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## Recommendations for the management of children with influenza in a primary care setting – COMPAS INFLUENZA. Update for the 2023/2024 season

Rekomendacje postępowania w grypie u dzieci – KOMPAS GRYPY 23/24.

Aktualizacja na sezon 2023/2024

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### Abstract

Five years after publishing the first Polish recommendations on the management of influenza, especially after the COVID-19 pandemic, there was a need to update the recommendations. Influenza is an acute infectious disease of the respiratory tract that occurs in all age groups. The course of the disease may vary in severity and clinical picture, from asymptomatic to severe with symptoms of respiratory failure. The possibility of pandemic infections and serious complications distinguish influenza from other viral respiratory diseases. Diagnosis is most often clinical, and in justified cases additional tests may be helpful. The disease is characterised by a sudden onset with general symptoms such as fever, feeling cold, chills, headache, muscle and joint pain, malaise, lack of appetite and severe weakness. General symptoms are accompanied by respiratory manifestations. Physical examination shows no characteristic features. In outpatient settings during the epidemic season (October – April), the diagnosis should be made based on clinical symptoms and physical examination. Oseltamivir is recommended for both treatment and chemoprophylaxis. Clinical benefits are greatest when treatment is started as early as possible, within 48 hours of symptom onset. Clinical trials indicate that early treatment with oseltamivir may reduce both the duration of the disease and the risk of complications. Annual vaccination is the most effective method of preventing influenza, with severe anaphylactic reaction after previous vaccination being the only absolute contraindication.

**Keywords:** children, treatment, influenza, vaccinations, recommendation

### Streszczenie

Po 5 latach od opublikowania pierwszych polskich rekomendacji postępowania w grypie, zwłaszcza po pandemii COVID-19, zaistniała potrzeba aktualizacji tych zaleceń. Grypa jest ostrą chorobą zakaźną dróg oddechowych występującą w każdej grupie wiekowej. Jej przebieg może mieć różne nasilenie i zróżnicowany obraz kliniczny – od bezobjawowego po ciężki z objawami niewydolności oddechowej. Możliwość występowania zakażeń o charakterze pandemicznym oraz poważnych powikłań w przebiegu grypy wyróżnia ją spośród innych wirusowych chorób układu oddechowego. Rozpoznanie najczęściej ma charakter kliniczny, w uzasadnionych przypadkach pomocne mogą być badania dodatkowe. Grypę charakteryzuje nagły początek z występowaniem objawów ogólnych, takich jak: gorączka, uczucie zimna, dreszcze, bóle głowy, mięśni i stawów, złe samopoczucie, brak apetytu i dojmujące osłabienie. Objawem ogólnym towarzyszą objawy ze strony układu oddechowego. Badanie przedmiotowe nie wykazuje specyficznych cech. W warunkach ambulatoryjnych w czasie trwania sezonu epidemicznego (październik – kwiecień) rozpoznanie powinno być ustalane na podstawie objawów klinicznych i badania

przedmiotowego. Lekiem rekomendowanym do leczenia i chemioprophylaktyki grypy jest oseltamiwir. Korzyści kliniczne są największe, jeśli leczenie rozpoczyna się jak najwcześniej, w ciągu 48 godzin od wystąpienia pierwszych objawów grypy. Badania kliniczne wskazują, że wczesne wdrożenie leczenia oseltamiwirem może skrócić czas trwania choroby i zmniejszyć ryzyko jej powikłań. Coroczne szczepienie przeciw grypie jest najskuteczniejszą metodą jej zapobiegania, a jedynym bezwzględny przeciwwskazaniem do szczepienia jest wystąpienie ostrej reakcji anafilaktycznej po poprzednim szczepieniu.

**Słowa kluczowe:** dzieci, leczenie, grypa, szczepienia, rekomendacje

## INTRODUCTION

In 2019, a team of specialists prepared and published the *ReCOMmendations for the treatment of INFLUENZA in children for Primary care physiciAnS – COMPAS INFLUENZA*<sup>(1)</sup>. It was the first such an extensive and comprehensive discussion on influenza in children, offering guidelines for paediatricians and family doctors. However, these recommendations needed updating after several years (especially after the coronavirus disease 2019, COVID-19 pandemic). In this paper, we present updated guidelines for the diagnosis, treatment and prevention of influenza. As in the previous edition, the recommendations are based on current knowledge and take into account the specificity of our country.

## INFLUENZA – BACKGROUND

- Influenza is an acute infectious disease of the airways that occurs across all age groups. It may vary in severity and clinical picture – from asymptomatic to severe with symptoms of respiratory failure<sup>(1,2)</sup>.
- Influenza is one of the most common acute viral respiratory infections.
- The risk of pandemic and serious complications distinguish influenza from other viral airway diseases<sup>(1,2)</sup>.
- The influenza virus belongs to the *Orthomyxoviridae* family and has a strong affinity for the airway epithelium. Human infections caused by influenza A and B are clinically important; type C is of less epidemiological importance. Influenza A and B are composed of a genome (segmented, single-stranded, negative-sense RNA), a protein capsid with antigenic proteins, neuraminidase (NA) and haemagglutinin (HA), on its surface, and a lipoprotein envelope<sup>(3)</sup>.
- Influenza A has many subtypes, which are distinguished based on the HA (subtypes H1 to H18) and NA (subtypes N1 to N11) antigenic properties. There are three common HA subtypes: H1, H2, H3 and two NA subtypes: N1 and N2 in humans. Influenza A is infectious to humans and many animal species, and the extent of the pandemic is unpredictable and depends on the type of interaction between the virus and host cells, as well as on ecological factors. Influenza A is characterised by high antigenic variation of HA and NA proteins, which results primarily from the relatively frequent mutations in their RNA. The mechanisms responsible for the antigenic variability

of influenza A are the phenomena of antigenic drift or antigenic shift<sup>(4)</sup>. These changes are mediated by an enzyme responsible for RNA replication (RNA polymerase), and new mutations resulting from RNA polymerase errors may increase virulence, facilitating viral attachment to the respiratory epithelium and its replication. Since the changes in the viral genome are continuous, the disease spreads annually among those who have not acquired immunity from vaccination or infection in a given season. The high genetic variability of influenza A viruses gives rise to new, sometimes highly pathogenic strains.

