeared, which is a mutant version of the swine flu virus, and led to a 15-month influenza A(H1N1) pandemic. This change is responsible for the emergence of epidemics and worldwide influenza pandemics. The largest of these that broke out in the 20th and 21st centuries are shown in Table 3.

Virus subtype	**Date**	**Number of cases**	**Number of victims**
A(H1N1) - “Spanish”	1918-1919	500 million	30-100 million
A(H2N2) - “Asian”	1956-1958	45 million	1-2 million
A(H3N2) - “Hong Kong”	1968-1969	50 million	0,7-1 million
A(H1N1) - “Russian”	1977-1978	no precise data	~1 million
A(H1N1) - “Mexican”/swine	2009-2010		~0,15-0,5 million

Table 3. The largest influenza virus pandemics in the 20th and 21st centuries
Source: Own elaboration based on: [14,15].

2.3. METHODS OF DIAGNOSIS

A wide range of both molecular and serological methods are used in the diagnosis of influenza. Many of them, used in the past, have been replaced by faster ones with higher sensitivity and specificity. However, in the acute phase of the disease, in the vast majority of cases only clinical diagnosis is performed, with 29-80% effectiveness [17]. The most commonly performed tests in virological diagnostics at present are those using molecular biology techniques, which include polymerase chain reaction (PCR) and its modifications - reverse transcriptase PCR (RT-PCR) and real-time PCR (qPCR). RT-PCR is the most sensitive method and currently replacing classical PCR. It is particularly important in virological diagnostics of respiratory viruses, most of which are viruses with genetic material recorded in the form of RNA. In the case of influenza, real-time PCR is becoming more and more popular, as it enables to obtain results several times faster, significantly affecting the time of diagnosis and treatment initiation. It also enables monitoring of the stage of the infection and observation of the effectiveness of the applied treatment [16]. The material for testing is nasopharyngeal swabs and aspirate or washings taken from the nose and throat [5]. The advantage of these methods is their sensitivity - they are able to detect a really small amount of viral genetic material in the tested sample. In addition, they identify the type of influenza virus, distinguish type A from type B, and differentiate influenza virus from other viruses. The specificity of PCR does not require immediate testing of the collected material,

unlike, for example, immunofluorescence tests. However, there are factors that may affect the accuracy of PCR measurements, which mainly boil down to human errors, such as incorrect preparation of clinical material for testing or errors in its collection, but also false results are obtained in the case of defective equipment and poor-quality reagents used in the reaction. Molecular biology methods are also used to identify the influenza virus in post-mortem samples and to isolate strains that are components of seasonal influenza vaccines [16].

Methods whose clinical utility has been severely limited by the popularization of molecular methods, but are still used by some laboratories are: direct and indirect immunofluorescence tests, ELISA (enzyme immunoassays) tests and rapid diagnostic tests. The latter are characterized by high specificity of virus antigens detection, but rather low sensitivity, therefore a positive result should be confirmed by other methods - often it is real-time PCR [5]. Immunofluorescence tests, despite the short time of obtaining the results (from 1 to 4 hours), lost the advantage over molecular biology methods due to the previously mentioned required fast transport of materials for research to the laboratory and storage at an appropriate temperature and a high probability of making a mistake by the person interpreting the result. Enzyme immunoassays currently exist mainly in the form of easy-to-use commercial tests that detect viral antigen reacting with specific enzyme-labelled antibodies [5,16].

In the field of serological tests, measurements of the titre of anti-influenza-specific antibodies in the patient's serum are performed. The tests are performed twice - in the acute phase of infection and about 10-14 days after the first test. A 4-fold increase in the antibody titer indicates a past infection. This test is not often used in the clinic [5].

2.4. CLINICAL MANIFESTATION

Infection with influenza virus can be asymptomatic, but it can also manifest itself in serious ways that can lead to death. Clinical symptoms depend on the type of virus, age, immune status of the patient, and the presence of underlying drug conditions. Initially, it is important to make a differential diagnosis and differentiate influenza from common cold, other aetiology of bacterial or viral respiratory infection, exacerbation of COPD or asthma and other related illnesses. The diagnosis of influenza is based on the described diagnostic criteria. In Poland, these are: sudden onset of the disease, high fever and other symptoms such as: cough, headache and muscle pain [5]. The influenza incubation period lasts 1-4 days, depending on the type of virus, and the infectious period ranges from 24 hours before the onset of symptoms up to 3-5 days after their cessation, except in paediatric patients and immunocompromised individuals, in whom it persists longer [19].

