Thesis

Epidemiology, risk factors and clinical features of severe pediatric influenza

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Berlin, 11.01.2026 Magdalena Scherrer m.p.

Zusammenfassung

Einleitung

Vor der SARS-CoV-2 Pandemie erkrankten jedes Jahr rund 5-15% der österreichischen Bevölkerung an der saisonalen Influenza. Besonders Kinder unter 5 Jahren und Kinder mit Vorerkrankungen haben ein erhöhtes Risiko für einen schweren Verlauf mit der Notwendigkeit einer stationären oder auch intensivmedizinischen Behandlung.

Patienten und Methoden

Über das elektronische Krankenhausinformationssystem des LKH-Universitätsklinikum Graz wurden alle Patient*innen mit ICD Diagnosen J09, J10 oder J11 der Intensivstation der Universitätsklinik für Kinder- und Jugendheilkunde Graz von 2005-2020 detektiert und zur retrospektiven Datenanalyse herangezogen. Es wurden Daten zu Alter, Geschlecht, Aufenthaltsdauer, Vorerkrankungen, Influenza Typ und Impfstatus erhoben und analysiert.

Ergebnisse

Insgesamt wurden im Untersuchungszeitraum 57 Patient*innen von 0-18 Jahren mit oder wegen einer Influenzainfektion intensivmedizinisch behandelt (33/57, 58% männlich). Bei 42/57 (74%) Patient*innen wurde die Influenza-Infektion als Hauptdiagnose zur stationären Aufnahme gelistet.
Im Untersuchungszeitraum gab es im Median 2 Fälle pro Saison, die meisten Patient*innen wurden in der Saison 2019/20 betreut (12/57, 21,06%). Die mediane Aufenthaltsdauer auf der Intensivstation betrug 3 Tage (IQR 4 Tage).
Das mediane Alter zum Zeitpunkt der Aufnahme auf die Intensivstation betrug 3 Jahre (IQR 7,0 Jahre, Range: 14 Tage-16 Jahre)
Influenza A war deutlich vorherrschend mit Nachweis bei 47/57 (82,46%) Patient*innen, Influenza B bei 7/57 (12,28%) und Influenza A und B Doppelinfektion bei 3/57 (5,26%) Patient*innen.
Bei 31 (54,39%) Patient*innen waren schwerwiegende Vorerkrankungen bekannt, wobei vor allem neurologische Grunderkrankungen vorherrschend waren. Von 28/57 (49,12%) dokumentierten Impfstatus war kein positiver Influenza-Impfstatus

vermerkt. Drei Patient*innen (5,26%) sind in den analysierten 15 Jahren auf der Intensivstation im Rahmen einer Influenza-Infektion verstorben.

Schlussfolgerung/Diskussion

Schwere intensivpflichtige oder auch tödliche Influenza–Infektionen betreffen sowohl Patient*innen mit als auch ohne Vorerkrankungen, wobei neurologische Grunderkrankungen am häufigsten beobachtet wurden. Intensivmedizinisch behandelte Kinder und Jugendliche sind vorwiegend ungeimpft. Unsere Daten zeigen, dass Influenza auch bei Kindern und Jugendlichen ohne Vorerkrankungen eine bedrohliche Erkrankung darstellen kann.

Abstract

Introduction

Before the SARS-CoV-2 pandemic, around 5-15% of the Austrian population contracted seasonal influenza each year. Children under the age of 5 and children with previous illnesses in particular have an increased risk of a severe course with the need for hospitalisation or intensive medical treatment.

Patients and Methods

All patients with ICD diagnoses J09, J10 or J11 in the intensive care unit of the University Clinic for Paediatrics and Adolescent Medicine Graz from 2005-2020 were detected via the electronic hospital information system of Graz University Hospital and used for retrospective data analysis. Data on age, gender, length of stay, previous illnesses, influenza type and vaccination status were collected and analysed.

Results

A total of 57 patients aged 0-18 were treated in intensive care with or because of an influenza infection during the study period (33/57, 58% male). In 42/57 (74%) patients, influenza infection was listed as the main diagnosis for inpatient admission.

During the study period, there was a median of 2 cases per season, with most patients being treated in the 2019/20 season (12/57, 21.06%). The median length of stay in the intensive care unit was 3 days (IQR 4 days).

The median age at the time of admission to the ICU was 3 years (IQR 7.0 years, range: 14 days-16 years)

Influenza A was clearly predominant with detection in 47/57 (82.46%) patients, influenza B in 7/57 (12.28%) and influenza A and B double infection in 3/57 (5.26%) patients.

In 31 (54.39%) patients, serious pre-existing illnesses were known, with underlying neurological diseases predominating. Of 28/57 (49.12%) documented vaccination statuses, no positive influenza vaccination status was recorded. Three patients (5.26%) died in the intensive care unit as a result of an influenza infection during the 15 years analysed.

Discussion

Severe influenza infections requiring intensive care or even fatal influenza infections affect both patients with and without previous illnesses, with underlying neurological diseases being observed most frequently. Children and adolescents in intensive care are predominantly unvaccinated. Our data highlight the importance of health measures, including vaccination, for both children and adolescents with pre-existing conditions and those who are otherwise healthy.

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List of abbreviations

HA *Hemagglutinin*

IAV *Influenza A Virus*

IBV *Influenza B Virus*

NA *Neuraminidase*

NAAT *nucleic acid amplification testing*

NIH *National Institutes of Health*

PCR *Polymerase chain reaction*

PEG *Percutaneous Endoscopic Gastrostomy*

RNA *Ribonucleic acid*

RSV *Respiratory Syncytial Virus*

Sars-CoV-2 *severe acute respiratory syndrome coronavirus 2*

WHO *World health organization*

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1 Introduction

1.1 Influenza Virus

Influenza viruses are part of the *Orthomyxoviridae* family and contain a segmented, negative stranded RNA as their genetic information.
Based on their immunological and biological properties four different groups can be distinguished: Influenza A, B, C and D. Out of these four groups just Influenza A – C infect humans, type D just infects cattle and pigs, therefore this type won't be discussed in this dissertation [1].

Seasonal influenza epidemics are mainly caused by Influenza A and B, whereas Influenza C is less pathogenic and mainly provokes mild respiratory symptoms [2]. Influenza A is most common during the flu season and Influenza B tends to cause smaller localized outbreaks [3,4]

The virion of Influenza A (IAV) and B Virus (IBV) encloses eight negative-sense RNA-segments, Influenza C (ICV) has only seven segments.
IAV can be classified based on their transmembrane glycoproteins hemagglutinin (HA) and neuraminidase (NA). Except for one protein the same proteins as in IAV can be found in IVB, but the surface glycoprotein NB occurs additional in IVB and is unique for it. The viral envelope of ICV does not consist of HA and NA but it carries the glycoprotein haemagglutinin-esterasefusion combining the function of HA and NA in one [1].

To infect a host the influenza virus must attach to the host cell and penetrate its membrane. HA is responsible for binding to the surface receptors and penetration into the cell. The primary binding site for HA is found in the respiratory tract, especially respiratory epithelium and type II alveolar epithelial cells. However, human influenza viruses demonstrate a preference for binding to cells in the upper respiratory tract. NA, on the other hand is responsible for virus replication and allows the virus to exit the host cell [5,6].
Furthermore, HA and NA are the main point of attack for neutralising antibodies [6].

1.1.1 Influenza A Virus

Influenza virus A is primarily responsible for infections during the flu season. As mentioned above it is possible to categorize the virus based on HA and NA. Until now, it was possible to detect 18 antigenic variations of HA and 11 antigenic variations of NA: H1-16 and N1-9 are found naturally in aquatic birds, while H17N10 and H18N11 are found naturally in bats. At present, only H1N1 and H3N2 are known to be endemic in humans [7]. The A(H1N1) strain is also referred to as A(H1N1)pdm09, as it led to the global pandemic in 2009. The previous A(H1N1) virus, which had circulated prior to 2009, was replaced [8].

Influenza A virus has the capacity to modify its molecular structure through antigenic shift and drift.
Antigenic drift is defined as the ongoing accumulation of point mutations in the viral HA and NA genes. This results in minor mutations to the viral surface proteins. These alterations are a continuous process. It is known that both HA and NA act as antigens and are recognized by the immune system. This means that mutations can prevent previously formed antibodies from binding to the virus leading to a reduced immune protection. This antigenic drift is a critical factor explaining why individuals can contract influenza on multiple occasions throughout their lives [9,10].

Antigenic shift is characterized by an abrupt major mutation that results in the formation of new HA or HA and NA proteins. Such instances are infrequent, occurring most often when an influenza virus that initially infected an animal subsequently transmits to humans. Therefore, most individuals have no immunity against this new virus, which can result in the outbreak of pandemics [9].

1.1.2 Influenza Virus B

Humans serve as the primary host reservoir for Influenza B virus. Moreover, in rare cases pigs and seals can get infected as well [11].

Like the influenza A virus, the influenza B virus changes its structure through antigen drift [12]. But in contrast to Influenza A virus, there are no subtypes of Influenza B virus [5]. Before the Covid-19 pandemic two genetically different lines circulated worldwide: Yamagata lineage and Victoria lineage [13]. As a result of pandemic measures the B/Yamagata line may now be extinct, as no naturally occurring cases have been confirmed since March 2020. This potential extinction has led to changes in vaccine composition recommendations: using a trivalent vaccine in the 2024 southern hemisphere influenza season instead of a quadrivalent one. However, ongoing surveillance is necessary to confirm this conclusion fully, as previous interruptions in the circulation of Influenza B virus have been noted [14,15].

Due to the limited host range and slower mutation rate, Influenza B causes epidemics and does not lead to pandemics. Nevertheless, it is widely recognized that Influenza B virus can cause substantial illness and death worldwide, with an increased incidence in children and adolescents [11,16].

1.1.3 Influenza Virus C

Although Virus C infect humans in the first instance it can also infect some animals, such as swine or dogs. Serological studies have revealed that the virus is widely distributed across the world, and most individuals develop antibodies against the virus at a young age. Therefore, the infection is limited to sporadic cases or minor localized outbreaks and the symptoms are usually mild. Rarely it can lead to bronchitis or pneumonia, especially in young children (< 2 years) [11,17,18].

1.2 Epidemiology

Influenza occurs all over the world and manifests as pandemics, epidemics, outbreaks, or isolated cases. Seasonal epidemics typically occur during winter in temperate regions of both hemispheres, while in tropical regions, flu outbreaks can happen throughout the year. In these regions, there may be undulations over the course of the year [13].

The World Health Organization (WHO) estimates that annual flu epidemics cause around 4 million severe infections and roughly 500,000 deaths worldwide each year. The epidemiology of influenza reflects the virus's ability to change its antigenic properties, resulting in new strains. An antigenic shift involves major, rapid changes in surface proteins, especially the HA of Influenza A, resulting from genetic exchanges between animal and human strains. Although rare, antigenic shifts can lead to pandemics. Antigenic drift, on the other hand, involves smaller changes in the virus's HA or NA proteins and is often linked to localized outbreaks. In the case of Influenza B, only HA drifts have been identified [5].

Birds are a crucial reservoir for the influenza virus, with avian strains like H5, H7, and H9 causing outbreaks in humans. Of these, H5N1 is especially deadly, with a mortality rate of around 50%, leading to numerous hospitalizations. In 2013, the novel H7N9 virus emerged, causing 36 human deaths despite being less pathogenic in birds. Due to its rapid transmission potential, H7N9 is considered a future threat to human health, underscoring the need for continued vigilance [5].

Furthermore, species-specific influenza A viruses also circulate in pigs, dogs, and horses. Diseases in humans caused by non-human influenza viruses without sustained human-to-human transmission, are classified as zoonoses. Novel human influenza viruses can arise through adaptation of a zoonotic influenza virus to humans or through a combination of zoonotic and human influenza viruses. If a new pathogenic influenza virus emerges, which is continuously transmissible from person to person and there is no or only very limited immunity in the population, an influenza pandemic can result. The aim of influenza pandemic planning is to prepare for and manage such an event [13].

1.2.1 Seasonal Influenza

The seasonal pattern of influenza infections shows great variability in terms of severity and mortality for every season. While influenza can affect people of all ages, young children and older people account for the largest proportion of hospital admissions due to the virus [19].

Almost every year, Austria experiences a flu epidemic during the autumn and winter months, with 5-15% of the population becoming infected, many of them fall ill. Annually, approximately 1,000 people in Austria die from influenza virus infections. During the 2017/2018 flu season, nine children were confirmed to have died from the flu, and in the 2018/2019 season, there were at least five confirmed child deaths due to influenza [20].