- Influenza B contains only one type of HA and NA in its structure, originating from two cell lineages: Yamagata or Victoria. Influenza B usually causes milder infections than those caused by influenza A<sup>(1,3)</sup>. Influenza B viruses show high genetic stability.

## EPIDEMIOLOGY

- In the moderate climate zone (Poland), influenza cases occur annually in the winter months. The influenza season in the Northern Hemisphere can begin in October and last till April, most often peaking at the end of February<sup>(5)</sup>.
- According to the World Health Organization (WHO), every year up to 20–30% of paediatric and 5–10% of adult global population develop full-blown influenza<sup>(6)</sup>. Children aged 5–14 years are most likely to be affected.
- Meta-analyses of randomised trials show that during the epidemic season, on average, up to 10.5% of school-age children and up to 32% of children under 6 years of age are affected by influenza compared to approximately 2.5% of adults, which means that children constitute the largest group affected by influenza<sup>(7,8)</sup>.
- The European Centre for Disease Prevention and Control (ECDC) reported that influenza virus activity returned to almost pre-COVID-19 levels in the 2022/2023 season in European Union countries<sup>(9)</sup>. This season was characterised by an earlier onset of the seasonal epidemic and an earlier peak of positivity compared to the four previous seasons.
- In the 2022/2023 season, influenza A(H3N2) dominated, but a higher circulation of A(H1N1)pdm09 and type B viruses was observed.
- Both type A and type B influenza viruses were detected in patients hospitalised in intensive care units and other

departments, with type A influenza being the predominant variant.

- The majority of genetically characterised influenza viruses fall within the groups of recommended vaccine components. Interim vaccine effectiveness estimates for the 2022/2023 season indicate a  $\geq 50\%$  reduction in incidence among all-age influenza A and B vaccine recipients. Very few influenza viruses with antiviral resistance have been reported.
- Every year in Poland, several million suspected cases of influenza (flu-like illnesses), several thousand hospitalisations and an unknown number of deaths (from several to 100 deaths per year as per official reports, 6,000 deaths according to ECDC estimates) are reported<sup>(9)</sup>.
- According to data from the National Institute of Public Health – National Research Institute (PZH) (Poland), 5,792,177 cases or suspected cases of influenza were reported in the 2022/2023 season<sup>(10)</sup>. Similarly to the European Union, a similar or even higher number of cases and deaths was reported as before the COVID-19 pandemic (Tab. 1).

### REPORTING OF INFLUENZA CASES, INCLUDING SUSPECTED CASES, IN POLAND IN 2023

The amendment to the Statistical survey programme of official statistics for 2023, as of July 7, 2023 abolished the obligation for medical facilities to submit MZ-55 reports, “Weekly, daily report on incidence and suspicion of influenza cases”, to the State Sanitary Inspectorate (Journal of Laws of 2023, item 1282). As a result, the National Institute of Hygiene has discontinued publishing “Epidemiological reports: influenza and influenza-like illness in Poland”, which were based on data collected using these reports. Currently, the data for the report are derived from health services provided by entities performing medical activities in the “advice” category, which were reported to the e-Health Centre as part of the mandatory reporting of the so-called medical events.

### CLINICAL PICTURE

- The mean incubation period for influenza is 2 days (1–7 days). The patient is contagious one day before symptom

Reported cases	2018/2019	2019/2020	2020/2021	2021/2022	2022/2023
Morbidity	3,692,199	4,851,376	2,844,957	3,891,457	5,792,177
Mortality	143	65	0	6	121

Tab. 1. Reported cases or suspected cases of influenza in Poland according to data from the National Institute of Public Health – National Research Institute (PZH) before, during and after the COVID-19 pandemic<sup>(10)</sup>

onset and up to 5 days after falling ill. This period may be longer in young children and last  $\geq 10$  days after the first symptoms appear. Immunodeficient patients may be contagious for many weeks or months.

- Clinically, influenza is a set of symptoms resulting from acute viral respiratory infection. After entering the body, the virus multiplies in the airway epithelial cells. No viremia is observed – general symptoms are triggered by locally released pro-inflammatory cytokines.
- The clinical symptoms of influenza caused by type A and B viruses are similar. Influenza A is indistinguishable from influenza B based on clinical symptoms.