Uncomplicated influenza illness is characterised by the sudden onset of general symptoms. The most common ones that initially dominate include: fever, feeling cold, chills, muscle pain, headache (most often around the forehead and eyes), feeling of breakdown and weakness, general malaise. Respiratory symptoms usually appear after about three days and include: sore throat, symptoms of rhinitis (usually mild), and a dry and tiring cough. In children, these symptoms may also be accompanied by symptoms of laryngitis or middle ear infection, nausea, vomiting, mild diarrhoea. In the elderly, the main accompanying symptoms may be significant weakness or consciousness disturbances [5].

Most symptoms disappear after 3-7 days, except for coughing and malaise, which may persist for more than 2 weeks [5].

In individual cases, influenza virus infection can lead to a severe course of influenza or to serious post-influenza complications. The progressive (worsening) disease is characterized, apart from the usual symptoms, by the occurrence of: dyspnoea, haemoptysis, hypotension, prolonged high fever for more than 3 days, marked weakness, weakness in the lower limbs making it difficult to move, dizziness, dehydration with oliguria, disturbed consciousness and loss of consciousness. The occurrence of these symptoms is an indication for immediate hospitalization [5].

There are risk groups in society that are more likely to develop complications from the flu than others, including:

- adults over 65,
- children under 2,
- people who stay permanently in closed clusters, such as: residents of social welfare homes, senior care homes, long-term care homes and others,
- pregnant and postpartum women,
- adults with chronic diseases such as asthma, diabetes, heart disease, liver disease or chronic kidney disease, and people with obesity (BMI over 40) [18].

The most common possible complications from the flu include:

- disease of the lower respiratory tract - pneumonia
- convulsions, impaired consciousness, encephalitis, Guillain-Barré syndrome, acute transverse myelitis,
- myocarditis
- renal failure,
- multi-organ failure,
- sepsis and septic shock,
- exacerbation of the underlying chronic disease (including asthma, COPD, heart, liver, kidney diseases and diabetes),
- death.

2.5. TREATMENT

Influenza is a disease with an individually highly variable course and a broad spectrum of symptoms. As it is mild in the vast majority of patients, only symptomatic treatment is used, often without consulting qualified medical personnel. Dietary supplements and natural medicine preparations are also commonly used. Some of them are scientifically proven to be effective in treating influenza, but none can replace the effectiveness of treatment with antiviral drugs [20]. Positive effects are demonstrated by, among others, licorice root (stimulation of gamma interferon production), polyphenols contained in pomegranate fruit (elimination of type A influenza viruses), *Lactobacillus spp*. (stimulation of NK cells) or garlic (phytoncides with an immunostimulatory effect) [20]. Rest and isolation from other people for at least 24 hours after the cessation of fever and adequate hydration are also important in the treatment of influenza [21].

Widely used and recognized by doctors is the treatment of influenza with antipyretic, anti-inflammatory, analgesic and expectorant drugs. Preparations with acetylsalicylic acid, paracetamol and naproxen are especially effective. Extremely beneficial effects of treatment of A(H5N1), A(H7N9) or A(H1N1) influenza virus infections have been demonstrated in patients hospitalized using the combined therapy with oseltamivir, clarithromycin and naproxen [22].

Among the causal drugs, there are two generations of preparations: the so-called "old anti-influenza drugs" - M2 inhibitors and "new" - neuraminidase inhibitors [23]. The first group includes amantadine and rimantadine. These drugs, now more widely used in neurology for the treatment of Parkinson's disease, block the ion channel - the M2 protein, which prevents viral particles from entering the body's cells. However, they are effective for the treatment and prevention of influenza A virus infections; they do not act against the type B [24]. Furthermore, the Centers for Disease Control and Prevention (CDC) does not recommend their widespread use for this indication. The neuraminidase inhibitors include the drugs listed in Table 4. Oseltamivir and zanamivir have been used all over the world, including Poland, since the 1999/2000 season [25]. They work by inhibiting the action of one of the virion's surface proteins - neuraminidase (NA), contributing to the inhibition of the release of new virions from the infected cell, and thus the spread of the virus throughout the body. They are effective against both types of influenza virus - A and B. They slow down the development of infection by enhancing the activity of the body's immune system. They should be administered up to 48 hours after the onset of the first flu symptoms, as their effects become weaker in the later stages [25].