However, in the 2020/2021 season, the anticipated flu wave did not occur, largely due to contact-reducing measures and mask-wearing. Looking ahead to the 2022/23 season, where these preventive measures were not used as extensively or at all, there was a significant rise in flu activity. This increase could result from unrestrained transmission of the virus and a higher proportion of people who have not recently been exposed to influenza viruses [21].

1.2.2 Influenza Pandemics

An influenza pandemic is a global epidemic caused by a new, non-seasonal influenza virus. The new strain must be pathogenic to humans and capable of efficient person-to-person transmission. Since the virus is novel, there is little or no population immunity, which means it can spread rapidly around the world. The severity of the pandemic, i.e. the number of people who fall ill and die, is difficult to predict. It is possible that there will be significant variations in terms of its temporal and regional progression, as well as in comparison with previous pandemics [19].

To date, there have been four major pandemics for which there is documented data: The following periods have been identified: 1918/1919, 1957/1958, 1968/1969 and 2009/2010. It is observed that all these pandemics occurred in at least two waves outside the usual influenza season. Children have been demonstrated to play a significant role in the transmission of both pandemic and seasonal influenza viruses. This phenomenon is further elaborated in section

1.3.1. The pandemics differ greatly in terms of morbidity and mortality and are explained in more detail in the following sections [19].

1.2.2.1 1919/1918: Spanish Flu

The 'Spanish Flu', a major pandemic of influenza A H1N1 virus origin, took place in 1918 and is regarded as the most significant influenza pandemic until the present day. To date, the scientific community has been unable to determine the origin of the virus. Furthermore, no mutations have been identified that could account for its high degree of pathogenicity. It is assumed that the original 1918 virus serves as the ancestor of today's human-pathogenic and some swine-pathogenic influenza viruses [22].

The data indicates that the outbreak manifested in three distinct waves, with the incidence rate within the 15-64 age range decreasing from 43% to 29% in each cycle. The mortality rate increased from 0.7% in the initial phase to 3.3% and 2.7%, emphasizing the severity of the situation. The total number of people who died from the Spanish flu worldwide was approximately 50 million. A significant proportion of the fatalities were due to pneumonia, which was often the result of bacterial superinfection. At that time, there was no specific treatment for these [19].

1.2.2.2 1957/1958: Asian Flu

The 1957 influenza pandemic, triggered by the influenza virus A H2N2, spread from China to the rest of the world. The pandemic also manifested in multiple waves, with the infection rate in the initial wave estimated at 31%. On a global scale, the disaster resulted in the death of over one million individuals [19,23].

1.2.2.3 1968/1969: Hongkong Flu

The subsequent pandemic was caused by the influenza A virus H3N2 and spread from Hong Kong. The virus then spread rapidly to India and Australia, after which the spread of the pandemic slowed down. The disease also manifested in waves. The infection rate increased from 6% in the first wave to 21% in the second. The duration of the pandemic was a period of over three years, with a mortality rate ranging from 1 to 4 million cases reported on a global scale [19,23,24].

1.2.2.4 2009/2010: Swine Flu

The 2009 pandemic was also caused by an influenza A H1N1 virus, but it was a completely new H1N1 virus. It consisted of a combination of human, swine and avian genomes. This is the reason why it was able to cause another pandemic. The pandemic was characterized by three distinct waves, with children and young adults being most affected. The case fatality rate was approximately 0.4%.
Since 2010, the H1N1pdm09 virus has been circulating seasonally and has replaced the original H1N1 virus [19,25].

1.3 Transmission

The success of influenza viruses in spreading among people is largely due to their efficient transmission. There are three recognized modes of influenza transmission: aerosol, droplet, and contact transmission [2,26].

When an infected individual who sneezes, coughs or speaks, they release infectious particles ranging from 0.1 µm to 100 µm in size. Fine particles (aerosols) and droplet nuclei, which are created when larger droplets dry quickly, are smaller than 5 µm and primarily occur during activities such as singing, shouting and specific medical procedures. Aerosols can remain suspended in the air for minutes to hours. However, they are easily affected by changes in temperature and humidity.
These particles can be inhaled and deposited in either the upper or lower respiratory tract. Larger droplets typically settle closer to the infected individual or on surfaces in the environment within 2 to 3 meters [2,26].

Transmission through contact with contaminated surfaces to mucous membranes is also possible. While the virus remains infectious for a short period on hands, it can survive on non-porous surfaces for up to 48 hours [2,26].

To break through these transmission routes, it is essential to cover the nose and mouth when sneezing and coughing and to clean hands regularly with soap or alcohol-based hand sanitizer [27].

1.3.1 Transmission in Children

Children, particularly those of elementary school age and younger, are considered primary drivers of influenza transmission within communities. While adults may spread the flu across different geographic areas due to frequent travel, children are believed to be the main facilitators of flu spread within a community [28].

Several factors contribute to the significant role children play in flu transmission. Every year, the influenza strain is new to infants because they lack their own protective antibodies. Maternal antibodies provide protection only for the first few months of life. Therefore, primary infections occur more likely in early childhood and they the virus for a longer period of time than adults [29].

Preschool and school-age children are not only more likely to become infected but are also more prone to spreading the virus to others in their households. Their frequent close contact with peers in settings like schools and daycare centers, combined with behaviors such as poor hand hygiene and frequent touching of the face, creates an environment for rapid virus spread. These social behaviors, along with biological factors, make children key vectors for the flu [28].

1.4 Clinical presentation

After exposure to an influenza virus, it usually takes around 2 days for symptoms to appear, though the incubation period can vary from 1 to 4 days. Some individuals may be contagious 1 to 2 days before showing symptoms and can continue to be infectious for 5 to 7 days thereafter. On average, people remain contagious for about 6 days, although this period may be extended if they are immunocompromised [26].

The clinical presentation of an infection with seasonal influenza has a wide variability. Based on the characteristics of host and virus the symptoms range from an asymptomatic infection to a fulminant illness.
After the incubation period symptoms suddenly occur. The clinical presentation can be divided in respiratory symptoms, ocular symptoms, and other systemic symptoms [2].

Fever is the most important physical finding and can go up to 41°C in the first 24h. Other symptoms affecting the whole-body system are headaches, chills, myalgia, anorexia, muscle fatigue and general malaise.
Respiratory symptoms include non-productive cough, coryza, sore throat and pharyngitis. Ocular symptoms as photophobia, conjunctivitis, lacrimation, and pain with eye movement can also be present when getting infected with influenza [2,28].

How long the symptoms persist varies: constitutional symptoms endure in most cases up to 7 days, a sore throat usually last for 5 days, weakness and cough can remain for weeks. However, most patients with an uncomplicated infection get better within a few days [5].

1.4.1 Clinical presentation in children

Children present with a wide range of symptoms when it comes to influenza. Clinical manifestation is mostly based on the age and health status of the child. In most cases, the symptoms are very similar to those seen in adults.
However, there are some features which are more present in children but not in adults such as cervical lymphadenopathy. Moreover, children have usually higher temperature than adults, which may lead to febrile seizures, and they often experience gastrointestinal symptoms. These could be vomiting, diarrhea or abdominal pain [28,30].
Influenza in young children can present as laryngotracheobronchitis, bronchiolitis or bronchitis [2]. But it has been determined that a significant proportion of the burden of influenza in children originates from post-influenza side effects. Such

sequelae may include secondary bacterial pneumonia, acute otitis media and sinusitis [30].

1.4.2 High risk patients

Normally Influenza is a self-limiting illness but people especially with high risk factors can develop severe diseases. People with following conditions are at a higher risk for complications: elderly (>65 years), children (especially <5 years), pregnant women, within 2 weeks of giving birth, or living in group settings (such as nursing homes, dormitories, military barracks) and patients with chronic conditions like asthma, hematological disorders, neurological disorders, metabolic disorders, congenital heart disorders and those who are immunocompromised [6,26].
In the paediatric population, children younger than two years of age and those with underlying medical conditions are at the highest risk of complications associated with influenza [31].

1.4.3 Complications

The majority of influenza infections are known to be self-limiting, however, it is important to be aware that some complications can be severe, and in some cases, even life-threatening [31]. Complications of a severe Influenza infection can lead to diseases of many different organ systems. The most critical complication is pneumonia. It can manifest as primary viral pneumonia, secondary bacterial pneumonia and combined viral and bacterial pneumonia [5].

Besides pneumonia some other pulmonary complications can occur:
Acute respiratory distress syndrome, diffuse alveolar hemorrhage and hypoxic respiratory failure [5]. Furthermore, other respiratory complications, such as exacerbations of asthma, laryngotracheobronchitis and bacterial tracheitis may occur [31].

Extrapulmonary complications are less common but can affect multiple organ systems. Cardiovascular, hematologic, musculoskeletal, ocular, renal and neurological systems may be involved. These complications manifest as a range of inflammatory, ischemic or immune-mediated disorders. The following are illustrative examples: cerebrovascular events, ischemic heart disease, hemolytic uremic syndrome, rhabdomyolysis, conjunctivitis, acute kidney injury, multiorgan failure, Guillain-Barré Syndrome, postinfluenza encephalopathy, Reye syndrome, or aseptic meningitis [5,32].

1.5 Diagnosis

Diagnosing influenza clinically is often challenging due to the variability in symptoms and their similarity to other respiratory illnesses. The accuracy of clinical diagnosis depends on the case definition employed, the patient's characteristics, and the prevalence of influenza in the community [2]. In healthy adults, clinical diagnosis sensitivity ranges from 29% to 80% [33–36]. Clinicians are more likely to diagnose influenza correctly when fever and cough are part of the case definition, during periods of high influenza prevalence, and in patients who are severely ill or at risk of complications. Laboratory tests are available to assist in diagnosis, guiding treatment decisions, preventing inappropriate antibiotic use, and contributing to influenza surveillance efforts. Physicians should consider community influenza rates and utilize laboratory tests when their results will impact clinical management [2].

1.5.1 Clinical diagnosis

The clinical diagnosis of influenza can vary greatly depending on the circumstances. It can be straightforward when the epidemiological context aligns, the patient is an older child or teenager, and the presence of typical symptoms. However, it becomes challenging when these conditions are not met [37].

A favorable epidemiological context for diagnosing influenza includes being within the typical flu season (usually November to March in the northern hemisphere), having cases of flu in the patient's family or school environment, and the declaration of "influenza activity" in the community by health authorities [37].

During an epidemic, clinical diagnosis tends to be highly accurate, leading to many influenza cases being identified based on clinical symptoms alone [5].

1.5.2 Laboratory diagnosis

Ideally, laboratory testing for influenza should be affordable, highly sensitive in detecting the virus, and deliver quick results. Rapid testing is crucial as it allows healthcare providers to start antiviral treatment promptly.
There are different analyzing methods available: rapid influenza diagnostic tests, polymerase chain reaction (PCR), rapid molecular assays (e.g. nucleic acid amplification tests) or virus culture can be used. Out of these methods the best will be chosen depending on whether it is an outpatient or inpatient [5,26].

Rapid influenza diagnostic tests are designed to detect influenza virus antigens and the sample material is collected either from nasopharyngeal swabs or nasal swabs only. They deliver a test result within 10 to 15 minutes and are reported as either positive or negative [26]. Short time to result and the simply way to perform them are advantages of the rapid antigen tests, but they have poor sensitivity (about 70% for Influenza virus A and <30% for Influenza Virus B) compared to molecular assays and viral culture methods [5].

Due to its high sensitivity and specificity reverse transcriptase PCR is the first chosen laboratory test to diagnose influenza [5]. PCR can be used to detect the virus in various materials, such as nasopharyngeal swabs, throat swabs, nasopharyngeal or bronchial wash, nasal or endotracheal aspirate and sputum. It takes between one to eight hours depending on the assay [38]. The nasopharyngeal swab is currently considered the gold standard for diagnosis. It should be used in preference to other methods, especially if the highest possible viral load is required [39]. For patients with influenza-related lower respiratory tract manifestations, such as pneumonia, sputum is the preferred sample material [40]. A significant benefit of reverse transcriptase PCR is its capacity to simultaneously detect multiple pathogens and differentiate between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A and B and sometimes also respiratory syncytial virus (RSV) [31].

Rapid molecular assays can detect the nucleic acids of the influenza virus in samples from the upper respiratory tract. These assays provide highly sensitive (90-95%) and specific results in a short time (15-30 minutes) [41].