### Medical history

- The disease is characterised by a sudden onset with **general symptoms** such as fever, feeling cold, chills, headaches, muscle and joint pain, malaise, lack of appetite and severe asthenia.
- General symptoms are accompanied by **respiratory manifestations**: dry cough, nasal congestion (sometimes with watery discharge), pharyngeal pain, and hoarseness. Children may complain of photophobia and other ocular symptoms, such as conjunctival hyperaemia, tearing and burning eyes, and retrobulbar pain (approximately 20% of patients in the paediatric population). Diarrhoea sometimes occurs (<5%). General symptoms usually dominate over other manifestations.
- On days 2–3 of the disease, fever and general symptoms decrease, dominated by dry cough and weakness.
- Headache and myalgia, the severity of which is usually correlated with fever, are the most unpleasant initial symptoms. Myalgia may affect the limbs or the long muscles of the back. Non-arthritis joint pain is also common.
- The above symptoms usually last for 3–4 days after the fever subsides, although cough and severe asthenia usually persist or more than 2 weeks. Malaise and chronic fatigue may persist for several weeks in some patients.

### Physical examination

- Physical examination generally shows no characteristic abnormalities.
- Fever, which is a constant feature of influenza and usually lasts for 3–5 days, but may persist for 7–10 days or longer in some cases (approximately 20% of patients), is the most common symptom. Children develop a higher fever than adults, although the temperature in infants does not necessarily rise as high as in older children and young adults. The temperature usually rises rapidly in the first 12 hours of the disease, simultaneously with the onset of generalized symptoms. Fever can provoke febrile seizures, especially in the first 2 years of life.
- Although high fever and associated neurological symptoms (encephalopathy or febrile seizures) may be the only manifestations of influenza in young children,

a significant percentage of patients develop bronchitis. Auscultatory changes over the lungs are detected in <20% of patients.

- Facial redness and warmed and moist skin, as well as cervical lymphadenopathy (approximately 25%) may be occasionally observed.

## DIAGNOSIS

- In outpatient settings during the epidemic season (October – April), the diagnosis should be based on clinical symptoms and physical examination<sup>(11–13)</sup>.
- Additionally, the diagnosis depends on the current assessment of the epidemiological situation made by a doctor (increased reporting of patients with flu-like symptoms, reports on an increased incidence of influenza, confirmed medical history of contact with an infected person).
- Laboratory diagnosis of influenza is also available – rapid influenza diagnostic tests (RIDTs) to detect viral types A and B, but without specifying the strain. Short waiting time for the result (up to 30 minutes) is their advantage; however, due to the limited sensitivity of these tests, a negative result does not exclude influenza<sup>(14)</sup>.
- According to the position of the National Consultant in Family Medicine<sup>(15)</sup>, testing allows for a more precise diagnosis and, consequently, a more accurate selection of treatment (e.g. the decision to initiate antiviral treatment instead of unnecessary antimicrobial therapy in the case of influenza). Identifying the causative agent of the infection makes it easier to decide on the use of prophylaxis in people close to the patient who are at risk of severe disease and/or complications.
- An antigen test for influenza/COVID-19/RSV (respiratory syncytial virus) infection is recommended primarily in individuals who present with clinical symptoms of respiratory infections, especially during the season of increased incidence of influenza/COVID-19/RSV infections, and belong to groups at risk of severe infection and/or complications (Tab. 2).
- Blood cell count (leukopenia with lymphocytosis) is helpful in the diagnosis.
- Virological test result indicating the presence of influenza antigen in patient's specimen (nasal or nasopharyngeal swab, nasopharyngeal aspirate, etc.) no later than 7 days from the onset of symptoms is the final confirmation of infection. Identification of viral genetic material using the reverse transcription-polymerase chain reaction (RT-PCR) method is the most accurate and fastest method, usually used in clinically justified cases<sup>(18)</sup>.

## DIFFERENTIAL DIAGNOSIS

- In everyday clinical practice, influenza is differentiated from flu-like viral diseases, including COVID-19 (coronavirus infection), RSV infection, viral pharyngitis,

Children <5 years, especially <2 years
Adults ≥50 years
Individuals with the following chronic conditions: <ul style="list-style-type: none"> <li>• respiratory (including asthma)</li> <li>• cardiovascular (excluding isolated hypertension)</li> <li>• renal, hepatic</li> <li>• haematological (including sickle cell anaemia)</li> <li>• metabolic (including diabetes mellitus)</li> <li>• neurological (including central nervous system disorders; diseases of the spinal cord, peripheral nerves, muscles; epilepsy; stroke; intellectual disability; moderate-to-severe developmental delays; brain and spinal cord injuries)</li> <li>• immunosuppression (including HIV treatment)</li> </ul>
All women who are pregnant, planning pregnancy or have given birth during the influenza season
Morbidly obese patients – BMI >40 kg/m <sup>2</sup>
People <19 years of age on chronic acetylsalicylic acid therapy
Nursing homes residents
Hospitalised patients at high risk of influenza complications
<b>BMI</b> – body mass index; <b>HIV</b> – human immunodeficiency virus. * Recommended antiviral treatment in the case of suspected or confirmed influenza infection.

Tab. 2. General population at increased risk of influenza complications who are recommended antiviral therapy<sup>\*(1,16,17)</sup>

infectious mononucleosis, enterovirus infections (e.g. *Coxsackie* virus), rotavirus and norovirus infections (colloquially “enteric flu”), as well as atypical pneumonia and sepsis (bacterial or viral).

