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Received: 13.11.2025
Accepted: 27.11.2025
Published: 13.01.2026

Influenza in the paediatric population in 2024: a single-centre study

Grypa w populacji pediatrycznej w 2024 roku: badanie jednoośrodkowe

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https://doi.org/10.15557/PiMR.2025.0035

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Abstract

Introduction: Influenza remains a significant public health concern in the paediatric population, contributing to substantial morbidity, risk of complications, and burden on healthcare systems both globally and nationally. In Poland, between several hundred thousand and several million influenza cases are reported annually, with a considerable proportion occurring among preschool- and school-aged children. **Objective:** To analyse the incidence, clinical course, and selected laboratory parameters in children diagnosed with influenza in 2024 at the Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine, Warsaw, Poland. **Materials and methods:** A retrospective analysis was conducted on medical records of 166 children aged 6 months to 16 years with laboratory-confirmed influenza. Demographic characteristics, viral type, clinical course, vaccination status, laboratory findings, treatment setting, and therapeutic management were assessed. **Results:** The most frequently affected group comprised preschool-aged children (median age: 4 years; interquartile range, IQR: 2.0–7.0). Influenza type A was the predominant etiological agent (74.1%). Most infections occurred during the winter season (70.5% of cases). Hospitalisation was required in 7.8% of patients, primarily due to persistent fever unresponsive to antipyretic treatment. Household transmission was reported in 19.3% of cases. Influenza vaccination was documented in 18.1% of children. Antibiotic therapy was administered to 15.1% of patients. **Conclusions:** Influenza in 2024 was characterised was characterised by typical seasonality and a predominance of influenza type A virus. Low vaccination coverage among children contributed to viral transmission, increased incidence, and hospitalisations. The findings highlight the need to intensify educational efforts promoting vaccination as a key preventive strategy.

Keywords: epidemiology, influenza, vaccines, infectious disease, vaccine-preventable disease

Streszczenie

Wprowadzenie: Grypa stanowi istotny problem zdrowia publicznego w populacji pediatrycznej, generując znaczną chorobowość, ryzyko powikłań oraz obciążenie systemu opieki zdrowotnej zarówno w skali globalnej, jak i krajowej. W Polsce corocznie rejestruje się od kilkuset tysięcy do kilku milionów przypadków zachorowań, z istotnym udziałem dzieci w wieku przedszkolnym i szkolnym. **Cel pracy:** Analiza częstości zachorowań, przebiegu klinicznego oraz wybranych parametrów laboratoryjnych u dzieci z rozpoznaniem grypy w 2024 roku w Klinice Pediatrii, Nefrologii i Alergologii Dziecięcej Wojskowego Instytutu Medycznego. **Materiał i metody:** Retrospektywnej analizie poddano dokumentację 166 dzieci w wieku od 6. miesiąca do 16. roku życia z potwierdzonym rozpoznaniem grypy. Uwzględniono charakterystykę demograficzną, typ wirusa, przebieg kliniczny, status szczepienia, wyniki badań laboratoryjnych, tryb leczenia oraz stosowaną terapię. **Wyniki:** Najczęściej chorowały dzieci w wieku przedszkolnym (mediana: 4 lata, przedział międzykwartylowy: 2,0–7,0). Grypa typu A była dominującym czynnikiem etiologicznym (74,1%). Zakażenia najczęściej występowały zimą (70,5% przypadków). Hospitalizacji wymagało 7,8% pacjentów, głównie z powodu gorączki niereagującej na leczenie przeciwgorączkowe. Objawy u domowników wystąpiły w 19,3% przypadków. Szczepienie przeciwko grypie odnotowano u 18,1% dzieci. Antybiotykoterapię wdrożono u 15,1% pacjentów. **Wnioski:** Grypa w 2024 roku charakteryzowała się typową sezonowością i dominacją wirusa grypy typu A.

Niska wyszczepialność dzieci sprzyjała transmisji wirusa, zachorowaniom i hospitalizacjom. Wyniki podkreślają potrzebę intensyfikacji działań edukacyjnych w zakresie profilaktyki szczepiennej.