Name of the substance	**Form of application**	**Countries where the drug is authorized**
oseltamivir	orally	worldwide
zanamivir	inhaling	worldwide
peramivir	intravenously	Japan, China, South Korea
laninamivir	inhaling	Japan

Table 4. Characteristics of neuraminidase inhibitors in the world.
Source: Own elaboration based on: [25].

Favipiravir and Fludase® are in phase II clinical trials in the US. The composition of Fludase includes bacterial sialidase obtained from Actinomyces viscous, which blocks receptors on the surface of epithelial cells in the respiratory tract, preventing the penetration of virus particles into them. Favipiravir selectively inhibits viral RNA [25]. They are effective against both types of influenza virus - A and B. Favipiravir has been approved for treatment in Japan [25]. In addition, a large number of preparations are in the preclinical phase of research, which gives hope for further possibilities in the treatment of this virus infection. However, it should not be forgotten that no drug is as effective in preventing infections as a vaccine, and according to the Hippocratic idea - "prevention is better than cure".

2.6. VACCINATION

Thanks to the Edward Jenner's discovery over two hundred years ago, it became possible to combat the infectious diseases that had hitherto decimated the populations of Europe and the whole world. The introduction of vaccinations allowed for the eradication of smallpox, and also contributed to a significant reduction in the incidence and reduction of the number of serious complications caused by poliovirus, mumps, tetanus and diphtheria bacteria [26]. Unfortunately, the characteristics of influenza viruses prevent the disease from being successfully eradicated once and for all. Due to the occurrence of antigenic drift and antigenic shift phenomena, it is necessary to take a new vaccine every year in order to effectively prevent the disease due to the emergence of new virus strains and a different number of people infected by a given strain [27]. The arrival of another influenza pandemic is inevitable, but according to WHO recommendations, vaccination is the most effective method of protection against infection with this pathogen, which also enables greater epidemiological control, especially in the cool northern hemisphere [27,28]. It is worth mentioning that the recommended level of influenza vaccination in society is 75% [29]. A worrying fact is that influenza vaccines are taken by a very small percentage of the population, not only in Poland [30]. In the previous "flu season" 2020/2021, this was less than 2 million people, which is about 5.2% of the population [31]. For comparison, the average for the European Union was around 44% [32]. The highest flu vaccination rate among the inhabitants of Poland so far was recorded in the 2001/2002 season and it amounted to 10.57%. Since then, the vaccination rate has been declining. Equally worrying is the low influenza vaccination rate among the medical community. According to the research conducted in 2017, presented during the Flu Meeting conference, only 32.2% of doctors (most often: paediatricians and family doctors, least often: orthopedists and psychiatrists) and 19.9% of nurses declared being vaccinated for influenza [32]. Therefore, universal education is necessary in order to popularize vaccinations, especially among risk groups, exposed to a more severe course of the disease and a higher probability of developing life-threatening complications [28].

In Poland, flu vaccination is not mandatory. However, it is recommended for all people over 6 months of age who do not have any contraindications to taking the preparation, listed in Table 5. [32, 33]. Table 6 presents groups of people among whom influenza vaccination is particularly recommended for clinical or epidemiological reasons.

Absolute contrindications	**Relative contrindications**
● severe allergic reactions (anaphylaxis) to egg white (e.g. ovalbumin) or other ingredients of the administered preparation, in case of a slight reaction - it is recommended to observe the patient for 15 minutes after administration of the vaccine.	● history of Guillain-Barré syndrome within 6 weeks of previous flu vaccination, ● acute illness with or without fever.

Table 5. Relative and absolute contraindications for receiving influenza vaccination.
Source: Own elaboration based on: [32,33].

Clinical rationale	Epidemiological rationale
● organ transplant recipients, ● chronically ill patients over 6 months of age, especially with respiratory diseases (asthma, COPD), coronary artery disease, heart or kidney failure, ● people with morbid obesity (BMI> 40), ● people with impaired immunity, HIV-infected and patients with hematopoietic malignancies, ● children with heart defects, especially cyanotic defects, heart failure, pulmonary hypertension, immunological and hematological disorders ● pregnant women, especially in the second or third trimester or planning pregnancy.	● healthy children aged 6 months - 18 years (especially 6-60 months), ● people over 55, ● people who have close professional or family contact with children up to 6 months of age, seniors and the chronically ill, ● employees of the healthcare system, schools, trade, public transport, public servants, ● people residing in nursing homes, hospices or other therapeutic, rehabilitative or nursing care facilities.

Table 6. Groups of people for whom influenza vaccination is particularly recommended, taking into account the causes of this state.
Source: Own elaboration based on: [32,33].