## COMPLICATIONS

- Influenza is uncomplicated in most children, with high fever lasting for 3–4 days, sometimes for 6–8 days. Patients usually recover after 1–2 weeks.
- Complications of influenza may include severe disease, organ complications and bacterial superinfections. Groups in the general population who are at increased risk of influenza complications are listed in Tab. 2.
- The most common complications in the paediatric population are shown in Tab. 3.
- Secondary bacterial pneumonia occurs during the period of influenza symptom resolution or during the convalescence phase (recurrence of fever, worsening of dyspnoea, cough, weakness after clinical improvement). Pneumococci are the most common microbes responsible for pneumonia, followed by staphylococci, *Haemophilus influenzae* and other bacteria.
- Disturbing clinical symptoms, the so-called alarm symptoms, indicating possible complications are presented in Tab. 4. They require re-evaluation of the patient's clinical condition and, at the same time, are an indication for further laboratory work-up and diagnostic imaging (chest radiology, lung ultrasound).
- Typical laboratory abnormalities, such as leucocytosis >15,000/mm<sup>3</sup>, especially neutrophil count >10,000/mm<sup>3</sup>, elevated inflammatory markers (erythrocyte sedimentation

Respiratory: bronchitis, acute otitis media, primary viral pneumonia, secondary bacterial pneumonia, tracheitis, subglottic laryngitis
Mild myositis (usually influenza B, possibly myoglobinuria, occasionally with kidney damage)
Myocarditis and pericarditis
Central nervous system: febrile seizures, encephalopathy, transverse myelitis, Guillain-Barré syndrome, Reye's syndrome
Rare: toxic shock syndrome, Goodpasture's syndrome, anosmia, ageusia (loss of the sense of smell and taste) and balance disorders

Tab. 3. The most common influenza complications in the paediatric population<sup>(18-20)</sup>

• Persistent or recurrent high fever or other symptoms after 3 days
• Symptoms of cardiorespiratory failure: dyspnoea, cyanosis, haemoptysis, chest pain, hypotension, decreased haemoglobin oxygen saturation
• Symptoms indicating central nervous system involvement: disturbance or loss of consciousness, abnormal drowsiness, recurrent or persistent seizures, severe asthenia, paralysis or paresis
• Signs of severe dehydration – prolonged capillary refill, decreased activity, dizziness or fainting when trying to stand up, or decreased diuresis
• Laboratory signs of secondary bacterial infection

Tab. 4. Disturbing clinical symptoms in the course of influenza, which indicate potential complications<sup>(1)</sup>

rate, ESR; C-reactive protein, CRP >50 mg/L indicates bacterial pneumonia, and CRP <10 mg/L indicates viral pneumonia) are also indicative of bacterial superinfection.

- Mortality rates due to influenza and its complications in the paediatric population are highest in the first 2 years of life, high in young children and chronically ill children, especially those with immune and neurological disorders that impair lung ventilation and make it difficult to expectorate secretions.

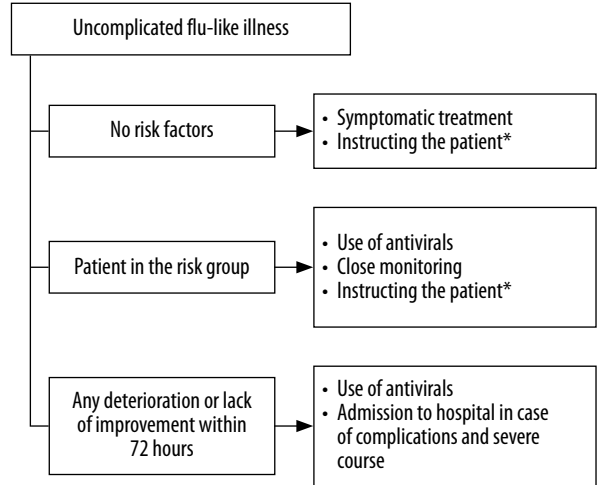
## TREATMENT

Influenza is usually self-limiting and uncomplicated in healthy individuals<sup>(21)</sup>. In such cases, symptomatic treatment is sufficient (Fig. 1)<sup>(1,22)</sup>.

### Symptomatic treatment

Symptomatic treatment strategies for influenza include<sup>(13,23)</sup>:

- Proper hydration of the patient – recommending high oral intake of fluids, which is crucial in the course of fever, and at the same time moisturizes the airways, as well as facilitates breathing and evacuation of secretions (especially important in children).
- Administration of antipyretics and analgesics (ibuprofen, naproxen, paracetamol, metamizole) to reduce chills, muscle pain and tachycardia, which accompany influenza. However, it should be emphasised that clinical data indicating that antipyretic and anti-inflammatory treatment shortens the duration of influenza symptoms are missing. Acetylsalicylic acid is not recommended in children under 18 years of age due to the possibility of Reye's syndrome.



\* When to make another appointment (alarm symptoms).

Fig. 1. Initial clinical management of uncomplicated influenza-like illness or influenza<sup>(1)</sup>

- Rest and staying at home for up to 24 hours after the fever subsides; this is particularly important for minimising complications and the transmission and spread of the virus<sup>(21)</sup>.
- Antitussives may be used for severe, exhausting, dry cough<sup>(24)</sup>; the use of codeine as an antitussive is not recommended due to its hepatic metabolism and various pharmacogenetic variants of drug metabolism. Dextromethorphan, butamirate, and levodropropizine are recommended antitussives.
- Medications to reduce nasal mucosal oedema (decongestants, saline solutions).
- There are currently no animal or human clinical trials showing a beneficial effect of natural or herbal therapies for influenza. There are no indications and no recommended herbal, natural or other over-the-counter (OTC) preparations for the symptomatic treatment of influenza in adults and children<sup>(25)</sup>. There is no evidence to support the efficacy of dietary supplements. On the contrary, they should be avoided due to possible interactions with pharmacological treatment, which has a proven therapeutic effect in influenza.

### Antiviral treatment

The medications described below are used in the causal/antiviral treatment of influenza<sup>(26-31)</sup>.