Słowa kluczowe: epidemiologia, grypa, szczepienia, choroby zakaźne, choroby podlegające profilaktyce szczepiennej

INTRODUCTION

Influenza is an acute viral respiratory infection of major epidemiological and clinical importance, representing one of the leading public health concerns worldwide[1,2]. The etiological agents are influenza viruses of types A, B, and C, belonging to the *Orthomyxoviridae* family, with types A and B being primarily responsible for seasonal epidemics[3,4]. Influenza A virus exhibits the greatest pandemic potential due to its ability to undergo antigenic variation, leading to the emergence of new strains and recurrent large-scale epidemic waves[1,3,5,6].

Depending on the epidemic season, between several hundred thousand and several million influenza cases or suspected cases are reported annually in Poland[7]. Data on influenza incidence and influenza-like illnesses are available from the National Institute of Public Health–National Institute of Hygiene–National Research Institute (NIPH–NIH–NRI) (up to the 2022/2023 season)[8], while current surveillance data are accessible via the e-Health platform[9]. According to the Chief Sanitary Inspectorate, over 2 million influenza cases were registered in Poland during the 2024/2025 season[10]. Seasonal epidemics are typically observed between October and April, with peak incidence occurring from January to March[8,10,11]. During peak activity, up to 130,000 new cases per week were reported in Poland[7,9,10]. Analysis of NIPH–NIH data from 2018–2023 demonstrated daily influenza incidence ranging from 10 to 100 cases per 100,000 population, with the highest rates recorded in the 2022/2023 season[8]. Among children under 14 years of age, these cases accounted for approximately 30% of all reported infections[8]. These findings are consistent with data from the European Centre for Disease Prevention and Control (ECDC), which highlight the increasing contribution of paediatric infections to overall influenza morbidity[12].

Influenza transmission occurs primarily via respiratory droplets or direct contact with respiratory secretions of infected individuals[3,13]. The incubation period typically ranges from 1 to 4 days, and viral shedding lasts for approximately 5–7 days after symptom onset, though it may be prolonged in children[3,5,14]. Notably, children may shed the virus before the onset of symptoms, contributing to increased transmission risk[15]. Factors influencing disease severity include age, genetic predisposition, immune status, and excessive neutrophil activation[16,17]. The typical clinical presentation involves an abrupt onset of fever, chills, myalgia, fatigue, dry cough, sore throat, headache, and nasal congestion[3,6]. In children, symptoms are often less specific and may include vomiting, diarrhoea, and neurological manifestations such as febrile seizures[3,6]. In severe cases, influenza may result in pneumonia, myocarditis, encephalopathy, or exacerbation of chronic diseases[2,14,15].

Diagnosis is based on clinical assessment and laboratory confirmation using antigen detection, serological tests, or molecular methods such as reverse transcription polymerase chain reaction (RT-PCR)[4,14,18].

In paediatric patients, early administration of neuraminidase inhibitors such as oseltamivir is recommended, particularly in severe cases, those requiring hospitalisation, or in children with risk factors for complicated disease[6,14,19]. The greatest therapeutic efficacy is observed when antiviral treatment is initiated within 48 hours of symptom onset[6,14]. Supportive care including antipyretics (paracetamol or ibuprofen), adequate hydration, and rest remains the cornerstone of management for most patients[14]. In cases of suspected bacterial superinfection, antibiotic therapy may be justified; however, empirical use should be guided by clinical indications[2,14].

From a public health perspective, prevention particularly vaccination plays a crucial role, representing the most effective strategy for reducing influenza incidence and preventing complications[20,21]. Despite recommendations from the World Health Organization (WHO) and ECDC advocating annual influenza vaccination and the availability of effective vaccines, vaccination coverage among children remains low[20,21].

According to the 2025 report of the National Program for the Control of Infectious Diseases, during the 2024/2025 influenza season in Poland, over 2 million cases were reported, including 25,000 hospitalisations and nearly 1,000 deaths, predominantly among elderly individuals[22]. Vaccination coverage in children under 5 years of age was only 2%, and 1.9% among those aged 5–14 years[22].

Children, especially those attending preschool and primary school, play a key role in influenza transmission due to frequent social contact, underdeveloped hygiene habits, and lack of prior immunity[23]. Additionally, influenza-related complications in children contribute substantially to both direct and indirect healthcare costs. These include prolonged hospitalisations, increased healthcare expenditures, and indirect economic losses such as parental work absenteeism and reduced productivity[2].