Virus cultures are helpful for strain typing and specific influenza diagnosis. They can be grown from endotracheal aspirates, nasopharyngeal and sputum samples. However, because they take 3-10 days to produce results, they cannot be used for clinical decision making [5].

The World health organization (WHO)'s current recommendation for the diagnosis of influenza is as follows: in cases where non-severe influenza is suspected, the use of nucleic acid amplification testing (NAAT) or digital immunoassay is recommended; in cases where severe influenza is suspected, the use of high-sensitivity and -specificity tests (NAAT or PCR) is suggested [42].

1.6 Treatment and prevention

Preventing influenza infection requires a combination of strategies, including annual vaccination, targeted antiviral chemoprophylaxis and non-pharmaceutical interventions, such as wearing masks, practising good hand hygiene and improving indoor air quality through ventilation, filtration and air disinfection [26,43]. Influenza vaccination is widely regarded as the most important aspect of disease prevention. Chemoprophylaxis remains important, particularly for post-exposure prophylaxis [26]. These points are explained in more detail below.

1.6.1 General Treatment

Symptomatic and supportive treatment plays an important role in the treatment of an influenza infection. This primarily includes sufficient fluid intake for rehydration following fever and the use of non-steroidal anti-inflammatory drugs such as ibuprofen, diclofenac sodium, naproxen or aspirin. These drugs help reduce symptoms like fever, headache, muscle aches, shivering and myalgia [5].

The potential benefits of vitamin D supplementation can be discussed in patients in the context of both an influenza infection and as a supplementary pre-infection treatment during the influenza season. Vitamin D is essential for maintaining bone health and regulating immune function, in addition to its anti-inflammatory properties. Therefore, the National Institutes of Health (NIH) suggests vitamin D supplementation at a rate of 600 units per day for individuals between the ages of 1 and 70 and 800 units per day for those above the age of 70, during the summer months. However, during the winter months, the NIH has set the upper intake limit of vitamin D supplementation at 4,000 units per day. No studies have reported adverse effects associated with the use of supplements containing less than 10,000 units per day for adults. To prevent infection, it is recommended that people who are at risk of influenza should consider taking 10,000 units of vitamin D daily for a few weeks to rapidly raise vitamin D levels, followed by 5,000 units daily. It is possible that infected patients may need even higher concentrations than those mentioned above [26].

1.6.2 Antiviral Drugs

Clinical studies have shown that initiating therapy early, ideally within 48 hours of the onset of symptoms, reduces the duration of illness, lowers the risk of complications, and decreases hospitalisation rates. This is especially the case in populations with a high risk of illness, such as pregnant women, children younger than 4 years of age, the elderly, and patients with long-term health problems [5].

There are currently four drugs used for the medical treatment of influenza: oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab) and baloxavir (Xofluza). Oseltamivir, zanamivir and peramivir are neuraminidase inhibitors. They work by interfering with the function of the NA enzyme and stop the virus from leaving the infected cell [5]. Baloxavir, on the other hand, inhibits an influenza virus-specific enzyme. This prevents the transcription of viral RNA and, consequently, the replication of the virus [44].

Oseltamivir is generally used as first-line therapy. It is usually taken orally in the form of capsules or a suspension. Children receive their dosage based on their weight as outlined below:

- Infants under 12 months: 3mg/kg body weight
- Children 1-12 years:
  - 10-15kg body weight: 30mg
  - More than 15 to 23kg: 45mg
  - More than 23 to 40kg: 60mg
  - Over 40kg: 75mg

For Children over 13 years old and adults the standard treatment regimen is 75mg. This is taken orally twice daily for five days regardless of age and dosage. For immunosuppressed patients the duration of treatment is 10 days. An adjustment to the dose is not necessary [45,46]. Oseltamivir is also approved for use in post-exposure prophylaxis. The same dosage as above is used for this application. The administration of the drug is once-daily for a period of 10 days [46].

In the absence of a response or indications of inadequate gastrointestinal absorption, second-line therapy with zanamivir may be initiated. It is preferably administered by inhalation but can also be given intravenously. It is approved for use in children aged five years and over and can also be used in adults (13 years and over). The recommended dosage is 10 mg per day, divided into two doses, for five days, regardless of age or weight [46].

Peramivir is not currently approved for use in Austria (as of 2025). Consequently, it will not be discussed in detail [47].

Baloxavir is administered as a single dose, depending on body weight from the age of one year. Patients weighing between 20 and 80 kg should take 40 mg in tablet form, while those weighing more than 80 kg should take 80 mg [48]. Oral suspensions can be prepared using granules. Dosage is based on body weight: up to 20 kg: 1 ml per kg of body weight, 20 kg to less than 80 kg: 20 ml and more than 80 kg: 40 ml [49].

1.6.3 Vaccines

Influenza vaccinations are known as one of the best public health interventions to prevent infection [5].

Vaccination coverage depends on the vaccination rate of the population and on the vaccine used matching the seasonally circulating influenza virus antigen [50,51].

To guarantee protection people should get vaccinated before the start of the flu season, which normally lasts from October to May in the northern hemisphere. There are different types of vaccine available: inactivated influenza vaccine, live attenuated influenza vaccine and recombinant influenza vaccine. Depending on age, physical conditions such as pregnancy or immunodeficiencies and individual contraindications the right vaccine will be chosen [5].

The following recommendations for vaccinations in Austria are currently in use for the 2024/2025 season: Vaccination is recommended for everyone older than six months. It is advised that children up to the age of two years, and those with contraindications for the live vaccine, receive an inactive vaccine. Otherwise, an intranasal live vaccine is used until the age of 18. The active nasal vaccine is a trivalent vaccine, while the inactivated vaccine is a tetravalent vaccine.

The Austrian Vaccination Commission recommends two vaccinations at least four weeks apart for children under the age of nine, followed by an annual booster. From the age of nine, an annual vaccination with the inactivated vaccine is recommended. [52].

A vaccine that has been modified to enhance its effectiveness and is capable of inducing a stronger immune response is available for adults above the age of 50. For adults over the age of 60, an inactivated high-dose vaccine is available. It is recommended that individuals between the ages of 18 and 60 receive an inactivated vaccine [52].

All the influenza vaccine compositions include the following strains: A(HN1)pdm09, A(H3N2), a representative of the B/Victoria lineage, and, in the case of the quadrivalent vaccines, an additional influenza B strain from the B/Yamagata lineage [52].

Although the influenza vaccine is recommended in all population groups, there are some reasons why vaccination is contraindicated. These include previous anaphylactic reactions to influenza vaccines, a history of Guillain-Barré Syndrome within six weeks of receiving an influenza vaccine, and the presence of an active infectious disease with a fever as a presenting symptom [5]. In the event of specific contraindications to the live vaccine, such as conditions or medications associated with immunosuppression or immunodeficiency, high-dose corticosteroid treatment or long-term aspirin therapy, the Austrian Vaccination Commission advises the use of an inactivated tetravalent vaccine as a suitable alternative [52].

2 Material and Methods

For this thesis, a search query for children with the diagnoses J09 “Influenza due to identified zoonotic or pandemic influenza virus”, J10 “Influenza due to identified seasonal influenza virus" and J11 “Influenza, virus not identified" according to ICD10 was carried out in the hospital information system “Medocs” of the Department of Paediatrics at Graz University Hospital.

Children with these diagnosis codes and treatment diagnosis “yes” who were admitted to intensive care from 2005 – 2020 were included.
Out of these parameters the Institute of medical informatics, statistics and documentation (IMI) prepared a list involving 69 patients from 2005 until 2020.

From these children following parameters were recorded:

- Gender
- Age at the time of recording
- Admission into and discharge from the hospital
- Admission into and discharge from intensive care unit
- Whether there is a fever chart or not
- Vital signs by admission to the hospital such as:
    - Weight and hight
    - Oxygen saturation
    - Breathing and heart rate, blood pressure
- Pre-existing disease
- Principal and secondary diagnosis at the time of discharging into the hospital
- If there was a diagnosed bacterial infection and if yes which bacterium could be detected
- Whether a blood culture was taken and if so, what the result was of this blood culture
- Whether they got lumbar puncture or not
- Method and sample of diagnostic confirmation of Influenza
- Influenza subtype

- first day of a positive influenza test
- Influenza vaccination status
- clinical presentation of the influenza infection
- Whether they got an antibiotic and/or antiviral therapy and if they got such a therapy which medication was given and for how long did, they receive it

After searching all these parameters, they have been precisely documented and retrospective analysis were performed. Excel was mainly used for documentation and as well as for analysis.

The source of quotation was mainly taken from PubMed by searching for reviews and current studies according to influenza in general. Particular attention was paid to the search for literature on influenza infection on children. Google scholar was used as an alternative data base to find suitable papers.

Furthermore, the most recent and pertinent literature and websites offering up-to-date data on influenza were consulted in order to obtain additional information.

Chat GPT 5.1 from Open AI (https://chatgpt.com) was used for linguistic and grammatical support, as well as for summarizing and paraphrasing in some sections throughout the entire duration of the preparation of this thesis. In addition, it was used to inspire rough ideas for content in the discussion section and occasionally as a search engine for finding sources for scientific papers.
Other frequently used tools for formulation variants and linguistic improvement were DeepL Write (https://www.deepl.com/de/write) and Reverso (https://synonyms.reverso.net/synonym/).

3 Results

From 2005-2020, a total of 1248 patients were hospitalised for the treatment of influenza at the University clinic of pediatrics in Graz. Overall, 69 (5.53 %) were admitted to the intensive care unit. Out of these we had to exclude 12 children where influenza could not be diagnosed by laboratory chemical methods, there was only a detection of antibodies against influenza viruses or because their age was above 18. Therefore, the total amount of 57 patients were included in the analyses.

3.1 Epidemiological data and patient characteristics

Children with an age range of 0-18 years were treated. The median age at the time of admission to the intensive care unit was 3 years with a range of 14 days to 16 years (Figure 1). The gender distribution was almost balanced, 24 (42%) children were female, and 33 (58%) children were male (Figure 2).