**1. Neuraminidase inhibitors (NAIs)** – oral oseltamivir (available in Poland) and inhaled zanamivir, intravenous peramivir, and laninamivir (not available in Poland).

Inhibitors of neuraminidase (oseltamivir), an enzyme essential for the release of newly formed viruses from infected host cells, effectively inhibit the spread of the virus in the body and prevent influenza symptoms<sup>(32)</sup>. Oseltamivir is effective against influenza A and B. It is estimated that current resistance of influenza A strains to the drug is less than 1%.

Type B virus is 100% susceptible<sup>(33,34)</sup>. The clinical efficacy of oseltamivir has been confirmed in many studies. Neuraminidase inhibitors reduce the severity of symptoms, duration of fever and other manifestations, as well as the risk of complications (including the need to use antibiotics) and hospital stay<sup>(21,35–37)</sup>. Antivirals were shown to reduce the time needed for outpatient care, the length of hospital stay, and the risk of death<sup>(16)</sup>. The American Academy of Pediatrics (AAP) recommends neuraminidase inhibitors for the treatment and chemoprophylaxis of influenza in children in the 2023/2024 season as the best-studied antivirals to date; indications for their use are specified in Tab. 5<sup>(37)</sup>. The inclusion of antiviral treatment (oseltamivir) is also recommended in the case of suspected influenza (even mild) and for those at increased risk of complications<sup>(17,38)</sup>. At the same time, it should be emphasized that every patient with influenza symptoms (severe in particular) can be treated with antivirals, which will significantly reduce the spread of the virus in the population, especially during the epidemic period.

Four oseltamivir preparations have been registered and are available for the 2023/2024 season in Poland (Tab. 6). Three of them (Tamiflu, Ebilfumin, Segosana) are registered and can be used from the first day of life.

In standard protocol, the drug is administered twice daily (75 mg) at regular 12-hour intervals, for 5 days. In children, the dose depends on body weight (Tab. 7). It is important to complete the full 5-day treatment. It should not be discontinued, even in the case of complete symptom resolution. Oseltamivir should be administered within 48 hours of symptom onset, preferably as soon as possible, without waiting for the results of viral testing. In exceptional situations (severe course of confirmed influenza, late presentation of the patient to the doctor, patient at risk of complications), it is worth to use the drug in the first hours and days after symptom onset, although the therapeutic effect may be weaker in such cases<sup>(17)</sup>.

Oseltamivir is administered orally without regard to meals, although taking the drug with a meal may improve its gastrointestinal tolerability. Children should receive oseltamivir in the form of syrup. The suspension can be prepared from available capsules by a pharmacist in a pharmacy (preferred method) or, if this is not possible, by parents/guardians at home. Detailed information on the home preparation can be found in the package leaflet. There is also a detailed dosage table for the prepared suspension for children, starting from 3 kg of body weight.

Oseltamivir is a safe drug with few adverse effects. The majority of reported cases were single episodes of symptoms occurring on days 1 and 2 of treatment, which resolved spontaneously within 1–2 days<sup>(38)</sup>. Gastrointestinal symptoms, such as nausea and vomiting (Tab. 8), were the most common adverse effects<sup>(26,27,39)</sup>. The pharmacokinetic properties of oseltamivir, such as poor protein binding and metabolism independent of the CYP450 and glucuronidase systems, suggest that clinically significant drug interactions via these mechanisms are unlikely<sup>(17)</sup>.

<b>Administer treatment (as soon as possible) to:</b>
• a hospitalised child with likely influenza
• a child hospitalised for severe, complicated or progressive influenza-related illness, regardless of symptom duration
• a child with suspected influenza (regardless of symptom severity) and a high risk of complications
<b>Consider treatment in:</b>
• each healthy child with suspected influenza
• a child with suspected influenza who shares a household with children aged <6 months or with a person predisposed to complications

Tab. 5. Indications for antiviral treatment in children<sup>(1,16,17)</sup>

Trade name	Pharmaceutical form	Approved for	Marketing Authorization Holder
Tamiflu	Hard capsules 30 mg, 45 mg, 75 mg (a pack of 10 capsules)	≥1 months	Roche
Ebilfumin	Hard capsules 30 mg, 45 mg, 75 mg (a pack of 10 capsules)	≥1 months	Actavis
Segosana	Hard capsules 30 mg, 45 mg, 75 mg (a pack of 10 capsules)	≥1 months	Zentiva
Tamivil	Tablets 75 mg (a pack of 10 capsules)	>6 years	Biofarm

Tab. 6. Commercial forms of oseltamivir<sup>(26–29)</sup>

Data on the safety and efficacy of oseltamivir in children (up to 12 years of age) with renal impairment are missing. Adolescents (13–17 years) and adults (especially those >65 years of age) with renal impairment require dosage adjustment based on creatinine clearance. Patients with a creatinine clearance of 10–30 mL/min should receive a dose of 75 mg once daily for 5 days. Patients with a creatinine clearance of 10–30 mL/min should receive 30 mg once a day for 10 days after exposure or 75 mg once every 2 days for 10 days after exposure (5 doses) as part of chemoprophylaxis. It is not necessary to reduce the therapeutic or prophylactic dose in patients with liver failure<sup>(17)</sup>.

Oseltamivir should not replace vaccination. The protection against influenza lasts only as long as oseltamivir is administered. The drug should be used to treat and prevent the disease only when reliable epidemiological data indicate that the virus is circulating in a given environment and the symptoms suggest an influenza infection.