Historically, influenza has caused multiple global pandemics associated with high mortality, including the "Spanish flu" (1918–1919), "Asian flu" (1957–1958), "Hong Kong flu" (1968–1969), and the A/H1N1 pandemic in 2009[5,24,25]. In this context, local analyses encompassing hospitalised and ambulatory paediatric cases provide valuable

 DOI: 10.15557/PiMR.2025.0035

epidemiological and clinical insights. Such studies facilitate identification of trends in incidence, clinical presentation, therapeutic efficacy, and the impact of local factors including vaccination coverage and healthcare accessibility on the course of seasonal influenza epidemics.

OBJECTIVE

The objective of this study was to analyse influenza cases in the Department of Paediatrics, Paediatric Nephrology and Allergology of the Military Institute of Medicine in 2024, with respect to incidence, clinical characteristics, epidemiological aspects (seasonality and occurrence of symptoms among household contacts), and therapeutic management (outpatient versus inpatient treatment, and antibiotic therapy). The findings of this study aim to improve understanding of the local dynamics of influenza infections within the paediatric population.

MATERIALS AND METHODS

This study was designed as a retrospective analysis of medical records of children presenting to the Emergency Department of the Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine, Warsaw, between January 2024 and December 2024, with a diagnosis of influenza. A total of 166 patients aged 6 months to 16 years were included.

Cases were eligible for inclusion if influenza was documented as a primary or secondary diagnosis (ICD-10 codes: J10.0, J10.1, J10.8, J11.0, J11.1, J11.8). Diagnosis was established based on clinical presentation and confirmed by diagnostic testing. Only patients with laboratory-confirmed influenza were included in the analysis. Cases presenting with typical influenza-like symptoms, but negative virological test results were excluded.

The following parameters were analysed: patient age and sex, influenza virus type, fever characteristics, presence of symptoms among household contacts, influenza vaccination status, mode of treatment (outpatient or inpatient), selected laboratory parameters (complete blood count, C-reactive protein – CRP, erythrocyte sedimentation rate – ESR), and the need for antibiotic therapy.

Statistical methods

Statistical analysis was performed using SPSS Statistics for Windows, version 29.0.0.0 (IBM Corp., New York, USA). Prior to analysis, data distribution was initially assessed visually using normality plots and subsequently verified with the Kolmogorov–Smirnov and Lilliefors tests.

Given that several variables did not follow a normal distribution, non-parametric tests not requiring distributional assumptions were applied for those cases. For variables with a normal distribution, comparisons were conducted using the Student's *t*-test.

Correlations between continuous variables were evaluated using Pearson's linear correlation coefficient. A p value <0.05 was considered statistically significant.

RESULTS

In 2024 a total of 166 paediatric patients with a diagnosis of influenza were admitted to the Emergency Department of the Department of Paediatrics, Paediatric Nephrology and Allergology at the Military Institute of Medicine. The patients' ages ranged from 6 months to 16 years, with a median age of 4 years (interquartile range, IQR: 2.0–7.0). Girls constituted 50.6% (n = 84) of the study group, while boys accounted for 49.4% (n = 82). A detailed overview of the study population is presented in Tab. 1.

The highest incidence of influenza was observed during the winter months, with 117 patients (70.5%) presenting during this season. In contrast, 35 children (21.1%) fell ill in spring, 8 (4.8%) in autumn, and only 6 (3.6%) in summer. These findings confirm the typical seasonality of influenza in temperate climates, with a distinct peak during winter months (Fig. 1).

Analysis of influenza cases reported between 2020 and 2024 demonstrated the highest incidence in 2022 (547 cases). Comparable numbers were noted in 2020 (386 cases) and 2023 (396 cases), while considerably fewer cases were recorded in 2021 (151 cases) and 2024 (166 cases). These results illustrate clear year-to-year variability, with a marked increase in cases during 2021–2022 followed by a decline in subsequent seasons (Fig. 2).

In the study cohort, influenza type A infections predominated, accounting for 74.1% (n = 123) of all cases. Influenza type B infections were observed in 12.6% (n = 21), while mixed A + B infections occurred in 13.25% (n = 22) (Fig. 3).