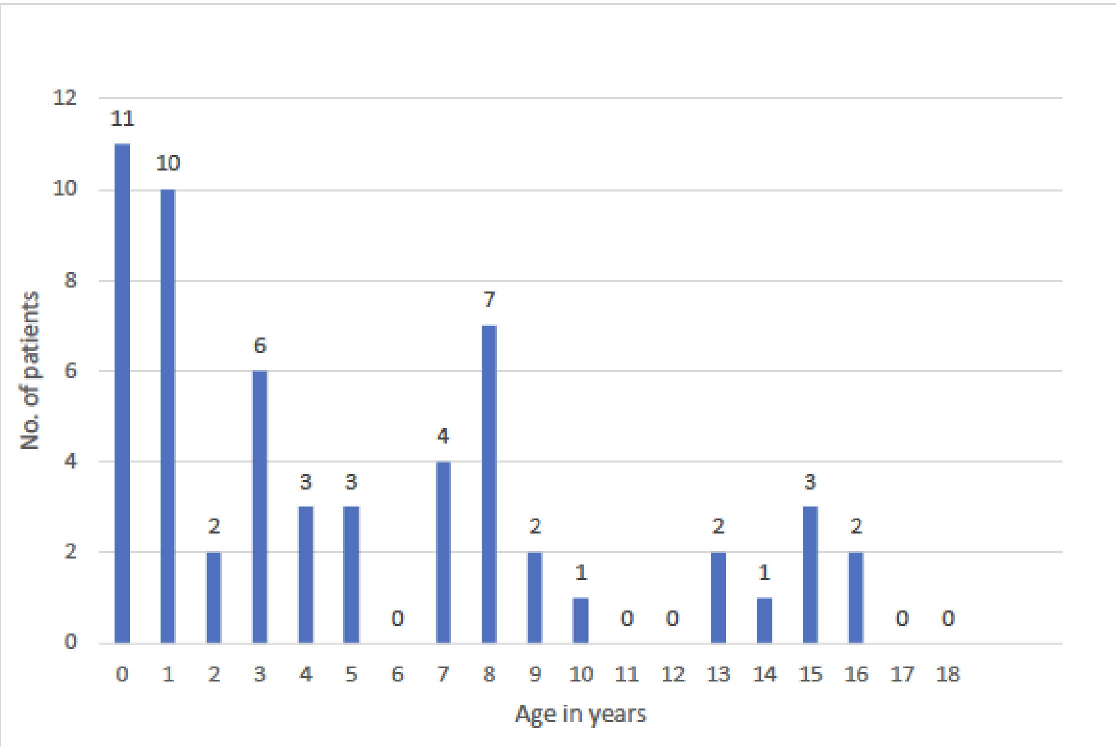

Figure 1: Number of patients by age in years

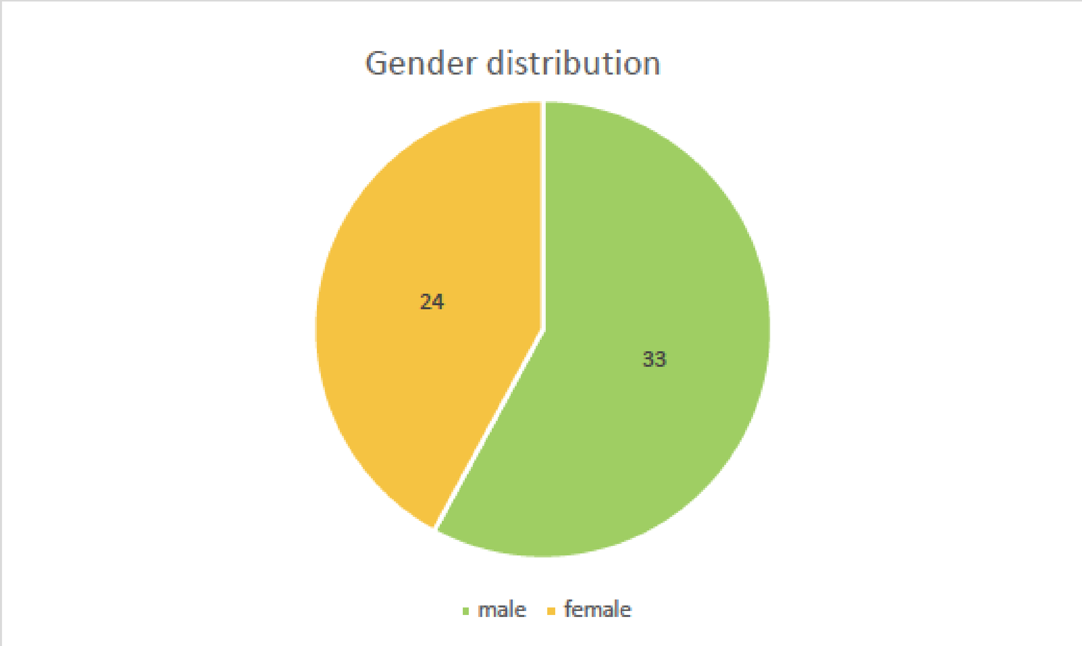

Figure 2: Gender distribution

The epidemiological evaluation shows that there was a median of 2 cases per season that had to be cared for in the intensive care unit. The highest number of patients requiring intensive care occurred in the season of 2019/2020. In season 2005/6, 2006/7, 2011/12 and 2013/14 no patients had to be treated in the intensive care unit due to an infection with influenza virus (Figure 3).

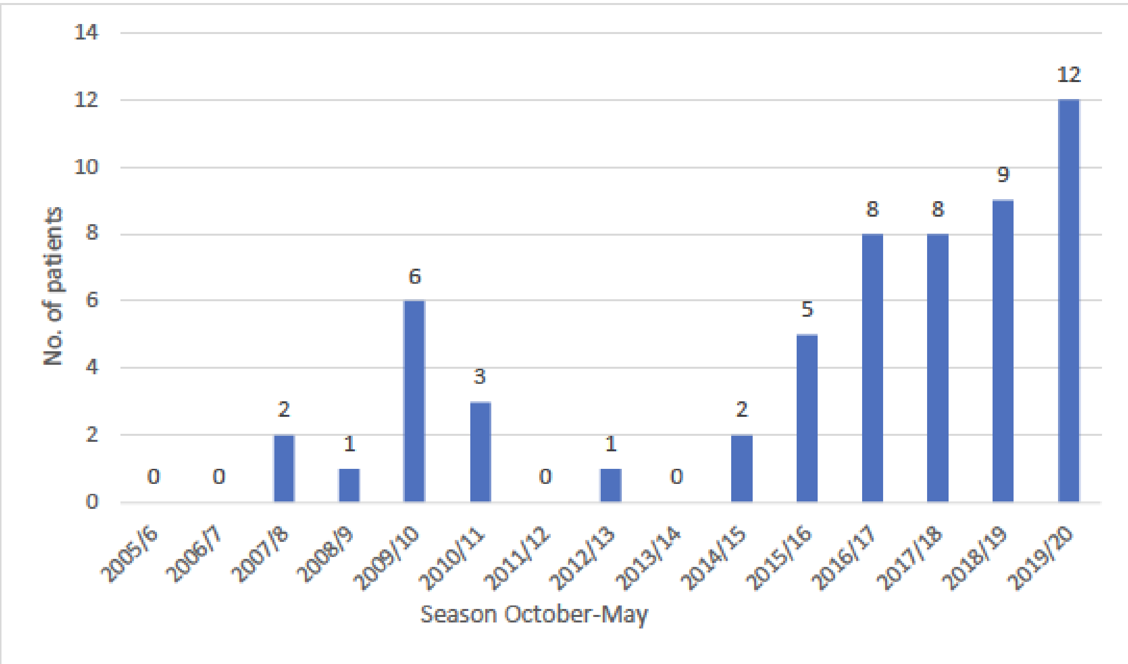

Figure 3: Number of patients per season

3.2 Clinical presentation and past medical history

3.2.1 Previous illnesses

Of the 57 patients, 31 (54.39%) had preexisting conditions. The severity of these conditions ranged from mild, barely debilitating symptoms to severe manifestations. Of the children with pre-existing conditions, 22 (70.97%) exhibited one or more complaints that were conducive to a severe course of influenza. These were also the previous conditions on which the analysis was focused.

The pre-existing conditions were grouped for better statistical analysis. Previous neurological conditions were clearly predominant with 18 (41.86%), followed by others (17.5%) and pulmonary conditions (10%). The distribution of categorised previous conditions is shown in figure 4.

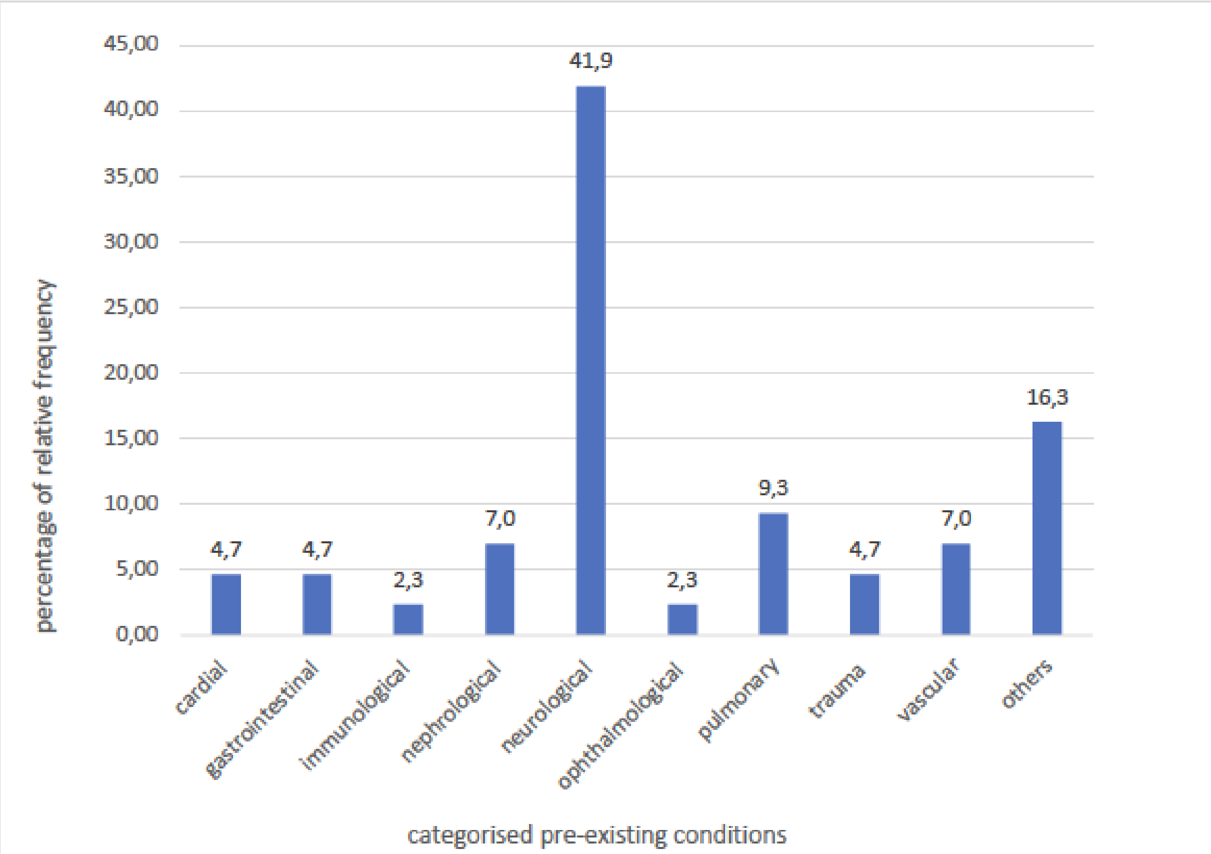

Figure 4: Distribution of pre-existing conditions according to classification in percent of relative frequency Category "Others" includes twin premature birth, neuromuscular scoliosis, Cytomegalovirus infection, glandular hypospadias, hyponatraemia, hypocalcaemia, hypomagnesaemia, condition following infected laceration of the forehead with lymphadenitis of the neck, condition following vagus nerve implantation, and condition following rhabdomyolysis.

Of the children with pre-existing conditions, the majority of children (50%) had a single pre-existing condition, six children (27.27%) had two, and the remaining children had more than two (Figure 5, table 1). In addition to a pre-existing condition that predisposes them to a high-risk course, three children had another pre-existing condition with less influence: atopic dermatitis and grass pollen sensitisation.

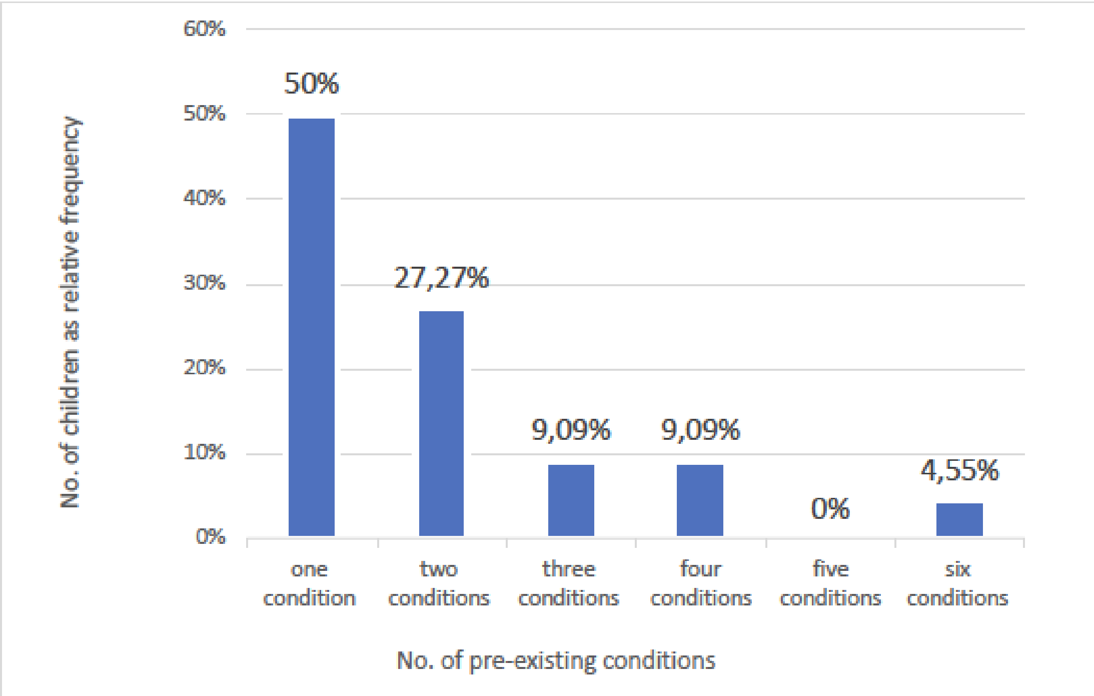

Figure 5: Frequency of the number of pre-existing conditions in percentage

Number of pre-existing conditions	**Number of children in absolute values**	**Relative frequency**
One condition	11	50%
Two conditions	6	27.27%
Three conditions	2	9.09%
Four conditions	2	9.09%
Five conditions	0	0%
Six conditions	1	4.55%

Table 1: Comparison of the distribution of pre-existing conditions in absolute numbers and relative frequencies

3.2.2 Clinical presentation

In order to be able to statistically analyse the clinical manifestation of influenza infection, the symptoms were also divided into categories.
The primary clinical manifestations of influenza were grouped as follows: neurological, respiratory, gastrointestinal, systemic symptoms, vascular and others.