**2. Baloxavir marboxil** (unregistered, not available in Poland). It is one of the latest drugs against influenza types A and B, registered in Japan (2018), the United States (2019) and Australia (2020). It acts by inhibiting a specific viral endonuclease and blocking RNA transcription in the infected cell. A single administration of the drug at a dose of 40 or 80 mg up to 48 hours after the onset of symptoms reduces viral load and shortens the duration of fever and other symptoms of the disease, usually without causing serious adverse reactions, and the drug can be administered to children after adjusting the dose to their body weight. Factors that limit its use include a higher price compared

Patient population	Treatment (5 days)	Chemoprophylaxis (10 days)
Adults	75 mg 2 × day	75 mg 1 × day
Children >12 months*: • ≤15 kg bw • >15–23 kg bw • >23–40 kg bw • >40 kg bw	30 mg 2 × day 45 mg 2 × day 60 mg 2 × day 75 mg 2 × day	30 mg 1 × day 45 mg 1 × day 60 mg 1 × day 75 mg 1 × day
Infants from 0 to 12 months	3 mg/kg bw per dose 2 × day	3 mg/kg bw per dose 1 × day**

\* The medication should be administered in the form of syrup in children. In Poland, the medication is not available in the form of syrup, but a suspension from capsules can be prepared by a pharmacist. If this is not possible, the patient can prepare a drug suspension from available capsules. Preparation instructions are included in the patient leaflet.  
\*\* Chemoprophylaxis is not recommended in children <3 months, except for life-threatening situations. There is insufficient literature data.

Tab. 7. Recommended oral doses of oseltamivir for the treatment and chemoprophylaxis of influenza infection in Poland<sup>(1,13,26–29,38)</sup>

to other therapies and the facts that it has not been approved for use in the European Union, which, however, does not exclude the possibility of its use (each case of use requires an approval of the Bioethics Committee). Adverse effects of baloxavir include diarrhoea, headache, increased blood alanine aminotransferase and aspartate aminotransferase, vomiting, and nausea. No serious adverse effects were observed. The rates of adverse effects were similar to those in the group put on placebo or other drugs: oseltamivir, peramivir, laninamivir. Vomiting that occurred at least one hour after administration of baloxavir did not reduce its plasma levels, suggesting its rapid absorption after oral administration. Baloxavir can be safely used in children 1–11 years after adjusting the dose to the patient's body weight, but the exact dose per kg body weight has not been proposed. The minimum child's body weight at which a standard dose (40 mg) of baloxavir

can be safely administered is 5–10 kg. Baloxavir has been shown to inhibit viral replication without cytotoxic effects. Potential interactions between baloxavir and food or dietary supplements containing polyvalent metal ions should be taken into account due to limited bioavailability. No adverse interactions were observed between baloxavir and oseltamivir; studies on mice have shown their synergistic effect. No cross-resistance to baloxavir and oseltamivir has been observed, which means that baloxavir can be used in a wide group of patients previously ineffectively treated with the above-mentioned drugs<sup>(40–42)</sup>.

In the case of severe or worsening influenza, hospital admission should be considered. Symptoms of pneumonia in the course of influenza are an indication for hospitalisation in patients from the risk group (Fig. 2)<sup>(22)</sup>. Indications for considering inpatient stay in the case of influenza are presented in Tab. 9. Patients with respiratory failure should be transferred to a centre offering extracorporeal membrane oxygenation (ECMO).

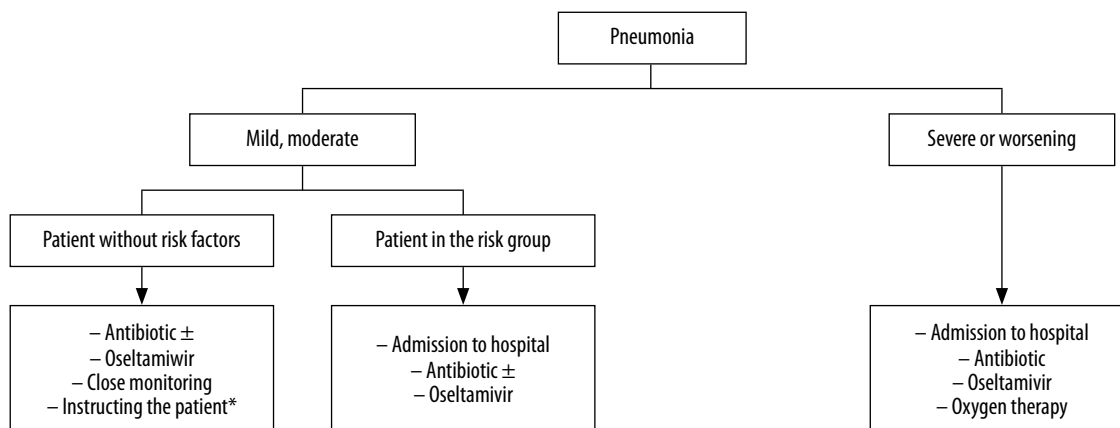
### Preventive use of antivirals

- Every child with no contraindications should be recommended vaccination against influenza, even during the season. However, the preventive use of oseltamivir may be also recommended in order to inhibit the spread of the virus and the development of the disease following contact with infected patients<sup>(22)</sup>. **Post-exposure prophylaxis** is recommended (following contact with a patient with clinically diagnosed influenza) for unvaccinated children<sup>(21)</sup>:
  - at high risk of complications;
  - in close contact with a sick person (sharing a household).
 Additionally, post-exposure prophylaxis is recommended for persons caring for children under 6 months of age as these children cannot be vaccinated.