The flu vaccine should be received before the peak of the seasonal flu epidemic. It is connected with the time that has to pass for the vaccinated person's organism to be able to develop the immunity against the pathogen before the period of the greatest number of illnesses, that is about 2-3 weeks. In Poland, this peak season falls on the coldest months of the year - from January to March, therefore vaccination should be taken in the autumn months - from September to December of the previous year [32]. Early vaccination (summer months) is not recommended, except in pregnant women in the third trimester, in order to reduce the risk of disease in the newborn that will be born in the autumn-winter period. When vaccinating children, attention should be paid to their previous intake of a flu vaccin. If a child up to the age of 9 years has not been vaccinated earlier, it should receive two doses of the preparation, at least four weeks apart [33].

In Poland, inactivated vaccines: split type (contain cleaved virus fragments) and subunit (contain viral surface protein subunits - haemagglutinin and neuraminidase), and from the 2019/2020 season - intranasal live vaccine are available [32]. In season 2021/2022, these are quadrivalent formulations containing antigens of related strains:

- A/Victoria/2570/2019 (H1N1)pdm09
- A/Cambodia/e0826360/2020 (H3N2)
- B/Washington/02/2019 (Victoria line)
- B/Phuket/3073/2013 (Yamagata line) [33].

The strains of the influenza B virus have remained the same as a year ago, only the strains of the A virus have changed.

The exact composition of the vaccines is determined by the WHO, based on global epidemiological reports specifying the most common strains of influenza A and B viruses causing seasonal epidemics in the preceding year. Reports are sent to WHO from over 142 centers - including the Polish National Institute of Public Health - National Institute of

Hygiene in Warsaw. After analyzing the submitted data, the most frequently isolated types are identified and this is communicated to the producers of vaccines, who have at least 6 months to make the product available on the pharmaceutical market [32]. Quadrivalent vaccines are preparations containing antigens of two strains of influenza A and two strains of influenza B viruses, multiplied on embryos of hen eggs. Each vaccine strain is present in the amount of $107^{(+/-0.5)}$ FFU (fluorescent focus units) [34]. From the 2020/2021 season, they are the only ones approved for general use, replacing the trivalent preparations used from the 2017/2018 season [32]. Available vaccines differ from each other in the possible ways of administration and the method of preparation of the product. There is an inactivated intravenous (IIV) vaccine and a live, attenuated nasal spray (LAIV-4), intended in Poland for children aged 24 months to 18 years, in other countries, such as the USA or Canada, also for adults [33, 34].

In the 2021/2022 season, three preparations will be available in Poland: Influvac Tetra (subunit type) by Mylan IRE Healthcare, Vaxigrip Tetra (split type) by Sanofi Pasteur and Fluenz Tetra (type LAIV-4) by AstraZeneca [32]. All of the above products have been reimbursed by the National Health Fund, for a 50% fee for specific groups of patients (Vaxigrip Tetra for people over 65, people from 18 to 65 from groups at risk of severe flu and children from 24 to 60 months of age; Influvac Tetra only for people at risk of severe flu, and the intranasal vaccine for children from 24 to 60 months of age). Sanofi's vaccine will be free of charge for those over the age of 75. and with Influvac for pregnant women [35].

In the era of the SARS-CoV-2 virus pandemic, when vaccination against it seems to be a priority, flu vaccination should not be forgotten either. Both diseases can coexist, worsening the patient's prognosis. No person should also give up vaccination against influenza at the expense of taking the preparation against coronavirus, because type IIV vaccines can be administered simultaneously with other vaccines at any interval, and when administering LAIV-4, it is important to remember about an interval of at least four weeks until taking the next attenuated vaccine [33].

Despite the availability of many flu vaccine preparations on the market, work continues on improving them or developing a new product with wider application. In 2020, a new peptide vaccine against influenza FLU-v, characterized by its universal action, was developed and confirmed [36]. This breakthrough specific would stimulate a cellular rather than humoral immune response as previously known vaccines, thus conditioning immunity against all strains and types of influenza viruses, without the need for annual vaccination. The immune response occurs through stimulation of Tc lymphocytes by influenza virus internal proteins - PB1, PB2, PA, NP, M2 and M1, which do not change as the surface proteins do [36].

2.7. INFLUENZA VS COMMON COLD VS COVID-19

Seasonal influenza, common cold and pandemic COVID-19 disease are remarkably similar clinical conditions with multiple manifestations, making their differentiation very difficult, which is a challenge even for specialists. However, correct diagnosis is crucial for further therapeutic management and a better prognosis for the patient.