Variable	Value
Age [years]; median (IQR)	4.0 (2.0–7.0)
Sex; n (%): • Female • Male	 84 (50.6) 82 (49.4)
Influenza type; *n* (%): • Type A • Type B • A + B coinfection	 123 (74.1) 21 (12.6) 22 (13.25)
Maximum body temperature [°C]; median (IQR)	39.0 (38.22–39.60)
Duration of fever [days]; median (IQR)	2.35 (1.00–3.00)
Household symptoms; *n* (%)	32 (19.3)
Influenza vaccination; *n* (%)	30 (18.1)
Mode of treatment; *n* (%): • Outpatient • Hospitalisation	 153 (92.2) 13 (7.8)
WBC [$\times 10^9$/L]; median (IQR)	9.19 (5.71–12.50)
CRP [mg/dL]; median (IQR)	0.9 (0.3–3.2)
ESR [mm/h]; median (IQR)	13.0 (9.00–74.00)
Antibiotic therapy; *n* (%)	25 (15.1)
IQR – interquartile range; ***n*** – number of cases.	

Tab. 1. Characteristics of the study population

DOI: 10.15557/PiMR.2025.0035

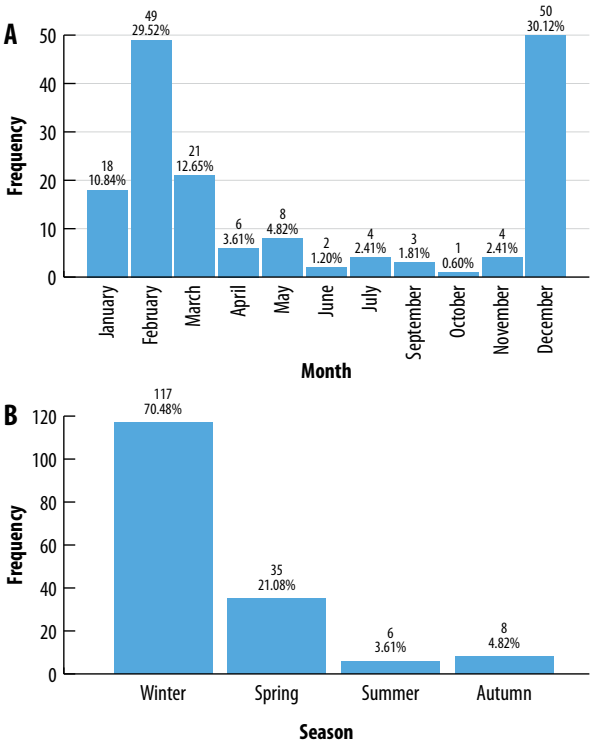

*Fig. 1. Distribution of paediatric influenza cases by month (**A**) and season (**B**) during the 2024 epidemic season*

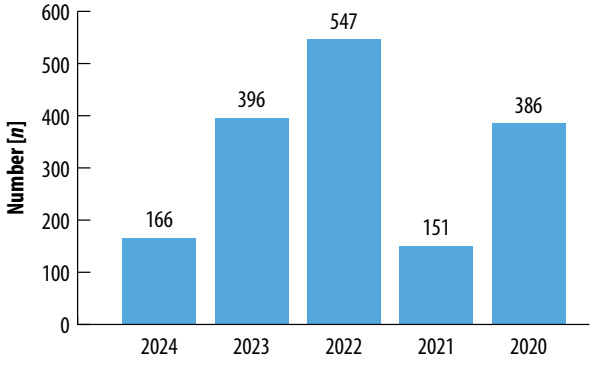

Fig. 2. Influenza cases in paediatric patients at the Department of Paediatrics, Paediatric Nephrology and Allergology between 2020 and 2024

Fever was the principal symptom, occurring in 100% of patients. The median maximum temperature was 39.0°C (IQR: 38.22–39.60), and the median duration of fever was 2.35 days (IQR: 1.00–3.00), with the longest recorded duration being 7 days.

In the majority of cases (79%, n = 131), no influenza-like symptoms were reported among household members. Symptoms among family contacts were noted in 32 children (19.3%).

Of all patients, 81% (n = 135/165) were unvaccinated against influenza in the preceding season.

Among the vaccinated cohort, only one patient required hospitalisation, antibiotic therapy was indicated in four cases while the majority experienced a mild clinical course.