Most of the infections manifested themselves in systemic, respiratory and neurological symptoms (Table 2). Fever was classified as systemic symptoms and vascular symptoms include marbled skin and petechiae.

Categories	Occurrence of symptoms in absolute terms	Occurrence of symptoms as relative frequency
Neurological symptoms	34	23.29%
Respiratory symptoms	38	26.03%
Gastrointestinal symptoms	14	9.59%
Systemic symptoms	40	27.40%
Vascular symptoms	9	6.16%
Others	11	7.53%

Table 2: Presentation of the frequency of categorised symptoms in absolute values and relative frequencies Category "Others" includes increased secretion, one-time blood in the stool, massive cytokine release in connection with the disease, otalgia, exanthema, a yellowish skin colour, otitis on both sides, flank pain, myalgia and electrolyte imbalance

In most children, the infection manifested itself in symptoms belonging to three distinct categories. The most prevalent combination (47.62%) of categories was neurological, respiratory and systemic symptoms.
It was observed that only three children were affected by symptoms from four categories, and five children were affected by symptoms from five categories. The detailed distribution of the categorised symptoms is illustrated in Chart 6.

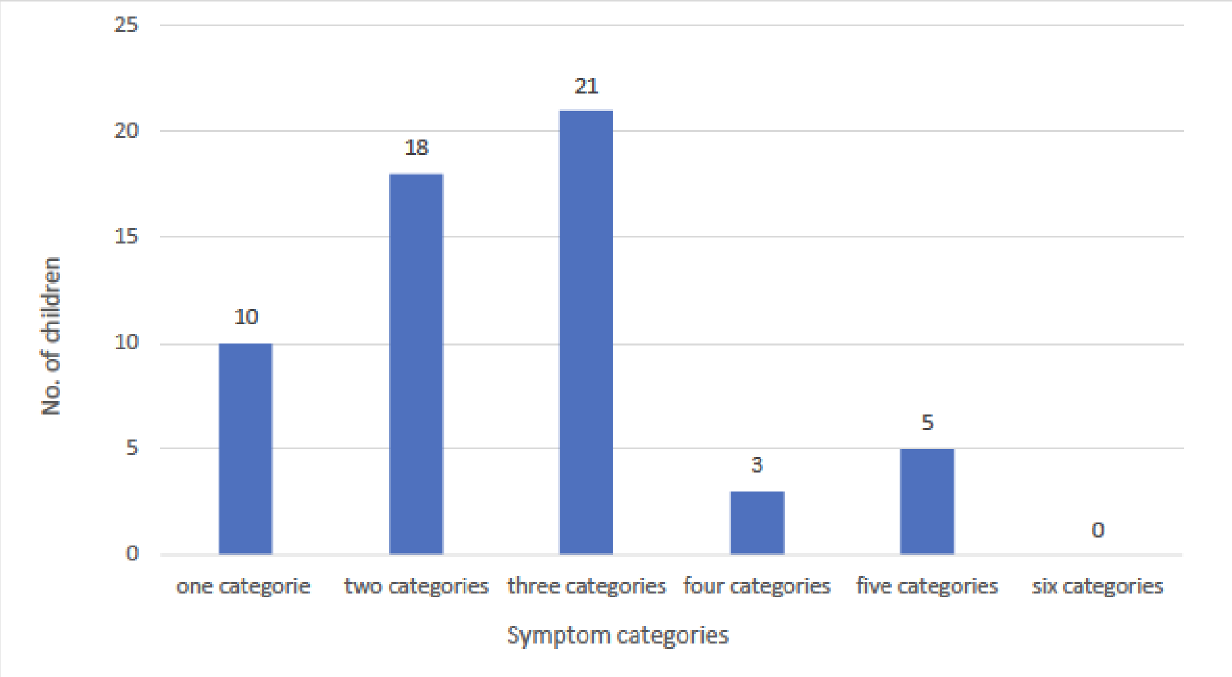

Figure 6: Clinical manifestation of influenza infection in symptom categories in absolute numbers

3.3 Inpatient stay

Of the 57 patients, 42 (74%) presented at the outpatient clinic primarily due to a clinical manifestation of influenza infection and were admitted as inpatients with a primary diagnosis of influenza. Three patients (5%) showed typical clinical signs of influenza, but concurrent RSV infection was also identified. Therefore, precise differentiation of the symptoms is not possible.

The total length of hospitalization (normal ward and intensive care unit) was between 1 and 29 days with a median of 7 days. Whereas the length of stay in the intensive care unit ranged from 1 to 26 days with a median of 3 days. For a better overview, the duration of hospital and intensive care unit stays was categorised as follows: 1-3 days, 4-7 days, 8-14 days, 15-21 days, 22-28 days, over 28 days (Figure 7, 8).

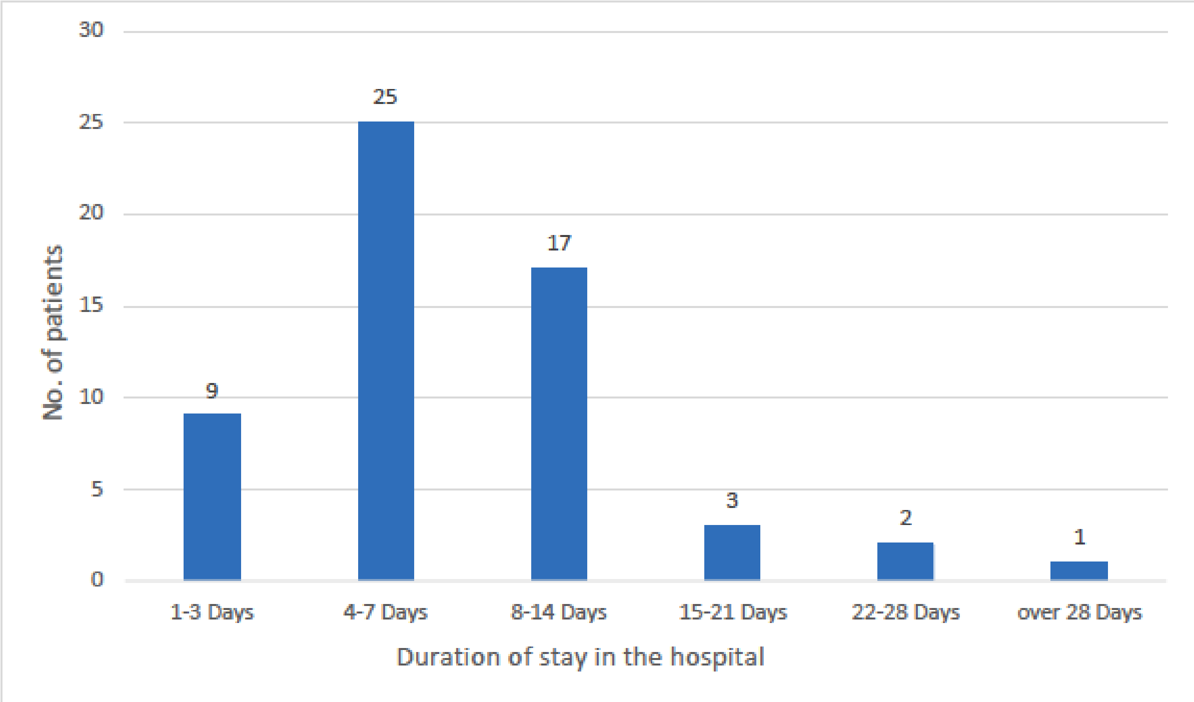

Figure 7: Duration of stay in the hospital

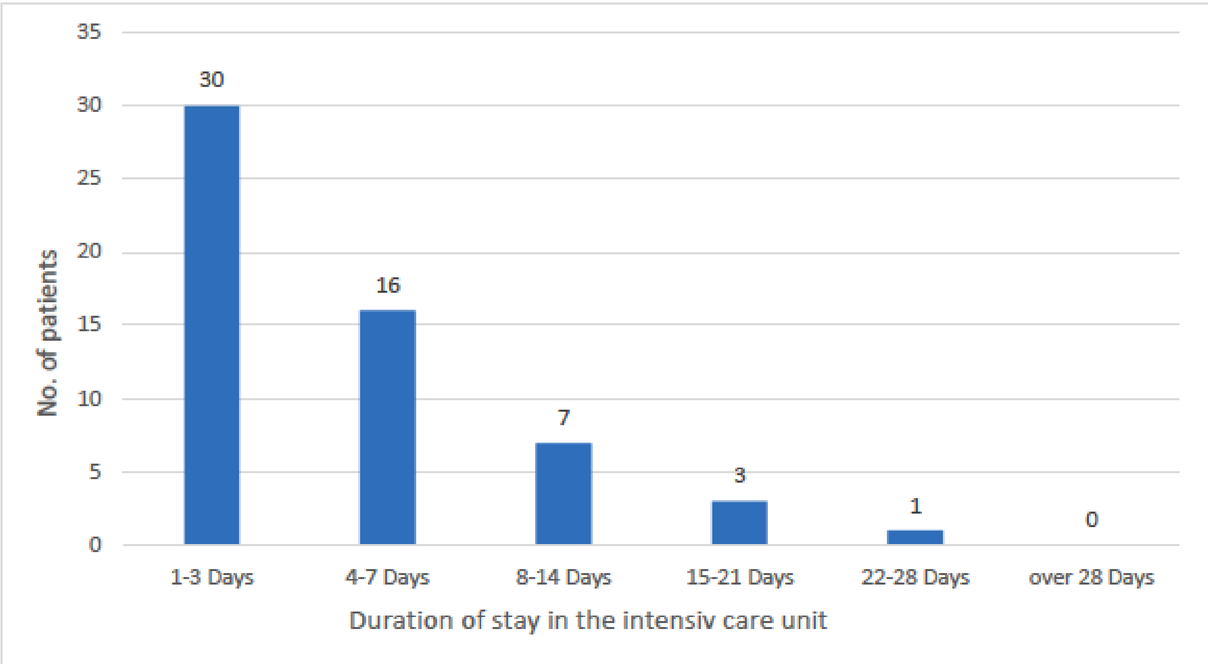

Figure 8: Duration of stay in the ICU

3.4 Influenza Virus subtype, vaccination status and method of detection

Three different laboratory chemical methods were used to confirm the suspected clinical diagnosis of "influenza": Rapid Antigen test, testing for antibodies and Polymerase Chain Reaction. Most common used was the laboratory analysis with PCR (Figure 9).