All of the above diseases are caused by viruses and affect the human respiratory tract [37]. The severity of their incidence is observed in larger groups of people, during autumn and winter months, which is associated with low temperature and high air humidity [38]. The

clinical course of these diseases is so similar that when the first SARS-CoV-2 virus infections were recorded in November 2019, it was initially considered to be a more severe variant of influenza [39]. The truth was only known after isolation and careful virological analysis of the pathogen. Initially, it was also much easier to distinguish coronavirus infection from cold disease. With the emergence of subsequent variants of the SARS-CoV-2 virus, including the highly infectious Indian Delta variant (B.1.617.2), which causes symptoms of upper respiratory tract infection, the differentiation of both diseases has become more difficult, sometimes even impossible without long observation of the patient or the result of RT-PCR or antigen tests [40].

Common cold is an acute inflammation of the nasopharyngeal mucosa, caused by over 200 viruses of various families and types, most often by rhinoviruses from the *Picornaviridae* family (30-80%), as well as coronaviruses, parainfluenza and RSV virus [41,42]. Viruses are transmitted by droplet or direct contact with infected secretions. The main symptoms of cold disease are wet, mild cough, rhinitis, fatigue, sore throat, loss of appetite or muscle pain. In adults, a subfebrile state is usually present, while fever is characteristic among younger patients [43,44]. The disease usually develops gradually, is mild, and symptoms disappear after about 7-10 days [44]. The common cold resolves spontaneously, with symptomatic treatment usually consisting of antipyretic, analgesic, anti-inflammatory or expectorant preparations [43].

COVID-19 is an acute respiratory disease caused by the SARS-CoV-2 coronavirus, which is transmitted by droplet. The first infection with this virus was reported in November 2019 in the Chinese province of Hubei, and on 11 March 2020 the WHO declared a pandemic state due to the rapid spread of this pathogen, causing many deaths on all continents [45]. The disease is characterised by a highly variable course. Some patients only become aware of the infection through virological tests, passing the disease asymptomatically, while in others it leads to severe respiratory failure and eventually death. The most common symptoms of Wuhan coronavirus infection are dry cough, high fever, chills, headache, muscle pain, sometimes diarrhoea, vomiting, chest pain or haemoptysis [46]. The incubation period ranges from 2 to 14 days, usually 5-6 days, usually the disease starts with a cough or runny nose, then progressing to more troublesome symptoms for the patient, sometimes it has a fulminant course [47]. Until then, no unequivocally effective drug in COVID-19 has been found. Numerous scientific studies are conducted around the world, trying to determine the effectiveness of individual agents, such as amantadine, ivermectin, chloroquine, remdesivir or convalescent plasma [48,49,50].

The characteristics, clinical manifestations and diagnosis of the flu are described in the sections above. The differential diagnosis of seasonal influenza, common cold and COVID-19 is presented in Table 3.

Symptom/ characteristic	Influenza	Common cold	COVID-19
incubation period	1-7 days	1-3 days	2-14 days
onset of the disease	sudden	gradual	sudden, sometimes gradual
body temperature	fever, >38°	subfebrile state, <38°	high, persistent fever
rhinitis	sometimes	very often	rarely
cough	very often, dry	often, wet, mild	very often, dry
breathlessness	absence	absence	often
sneezing	absence	very often	rarely
fatigue	often	sometimes	often
headache	very often	rarely	sometimes
muscle pain	very often	often, mild	often
sore throat	sometimes	often	sometimes
diarrhoea	often	absence	sometimes
nausea, vomiting	sometimes	rarely	sometimes
smell and taste disturbances	rarely, slight	rarely, slight	very often complete loss
vaccination	available	absence	available, some in clinical trials

Table 7. Differential diagnosis of influenza, common cold and COVID-19.
Source: Own elaboration based on [51].

3. CONCLUSIONS

Despite significant medical advances and a reduction in the spread of many infectious diseases, mankind is unable to tame seasonal flu epidemics. This disease continues to be underestimated by both the general public and medics. It is characterised by a very varied course, which is almost impossible to predict. For this reason, regular influenza vaccination is

essential, for both personal and epidemiological benefits. It is possible that, thanks to clinical research on the improvement of available therapeutic methods and vaccines and, above all, to the popularisation of knowledge about influenza and the mobilisation of society, in the future this disease, like smallpox, will remain only in the memories of the oldest people and in textbook descriptions.

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