Trade name	Adverse effects	Contraindications
Tamiflu	<ul style="list-style-type: none"> <li>• Nausea, vomiting and diarrhoea</li> <li>• Abdominal pain</li> <li>• Headaches, dizziness</li> <li>• Insomnia</li> </ul>	<ul style="list-style-type: none"> <li>• Hypersensitivity to oseltamivir phosphate or any other ingredient of the drug</li> </ul>
Ebiflumin	<ul style="list-style-type: none"> <li>• Nausea, vomiting</li> <li>• Headaches, dizziness</li> <li>• Insomnia</li> </ul> Rare: cardiac arrhythmias, impaired consciousness, convulsions	<ul style="list-style-type: none"> <li>• Hypersensitivity to the active substance or to any of the excipients</li> </ul>
Segosana	<ul style="list-style-type: none"> <li>• Headaches</li> <li>• Nausea, vomiting</li> </ul> Common: bronchitis, herpes virus, cough, dizziness, fever, pain, pain in extremities, rhinorrhoea, sleeping problems, pharyngeal pain, abdominal pain, fatigue, feeling of fullness in the upper abdomen, upper respiratory tract infections (rhinitis, pharyngitis and sinusitis), indigestion, vomiting*	<ul style="list-style-type: none"> <li>• Hypersensitivity to the active substance or to any of the excipients</li> </ul>
Tamivil	<ul style="list-style-type: none"> <li>• Headaches, dizziness</li> <li>• Abdominal pain</li> <li>• Nausea, vomiting</li> <li>• Insomnia</li> </ul> Rare: cardiac arrhythmias, impaired consciousness, convulsions	<ul style="list-style-type: none"> <li>• Hypersensitivity to the active substance or to any of the excipients</li> </ul>

\* Many of the above adverse effects may also be caused by influenza.

Tab. 8. Adverse effects of and contraindications to oseltamivir<sup>(26–29)</sup>



\* When to make another appointment (alarm symptoms).

Fig. 2. Initial clinical management of influenza-related pneumonia depending on indications and clinical situation<sup>(1)</sup>

- **Pre-exposure prophylaxis** may be used in exceptional situations. It is recommended for children at high risk of complications (e.g. children with immunosuppression), when it is not possible to achieve protection through vaccination<sup>(13)</sup>.

### PREVENTION OF INFLUENZA – VACCINATION

- In September 2023, Polish recommendations for vaccination against influenza were published: *Influenza vaccination of children and adolescents in the 2023–2024 season. Recommendations of the Polish Society of Paediatrics and the National Consultant in Paediatrics (September 2023)*<sup>(43)</sup>.
- Vaccinations are the most effective form of influenza prevention and protection against the severe course and complications of the disease<sup>(1,43)</sup>.
- The efficacy of influenza vaccine depends on how well vaccine strains match viruses circulating in the community in a given season.
- Two types of influenza vaccines are available in Poland in the 2023/2024 season<sup>(43)</sup>:
  - 1) live attenuated influenza vaccine (LAIV4) in the form of a nasal spray – Fluenz Tetra 0.2 mL<sup>(44)</sup>;
  - 2) quadrivalent inactivated vaccine (QIV4) administered intramuscularly: Influvac Tetra 0.5 mL<sup>(45)</sup>, VaxigripTetra 0.5 mL<sup>(46)</sup>.

- The inactivated intramuscular vaccine (QIV4 0.5 mL) is recommended in **children from 6 months to 2 years**.
- Both vaccines (LAIV4 0.2 mL or QIV4 0.5 mL) are recommended for **children aged 3–9 years**. QIV4 0.5 mL is recommended for children in clinical risk group and those who have household contact with an immunocompromised person.
- Two doses of the vaccine at an interval of at least 4 weeks are recommended during the first vaccination season in children **up to 9 years of age**.
- Both vaccines (LAIV4 0.2 mL and QIV4 0.5 mL) are recommended for children and adolescents **from 10 years of age**.
- According to the Polish Society of Paediatrics, the choice of vaccine is made by the doctor, parents/guardians and the child.
- Children at increased risk of influenza complications should be vaccinated (Tab. 2).
- Influenza vaccinations should be recommended in hospital discharge reports or outpatient recommendations for hospitalised children as well as for children under the care of specialist clinics, which will facilitate their implementation in primary health care<sup>(43)</sup>.
- In accordance with global recommendations and clinical trials confirming the efficacy and safety of vaccination in pregnant women, the Polish Society of Paediatrics recommends a single dose of QIV4 in all pregnant women or women planning pregnancy, as well as health care workers. Maternal vaccination protects infants against disease in the first 6 months of life as they receive antibodies that pass through the placenta and are too young to receive the vaccine<sup>(1,16,37)</sup>. Pregnant women can be vaccinated at any time during their pregnancy, and the vaccination is safe for both the mother and the child, also during the breastfeeding period. Furthermore, postpartum women who were not vaccinated during pregnancy should be encouraged to receive a vaccine as soon as possible after giving birth<sup>(1,17)</sup>.
- Effort should be made to vaccinate children as early as possible, preferably by the end of October.