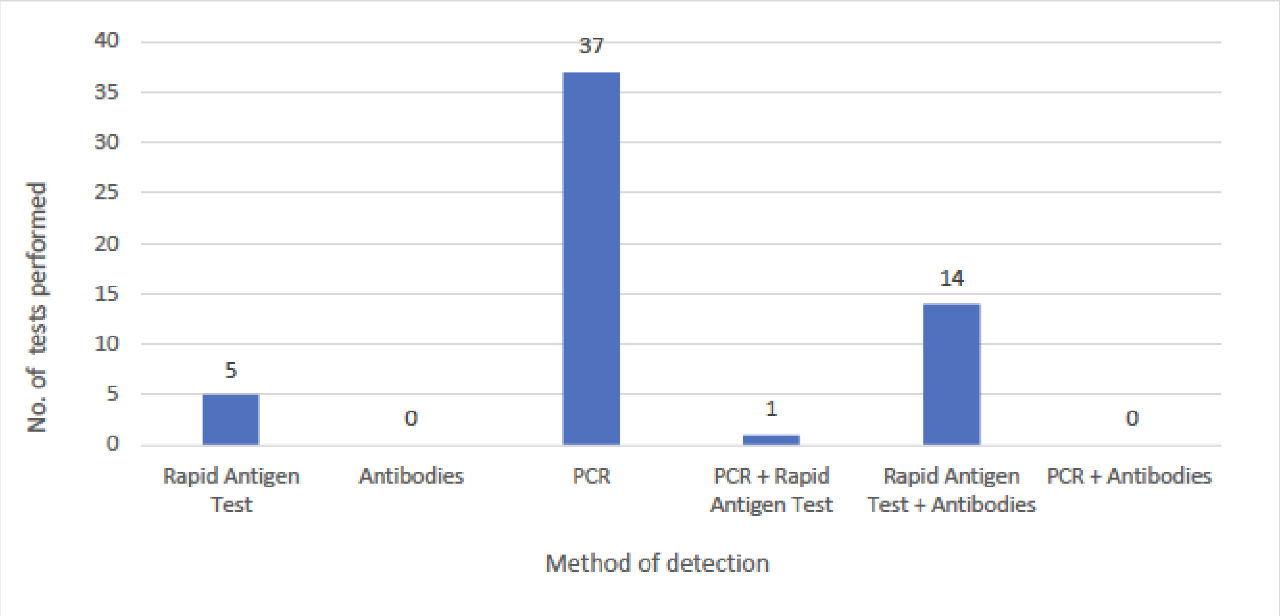

Figure 9: Test method frequency for detecting influenza

Subsequently, we examined the time interval between hospital admission and the first positive influenza test result for each patient. One patient was excluded from the analysis because his initial positive influenza test result had already been documented two days prior to admission during an outpatient visit.

In the majority of children (41.07%), influenza was detected for the first time on the day of admission. In one patient (1.79%), the first positive influenza test result was delayed until 19 days after admission to hospital (Figure 10).

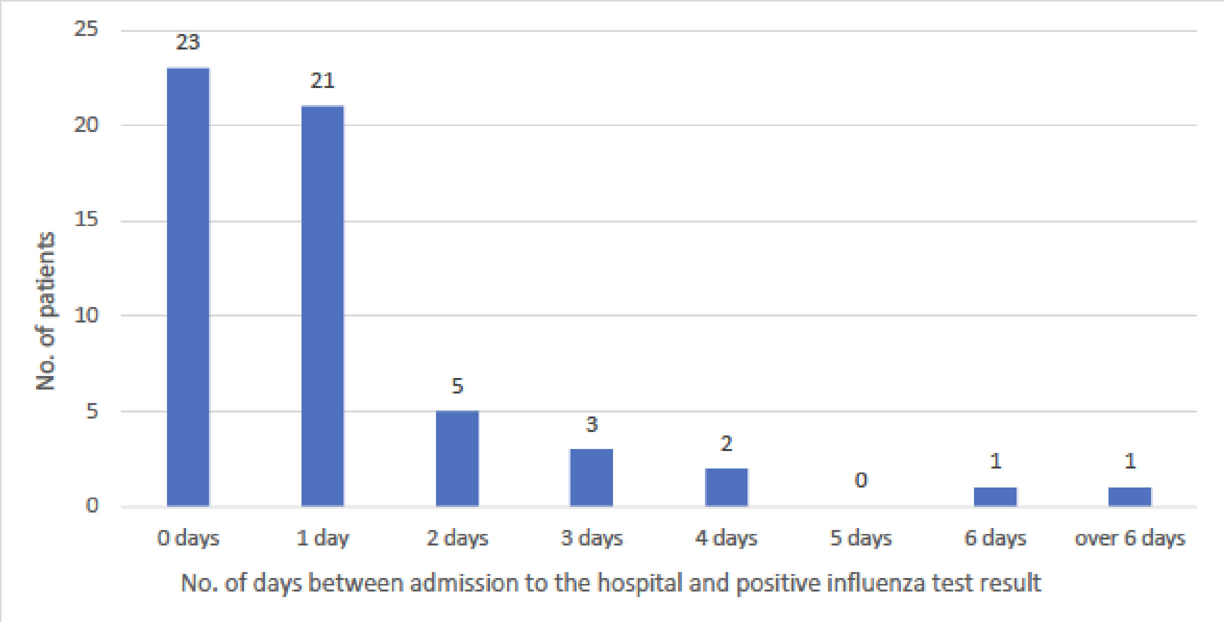

Figure 10: Illustration of the days between admission and first positive influenza detection

Three subtypes of the influenza virus were detected through these methods: Influenza A, Influenza B and combined infections with Influenza A and B. Influenza A was the most prevalent strain with a detection rate of 82.46% (Figure 11).

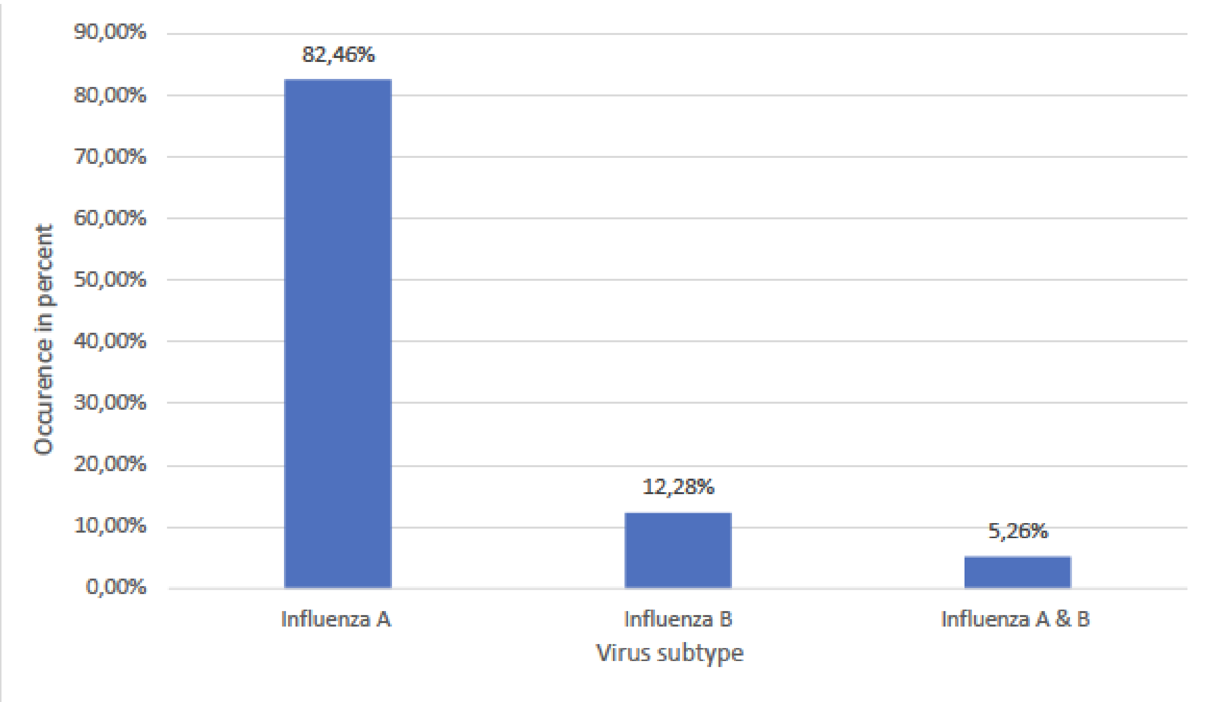

Figure 11: Influenza Subtype

For 29 (50.88%) of the 57 cases analysed, no documentation on the vaccination status of influenza vaccinations could be found. All of the 28 (49.12%) documented vaccination status were negative (Figure 12).

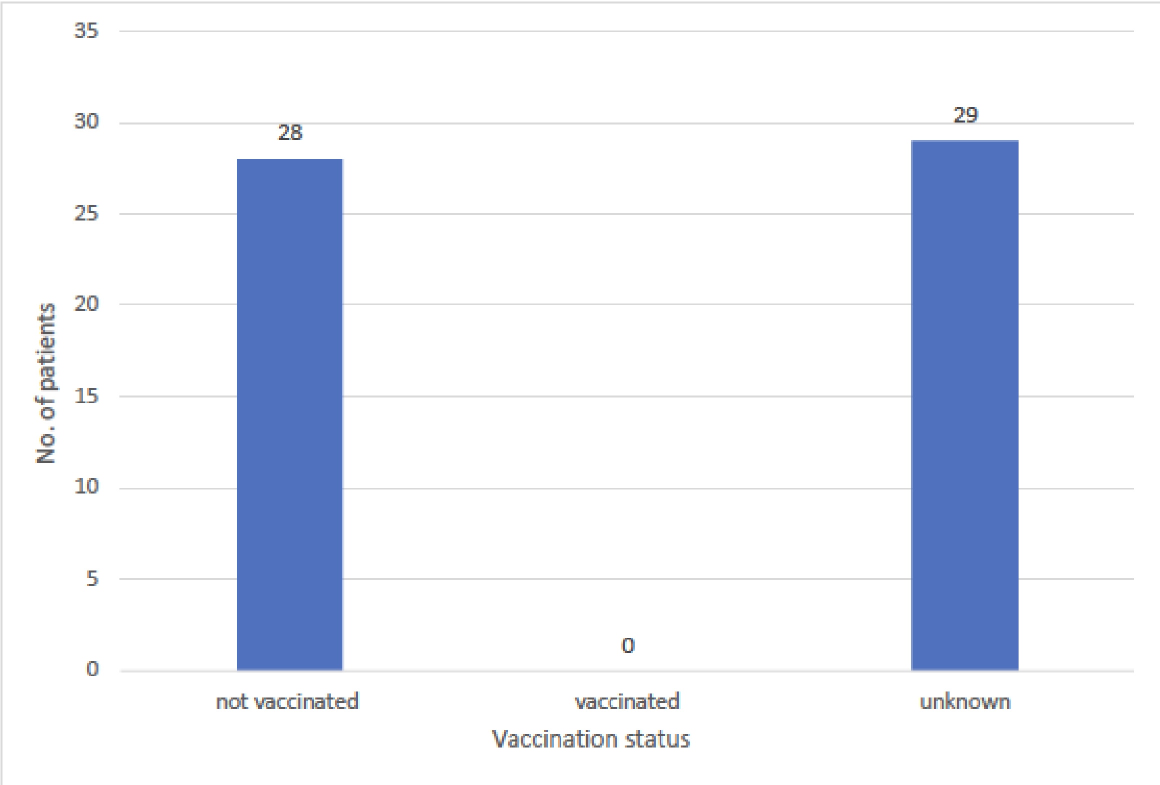

Figure 12: Distribution of vaccination status

3.5 Evidence of bacterial infection

In 34 (59.65%) children, laboratory tests detected one or more bacteria outside the normal flora at various swab sites (Figure 13).

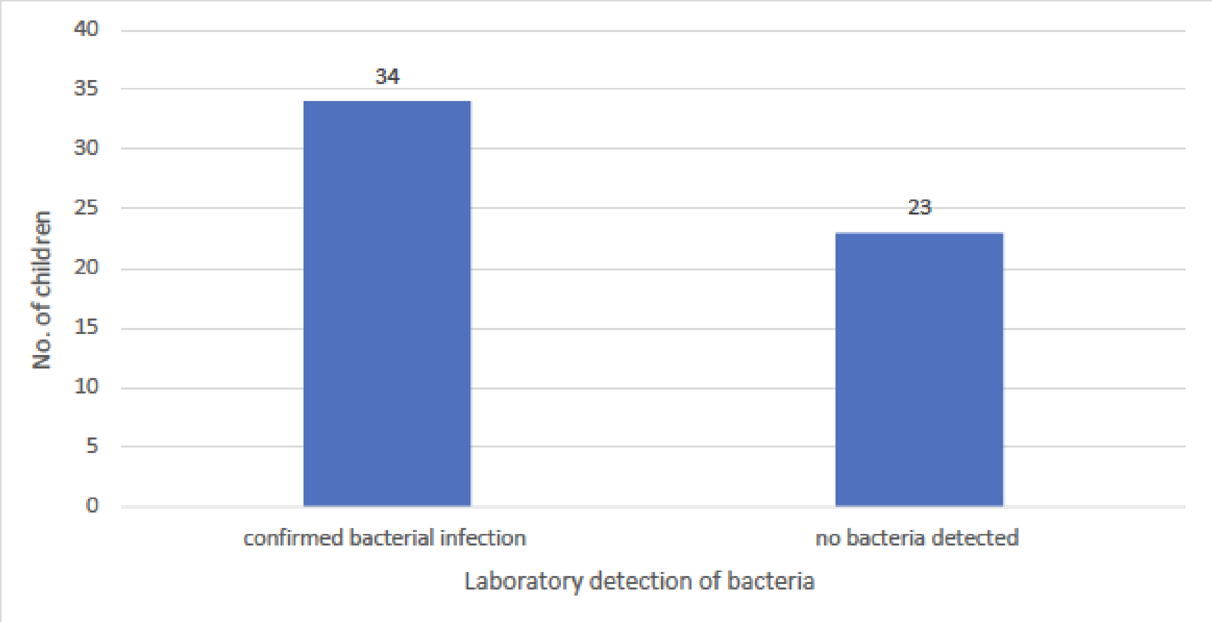

Figure 13: Number of children with laboratory-confirmed bacterial infection

Blood cultures were obtained from 22 (38.60%) patients during their hospitalisation.
In the case of three patients (13.64%), bacterial growth was observed in their blood cultures. Two (9.09%) of these cases were classified as probable contamination, and *Streptococcus pneumoniae* was detected in one blood culture. The remaining blood cultures (86.36%) showed no microbial growth (Table 3).