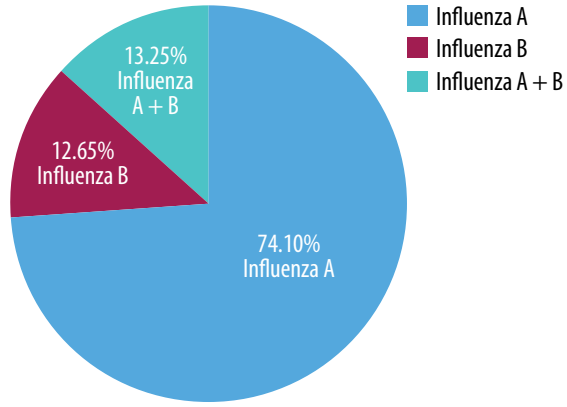

Fig. 3. Serological distribution of influenza virus types in 2024

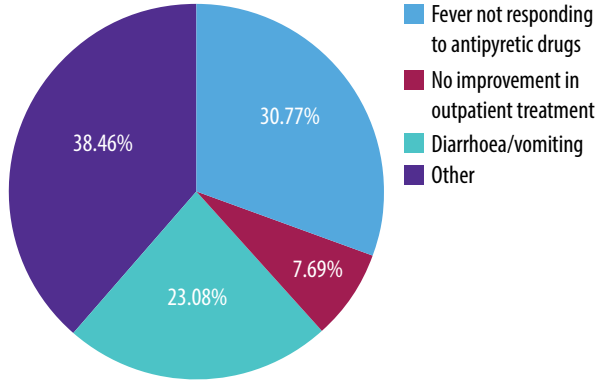

Fig. 4. Causes of hospitalisation due to influenza

The vast majority (92%, n = 153) were treated on an outpatient basis, while 13 patients (7.8%) required hospitalisation. The most frequent indication for hospitalisation was persistent fever unresponsive to antipyretics (30.8% of all hospitalisations). Other reasons included lack of improvement under outpatient care (7.7%, n = 1) and gastrointestinal symptoms (23.1%, n = 3). No febrile seizures were recorded in any child (Fig. 4).

In medically justified cases, blood samples were collected to assess inflammatory markers. Additional laboratory tests, complete blood count (CBC) with differential, CRP, and/or ESR, were performed in 35 patients (22.9%).

The median CRP level was 0.9 mg/dL (IQR: 0.3–3.2), with a maximum of 26 mg/dL. The median leukocyte count was 9.19×10^9/L (IQR: 5.71–12.50), with the highest value reaching 39.8×10^9/L. The median ESR was 13.0 mm/h (IQR: 9.00–74.00), and the maximum recorded value was 83 mm/h.

Antibiotic therapy was administered to 25 patients (15.1%), primarily due to suspected bacterial superinfections. The most commonly used antibiotic was amoxicillin with clavulanic acid, prescribed in 44% (n = 11) of treated cases (Fig. 5).

DISCUSSION

The results of the present study conducted at the Department of Paediatrics, Paediatric Nephrology and Allergology of the

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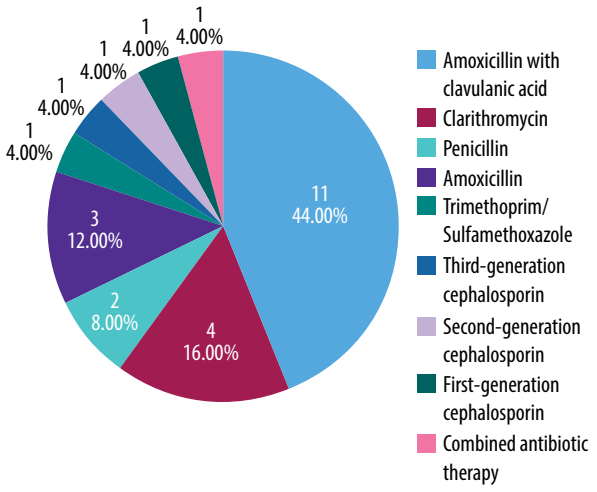

Fig. 5. Antibiotics used in cases of suspected bacterial coinfection during influenza

Military Institute of Medicine in 2024 confirm that influenza remains a major public health concern in the paediatric population. These findings are consistent with national epidemiological trends for recent influenza seasons in Poland[26]. A typical temperate-climate seasonality pattern was observed, with a distinct peak during the winter months, which aligns with data reported by the National Institute of Public Health and the European Centre for Disease Prevention and Control (ECDC)[8,9].