Indications for hospital admission
1. Severe dehydration
2. Severe or rapidly worsening disease
3. Pneumonia in patients at high risk of complications
4. Respiratory failure and hypoxia
5. Cardiopulmonary disorders
6. Consciousness disorders
7. High fever (>39°C), lower body temperature
8. Alarm symptoms (Tab. 4)

Tab. 9. Indications for hospital admission of a patient with influenza<sup>(1)</sup>

- The vaccine may be co-administered with other vaccines (in anatomically distant places), in accordance with the general principles of vaccine co-administration. In the case of medical history of febrile seizures, separate administration of vaccines and/or prophylactic antipyretics may be considered<sup>(1)</sup>.
- According to the AAP recommendation, if LAIV4 is not co-administered with other live vaccines (measles, mumps, rubella, varicella), the live vaccines should be separated by 4 weeks<sup>(37,43)</sup>.
- One dose of the vaccine should provide protection against influenza as soon as 2 weeks after vaccination. This protection lasts for one season.

### Contraindications and precautions

- Anaphylaxis or severe allergic reaction to a previous dose of influenza vaccine is the only **absolute contraindication** to vaccination (with both vaccines).
- Live attenuated influenza vaccine (LAIV4) is additionally contraindicated in children <24 months and in adults >18 years of age, children with severe immune deficiency, children receiving high doses of glucocorticoids, treated with salicylates, pregnant women and people with gelatine allergy.
- Relative contraindications to LAIV4 include asthma in the period of exacerbation and wheezing requiring anti-spasmodics 72 hours before vaccination.
- Mild symptoms of upper airway infection or allergic rhinitis with or without fever are not contraindications to influenza vaccines. Children with moderate-to-severe fever should have their vaccination postponed until the symptoms resolve.
- In the case of absolute contraindications to influenza vaccination (anaphylaxis following previous vaccination), the patient should be informed about the possibility of vaccinating their closest people (family, caregivers) in order to reduce the risk of transmission (cocoon strategy). In the case of relative contraindications, information should be provided about the earliest possible date of vaccination<sup>(16)</sup>.

### Adverse event following immunisation

- Rhinorrhoea, cough and other cold symptoms following vaccination may result from an accidental coincidence with infection caused by completely different viruses or bacteria that often occur in the same period (i.e. in autumn and winter).
- Correct patient qualification for vaccination, which includes an interview and physical examination, as well as determining relative and absolute contraindications to vaccination, significantly reduces the risk of potential adverse events following immunisation (AEFIs).
- Injection-site pain (65%), redness and oedema, which persist for 1–2 days after vaccination, are self-limiting and resolve spontaneously, are the most common **local reactions** following influenza vaccination<sup>(13)</sup>.
- **Generalised reactions** (most often fever, asthenia and myalgia) occur with a similar frequency after

intramuscular administration of influenza vaccines and placebo, more often in children vaccinated for the first time in their life<sup>(1)</sup>. Mild symptoms of upper respiratory tract infection or allergic rhinitis with or without fever are not contraindications to influenza vaccines. Children with moderate-to-severe fever should have their vaccine postponed until the symptoms resolve.

- There was no increased risk of Guillain–Barré syndrome (GBS) following influenza vaccination in children. However, vaccination is not recommended in children who had developed symptoms of GBS within 6 weeks of influenza vaccination in the past, but who are not at high risk of severe influenza and/or its complications<sup>(16)</sup>.

### Vaccination in children with egg allergy

- As with all vaccines, certain vaccine components (e.g. egg white) may cause allergic reactions of varying severity (pruritus, urticaria, angioedema, anaphylaxis)<sup>(1,13)</sup>.
- Qualification for vaccination by a doctor, including medical history of allergic reactions after previous vaccinations, is an important element in minimizing the risk of allergic reaction after vaccination.
- Allergic reaction after vaccination may be local (erythema, swelling and pain) or generalised (urticaria). Anaphylaxis, which is very rare (approximately 1 case per 1 million doses of the vaccine administered), is the most severe allergic reaction following vaccination.
- Anaphylaxis or other serious allergic response to any vaccine component is the only absolute medical contraindication to influenza vaccination<sup>(16)</sup>.
- Children who have previously developed a reaction to any component of the vaccine should be assessed by an allergist to determine whether they should receive another dose.
- If the reaction after previous vaccination was not anaphylactic, vaccination can be performed in accordance with general recommendations; however, special caution and patient monitoring for a specified period of time after vaccination are necessary. Research indicates that patients with egg allergy can safely receive the influenza vaccine with standard precautions as for all vaccines, and that egg allergy, regardless of its severity, is not a contraindication to vaccination<sup>(43)</sup>.
- The standard procedure for vaccinating children against influenza should include medical personnel skills in the field of managing rare acute hypersensitivity reactions.
- Children with egg allergy who receive vaccination against influenza are not at greater risk of a systemic allergic reaction than those without the allergy.

### CONCLUSIONS

1. Influenza is an acute viral disease with high infectiousness and seasonal incidence variability – from local epidemics to general pandemics.

2. Diagnosis is most often clinical; a rapid test detecting the influenza virus may be helpful, but its negative result does not rule out influenza.
3. Oseltamivir is recommended for the treatment and chemoprophylaxis of influenza. Clinical benefits are greatest if treatment is initiated as early as possible, within 48 hours of symptom onset. Clinical trials indicate that early treatment with oseltamivir may reduce both the duration of the disease and the risk of complications.
4. Annual vaccination against influenza remains the most effective way to prevent this disease. Severe anaphylaxis after a previous dose is the only absolute contraindication to vaccination.

### Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

### Author contributions

Original concept of study: AJS, AMM, TJ, JW, EK, ZD. Writing of manuscript: AJS, TJ, JW. Critical review of manuscript: AJS, AMM, TJ, JW, EK, ZD. Final approval of manuscript: AJS, AMM, TJ, JW, EK, ZD.

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