Blood culture results	**Absolute number**	**Relative frequency**
Positiv	1	4.55%
Contaminated	2	9.09%
Negativ	19	86.36%

Table 3: Summary of blood culture results in absolute numbers and relative frequency

3.6 Antibiotic and antiviral therapy

The evaluation of antiviral therapy demonstrated that 35 (61.40%) children were treated with antiviral medications. Treatment with oseltamivir alone was clearly predominant (54.29%), followed by combination therapy with oseltamivir and acyclovir (22.86). The distribution is illustrated in Figure 14.

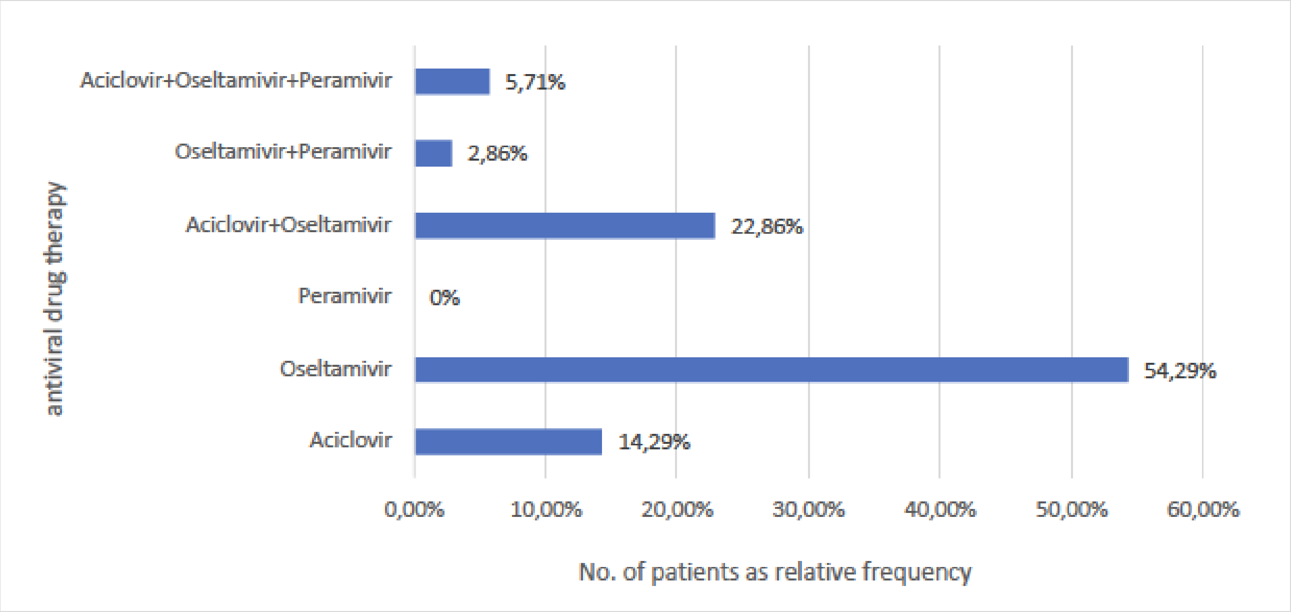

Figure 14: Frequency of antiviral drugs used as relative frequency

The next step was to look at how long the patients had been using the different antiviral drugs. Due to a lack of documentation, the treatment period could not be calculated for one child receiving oseltamivir and two children receiving aciclovir.

The analyses further revealed a median treatment duration of five days for oseltamivir, with a range of two to eleven days. The median duration of aciclovir treatment was three days, with a range of two to seven days. Three patients were treated with peramivir. All three received the drug for a period of just one day.

A similar analysis was performed on the treatment of children with antibiotics. This showed that 43 (75.44%) children were treated with antibiotics.
Most patients received only one antibiotic during their admission to hospital. Seven children (16.28%) required treatment with more than two different antibiotics.
When multiple antibiotics were administered, the therapy was either simultaneous or sequential (Table 4).

No. of used antibiotic drugs	Absolute number of patients treated	Relative frequency of patients treated
One antibiotic	23	53.49%
Two antibiotics	13	30.23%
Three antibiotics	3	6.98%
More than three antibiotics	4	9.30%

Table 4: Summary of number of used antibiotics in absolute numbers and relative frequency

Out of all the antibiotics used as monotherapy, the cephalosporin group was the most frequently used, with ceftriaxone being the most commonly prescribed (Figure 15).

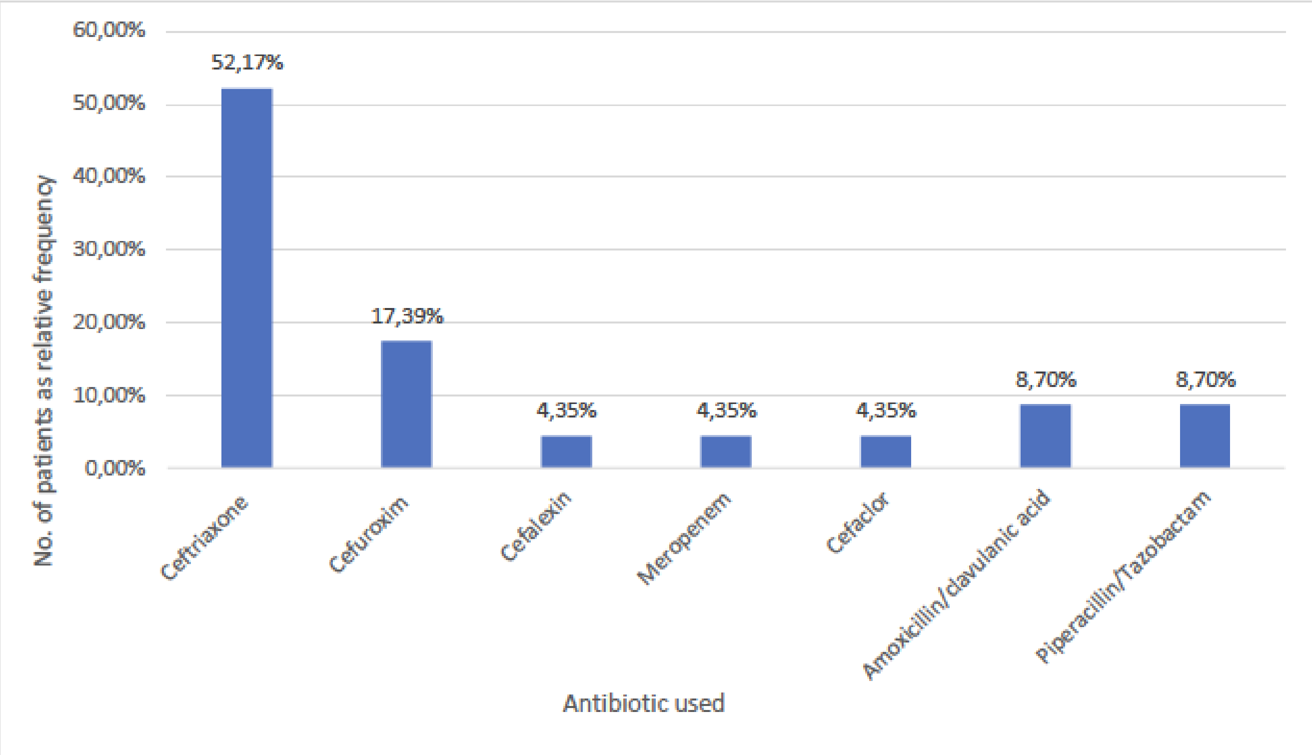

Figure 15: Frequency of antibiotics used as monotherapy, expressed as relative frequency

A more detailed analysis of the combinations of antibiotics used revealed eight different dual combinations.

Combination 4 was the most popular, with a relative frequency of 23.08%. Combination 1, combination 2 and combination 6 followed, each accounting for 15.38% of cases. The remaining combinations each accounted for 7.69% (Figure 16). Overall, cephalosporins are present in most of the combinations used, indicating their central role in antibiotic therapy.

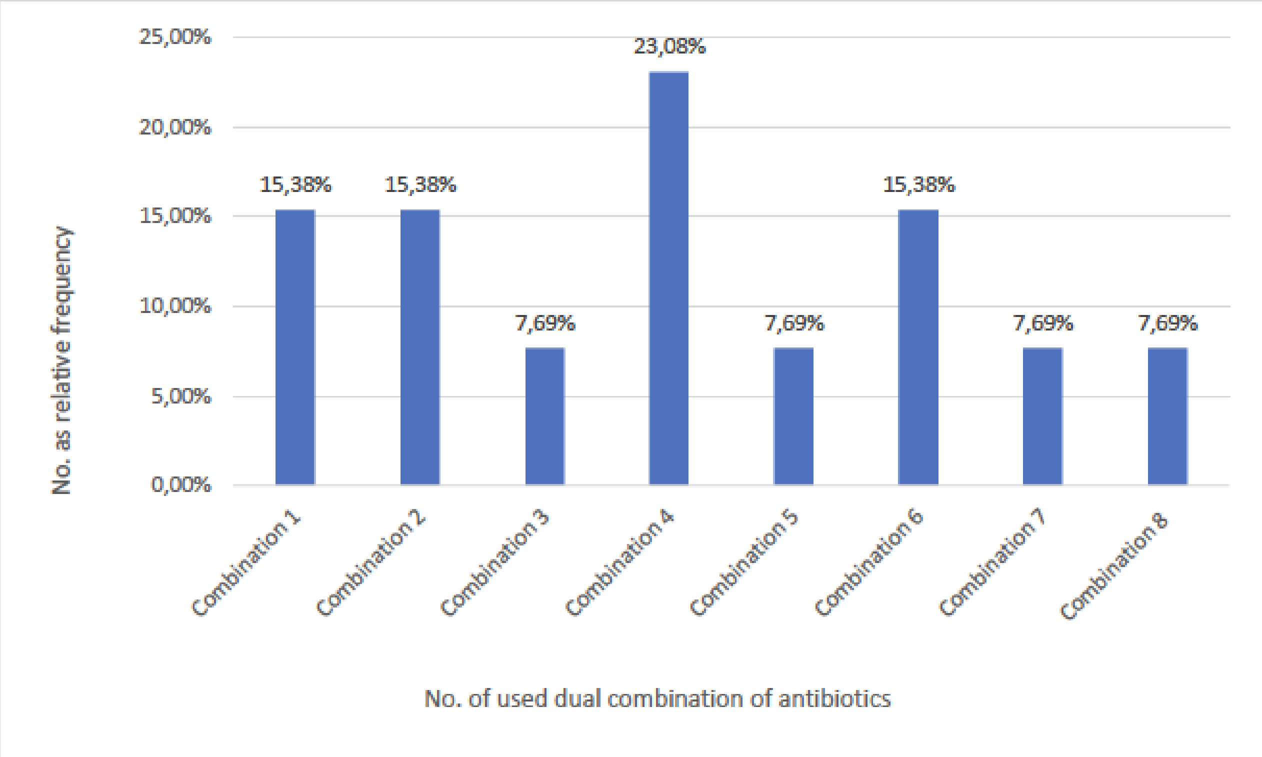

Figure 16: Detailed description of the combinations used:
Combination 1: Cephalosporins +Carbapenems
Combination 2: Cephalosporins + Lincosamides
Combination 3: Cephalosporins + Aminopenicillins/Betalactamase inhibitors
Combination 4: Cephalosporins + Cephalosporins, various subgroups
Combination 5: Acylaminopenicillins/betalactamase inhibitors + Fluoroquinolones
Combination 6: Carbapenems + Oxazolidinones
Combination 7: Cephalosporins + Oxazolidinones
Combination 8: Cephalosporins + Macrolides

The different triple combinations were used equally often, with each achieving a rate of 33.33%. While none of the individual combinations dominated, antibiotics from the cephalosporin group were present in all of them (Figure 17).