In the analysed period, 70.5% of all cases occurred during the winter season, reflecting the classic pattern of seasonal influenza epidemics in Poland. The results correspond with national and European observations, indicating that the 2024 influenza season was milder compared to preceding years. According to the ECDC data for the 2023–2024 season, viral activity was shorter than in 2022–2023; the proportion of positive samples exceeded 10% for 15 weeks, peaking at 39% in week 52 of 2023, and the season ended by week 12 of 2024[12]. Our findings mirror this trend, showing a decline in the number of cases following the intense 2022–2023 seasons. National surveillance data (NIZP–PZH) confirm that the 2024 season was less severe than the record 2022/2023 period, likely reflecting natural epidemic cycles and increased population immunity after previous waves.

In the present cohort, influenza type A infections predominated (74.1%), consistent with data from the SENTINEL surveillance system, where type A viruses accounted for most confirmed cases in the 2023/2024 season[22,26]. During that season, A(H1N1) pdm09 was the dominant subtype, while influenza B infections increased from week 13 of 2024 onwards[12]. Most circulating genotypes matched the vaccine strains, although some A(H3N2) viruses exhibited antigenic drift[12]. Preliminary estimates indicated vaccine effectiveness of 51% in primary care and 38% in hospitalised patients[12]. Furthermore, an increased proportion of A(H1N1) pdm09 and B/Victoria viruses with reduced oseltamivir susceptibility was observed compared with the 2022–2023 season[12].

Influenza A virus possesses greater epidemic and pandemic potential than type B due to its capacity for antigenic shift and drift in surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) facilitating the emergence of novel variants[1,25]. International studies have demonstrated that type A infections are associated with more severe clinical courses and a higher risk of hospitalisation than type B infections[27]. In our cohort, 7.8% of children required hospitalisation, most of whom were infected with type A virus. Literature data indicate that hospitalisation rates are higher among Black, Hispanic, and Asian children[16].

Between 2017 and 2022, the proportion of influenza-positive paediatric tests ranged from 3.03% to 25.71%, with a clear age-dependent increase: 23.23% in children >6 years compared with 7.54% in those <3 years and 13.18% in the 3–6-year group[17,28]. Studies from China (Zhengzhou, 2018–2023) reported a post-COVID-19 surge in influenza incidence among children, accompanied by an age shift toward older groups and a decrease in hospitalisation rates[29]. Global analyses suggest that pandemic-related restrictions substantially altered influenza dynamics, leading to shifts in epidemic peaks and reorganisation of circulation patterns[30]. This underscores the need for adaptive vaccination strategies and flexible surveillance systems responsive to evolving epidemiological contexts[30].

The age distribution in our study (median: 4 years) confirms that preschool-aged children are at highest risk for influenza infection, consistent with national and international reports[3,15,31]. This vulnerability is attributed to immature immune systems and high exposure in group settings such as kindergartens[3,15]. Household transmission was reported in 19.3% of cases, emphasising the strong infectious potential of paediatric cases and their role as key drivers of community spread. According to Tsang et al., the secondary attack rate within households may reach 38%, with a mean serial interval of approximately three days[32]. Children, who shed the virus for longer periods, represent a critical link in sustaining influenza circulation.

A persistently low vaccination rate remains a major concern. In the present study, only 18.1% of children were vaccinated against influenza, while nationwide coverage in the paediatric population remains below 10%[33]. Low vaccination uptake undermines herd protection and facilitates sustained viral transmission in schools and households.

The hospitalisation rate observed (7.8%) was lower than that reported in many European studies, suggesting a milder clinical course during the 2024 season. For comparison, in an Italian analysis of ten influenza seasons (2010–2020), approximately 50% of children presenting to the emergency department were admitted, though only 1.25% of all influenza cases required hospitalisation[31]. In a Polish study by Kanecki et al. (2015–2019), the hospitalisation rate for children under 5 years with laboratory-confirmed influenza was 0.09%[34,35]. Such discrepancies may reflect differences in hospitalisation criteria, demographic structure, and vaccination coverage. Among the vaccinated cohort, only

DOI: 10.15557/PiMR.2025.0035

a single patient required hospitalisation, while the majority experienced a mild clinical course; antibiotic therapy was indicated in four cases.

Globally, influenza accounts for approximately 7% of acute lower respiratory infections in children under five years and 5% of related hospitalisations[17,34]. A recent Polish retrospective analysis of hospitalised children with influenza (2023/2024) highlighted the importance of early diagnosis and targeted therapeutic interventions[6]. In our cohort, the most common reasons for admission were persistent fever refractory to antipyretic therapy (30.8%) and gastrointestinal symptoms (23.1%), differing somewhat from previous Polish studies. According to Wrotek et al., pneumonia (31%) and bronchiolitis (23%) were the leading complications among hospitalised children[2], whereas Angiel et al. reported pneumonia (22%) and acute otitis media (8%)[6].

Antibiotic therapy was administered to 15.1% of patients, primarily for suspected bacterial coinfections, with amoxicillin-clavulanate being the most commonly prescribed agent (44%). This aligns with current clinical guidelines emphasising antimicrobial stewardship and restricting antibiotics to cases with clear bacterial indications. In contrast, Schober et al. reported antibiotic use in 71.6% of hospitalised paediatric influenza cases, most often amoxicillin[36]. Angiel et al. found that 32% of patients received antibiotics, with 44% treated with amoxicillin-clavulanate[6].

In the analysed cohort, a subset of patients exhibited elevated inflammatory biomarkers, a finding consistent with the presence of bacterial superinfection. Nevertheless, evidence from the literature indicates that the overall incidence of bacterial superinfections in paediatric influenza remains relatively low and varies according to patient population and disease severity. In a study of children hospitalised with laboratory-confirmed influenza during the 2022–2023 season, conducted by Merişescu et al., secondary bacterial infections were identified in approximately 11.96% of patients, with *Staphylococcus aureus*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* constituting the most frequently isolated pathogens[37]. These observations reinforce current recommendations advocating for the judicious use of antibiotic therapy, restricting it to cases with clear and well-substantiated clinical indications.

From a public health perspective, our findings underscore the urgent need to increase paediatric vaccination coverage and strengthen influenza surveillance systems[30]. Educational programs targeting parents and caregivers promoting annual vaccination and appropriate management of influenza symptoms may significantly reduce community transmission. In the 2024/2025 season, the reimbursement policy for influenza vaccination in Poland was expanded, providing free vaccines for children aged 6 months to 18 years, adults ≥65 years, and pregnant or postpartum women[7]. A modelling study from Germany estimated that vaccinating 60% of children aged 0.5–17 years could reduce overall influenza incidence in the general population by approximately 34%[38]. These findings highlight not only the direct benefit of vaccination (protection of immunised children) but also a substantial indirect effect, namely reduced viral transmission, providing a strong rationale for the expansion of paediatric influenza vaccination within public health programs[38]. Further prospective studies, incorporating analyses of sociodemographic determinants of influenza seasonality, are warranted to more accurately assess epidemic dynamics and the effectiveness of implemented interventions.

In summary, the present study confirms that influenza in the Polish paediatric population maintains typical clinical and epidemiological characteristics: predominance of type A infections, marked seasonality, and a low hospitalisation rate. The persistently low vaccination coverage remains the greatest challenge, limiting preventive effectiveness. Optimisation of diagnostic, therapeutic, and preventive strategies should be a national health priority, with particular emphasis on children as a key reservoir of viral transmission. In clinical practice, expanding access to rapid molecular diagnostics, strengthening epidemiological surveillance, and implementing educational interventions for parents are essential. Although the study was retrospective and limited to a single-centre population, its findings contribute valuable insight into the local epidemiology of paediatric influenza. The analysis covers a calendar year rather than an epidemiological season, as is commonly reported in the literature, which limits direct comparability with other studies. Further multicentre, prospective studies incorporating molecular surveillance are warranted to comprehensively characterize influenza dynamics in children.

CONCLUSIONS

Influenza remains a significant public health issue in the paediatric population in Poland, characterised by typical temperate-climate seasonality and predominance of type A infections. Preschool-aged children are at the highest risk, although the clinical course is usually mild.

The persistently low vaccination coverage limits the effectiveness of preventive measures and facilitates ongoing transmission. Strengthening vaccination programs, enhancing public health education, and improving epidemiological surveillance are therefore essential.

Future multicentre studies are warranted to better elucidate influenza epidemic dynamics in the paediatric population and to develop more effective preventive and therapeutic strategies.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: AZ, AT. Collection, recording and/or compilation of data: MZS, JŚ, NS. Analysis and interpretation of data: AZ, NG. Writing of manuscript: AZ, MZS, NG. Critical review of manuscript; final approval of manuscript: AT, BK.

 DOI: 10.15557/PiMR.2025.0035

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DOI: 10.15557/PiMR.2025.0035