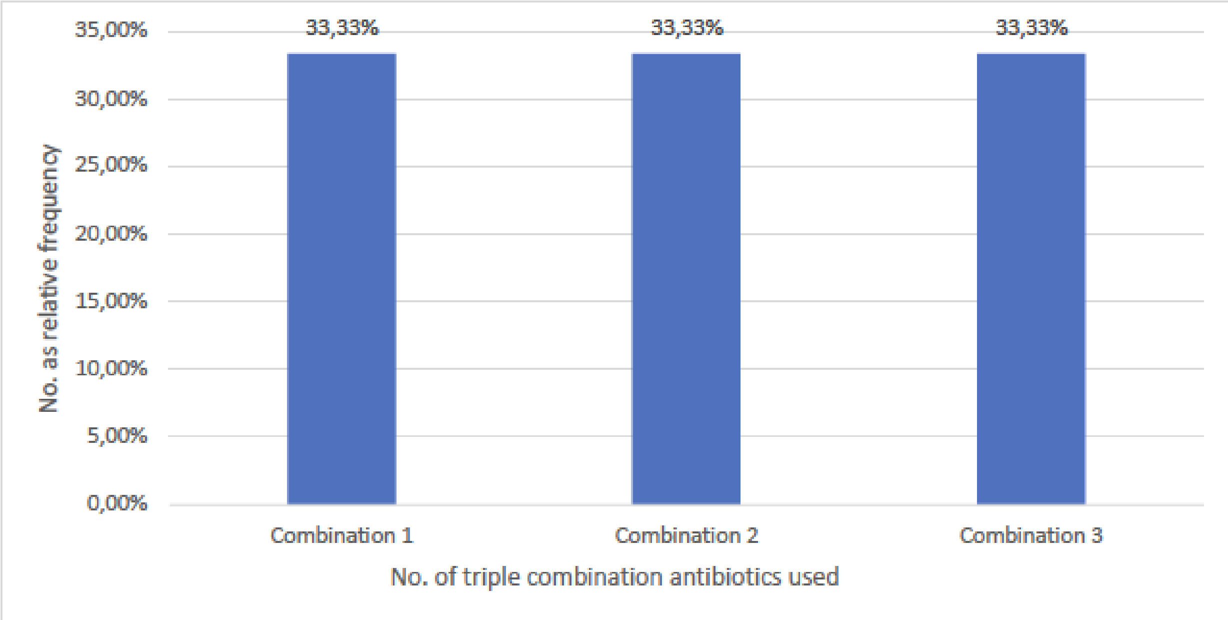

Figure 17: Detailed description of the combinations used:
Combination 1: Cephalosporins (two different subgroups) + Nitroimidazoles
Combination 2: Cephalosporins + Oxazolidinons + Rifamycins
Combination 3: Cephalosporins + Aminopenicillins + Aminopenicillins/Betalactamase inhibitors

The distribution of combinations of more than three different antibiotics is almost identical. All combinations achieved a relative frequency of 25%, with cephalosporins from at least two different subgroups used in each combination (Figure 18).

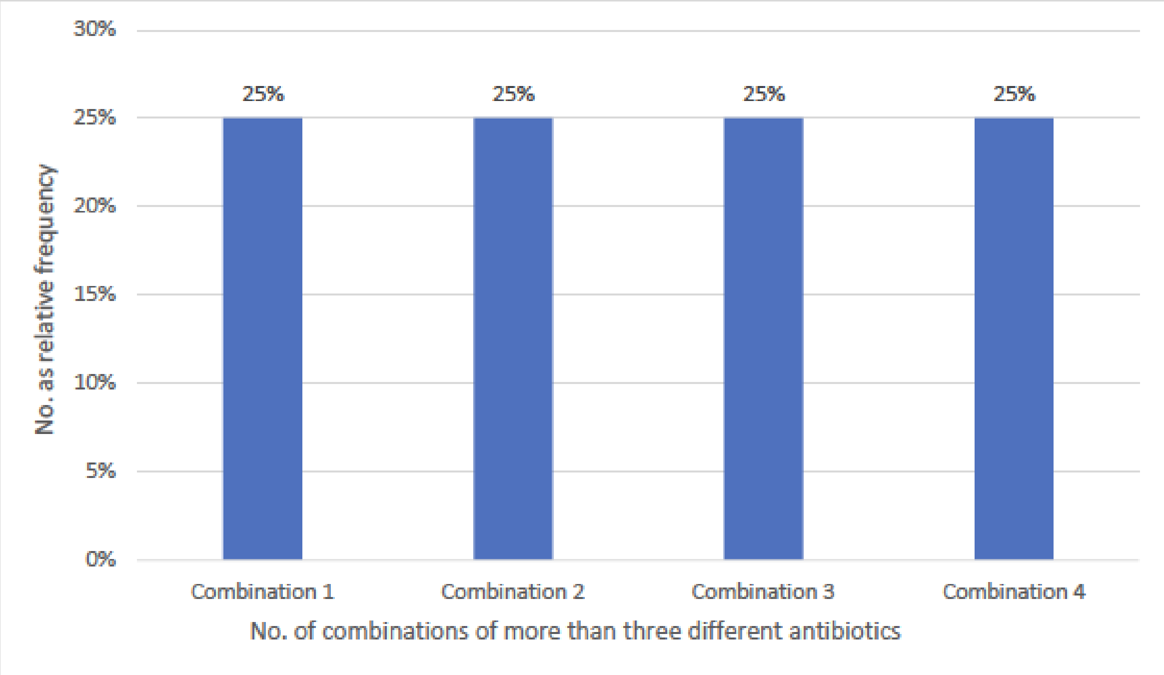

Figure 18: Detailed description of the combinations used:
Combination 1: Cephalosporins (two different subgroups) + Aminopenicillins/Betalactamase inhibitors + Acylaminopenicillins/Betalactamase inhibitors
Combination 2: Cephalosporins (two different subgroups) + Macrolides + aminoglycosides
Combination 3: Cephalosporins (more than two different subgroups) + Aminopenicillins/Betalactamase inhibitors + Macrolides
Combination 4: Cephalosporins (more than two different subgroups) + Aminopenicillins + Carbapenems + Macrolides

3.7 Deaths

In the last 15 years, there have been three deaths in the intensive care unit due to influenza. These occurred in the 2007/08, 2009/10 and 2017/18 seasons. The age ranged from 4 to 15 years and 67% of these patients were female.

Two of these patients had previously suffered from neurological conditions. One patient also had a pre-existing ophthalmological condition, while another patient had no such conditions recorded in their medical history. The vaccination status of all three subjects remains unclear.

The patients are presented in more detail below.

Patient 1

The first patient was a 10-year-old male. He was admitted directly to the intensive care unit, where he passed away within a day. He suffered from pre-existing neurological conditions, including quadriplegia and severe developmental delay. The rapid test showed a positive result for influenza A. The infection manifested itself in the form of hyperpyrexia and a high oxygen requirement. Staphylococcus aureus and Candida albicans could be isolated from the throat swab sample. Blood cultures were obtained, but no bacterial growth was observed. A diagnostic lumbar puncture was not performed. Antibiotic therapy with ceftriaxone was initiated on the day of admission. The patient received no antiviral therapy.

Patient 2

The second patient, a 15-year-old female, received intensive care for a period of five days prior to her death. The patient's medical history revealed several pre-existing conditions, including spastic tetraparesis, Dandy-Walker syndrome, optic nerve atrophy, symptomatic epilepsy and psychomotor developmental delay. The patient was receiving nutrition via a percutaneous endoscopic gastrostomy (PEG) tube.

A PCR test from the nasal secretions gave a positive result for influenza A with the H1N1 subtype. The symptoms manifested as obstructive bronchitis and respiratory decompensation.

Pseudomonas aeruginosa, Streptococcus viridans, Staphylococcus aureus and Haemophilus parainfluenza were detected in the sputum.

The initial antibiotic treatment administered was cefuroxime, there was no documentation regarding the administration of antiviral medication.

Patient 3

The youngest patient, aged four, required intensive care for a period of 11 days. The patient's tracheal and nasal secretions were examined using a PCR test, which revealed the presence of the influenza A virus and Bocavirus.

In this case, the infection manifested itself as necrotising encephalitis. The patient presented with no previous medical conditions.
Haemophilia influenza was detected in the nasopharynx and pharynx. The blood cultures revealed no bacterial growth.
Initial antibiotic therapy was administered as a three-day course of ceftriaxone, followed by a switch to cefuroxime. The patient was treated with antiviral therapy, including acyclovir for a period of five days and oseltamivir for a period of 11 days.

4 Discussion

4.1 Summary of Key Findings

In conclusion, the evaluations demonstrate that, although infrequently, intensive medical care is occasionally required for children who contract influenza. The average annual incidence in Graz during the period studied was 2.53 cases per 100,000 children per year.
Infection with the influenza A virus was found to be significantly more prevalent (82.46%).

It is evident that children suffering from pre-existing neurological conditions were particularly affected by severe cases.
In cases where the vaccination status was known, none of the affected children had received immunisation against influenza.

It is important to note that severe cases, and in some cases fatalities, have also been observed in children who did not have any pre-existing conditions. The case fatality rate during the study period among children treated in intensive care was 5.26%.

4.2 Comparison with existing literature

The outcomes of the study are in agreement with current literature and reporting data on influenza infection.

In accordance with previous studies, Influenza A is predominantly prevalent during severe seasons and is the primary type associated with pandemics. This phenomenon can be attributed primarily to its higher antigenic variability [2,12,30,32].
The Austrian Influenza Diagnostic Network has also demonstrated that influenza A has been the predominant subtype in recent seasons [53].

A substantial body of research has identified neurological and neuromuscular disorders as a high-risk condition regarding severe influenza and complications in children. This has been demonstrated by a multitude of reviews and guidelines [5,6,29,31,32,45].

Furthermore, current literature, as well as the present study, demonstrates that severe cases of influenza infection affect not only children with serious pre-existing conditions, but also previously healthy children. This underscores the significance of preventive vaccinations not only for high-risk groups, but for all children [6,28,29,31].

The findings of this study are consistent with the current vaccination data available for the Austrian population. The Austrian Association of Vaccine Manufacturers has demonstrated that the average vaccination coverage rate within the Austrian population was 10.27% over the period 2003/04-2023/2024. The highest recorded vaccination coverage rate was 22.13% in the 2020/21 season [54].
The European Union Commission has issued a recommendation for a vaccination coverage rate of 75% for designated risk groups [55].

Information on vaccination coverage rates among the paediatric population in Austria is hardly available from public figures. The available data relates to documented vaccine doses in the electronic vaccination record for the 2023/24 and 2024/25 seasons. The paediatric population was divided into three age groups: 0–4 years, 5–14 years, and 15–29 years [56].
A total of 155,430 vaccine doses were administered to these age groups in the 2023/24 season, with 38.53% going to those aged 0–4, 39.88% to those aged 5–14, and 21.59% to those aged 15–29. In the 2024/25 period, a total of 190,140 vaccine doses were administered, with the following distribution: 0–4 years: 37.49%; 5–14 years: 39.98%, and 15–29 years: 22.54% [56].
This represents a total increase of 34,710 vaccinations. The largest absolute increase was recorded in the 5–14 age group (+14,017, accounting for 40.38% of the total increase). Meanwhile, the largest relative increase was among 15–29-year-olds (+27.7%) [56].

In both seasons, the number of vaccinations administered and documented in the three specified age groups accounted for only a small proportion of the total (2023/24: 18.75%, 2024/25: 19.89%) [56]. This is consistent with the study results, which also indicate a low vaccination rate.

When comparing these vaccination data, it is important to note that the quoted coverage rates refer to a period when the flu vaccination for children was already included in the free childhood vaccination programme.
Influenza vaccination was integrated into the national vaccination programme for children in Austria during the autumn/winter of 2020 [57]. The data presented in this study refer to the period prior to that. Therefore, Influenza vaccination was a fee-based service for children throughout the entire study period.

4.3 Clinical Implications

The results of the present study provide some important points for dealing with children suffering from influenza in everyday clinical practice. This is particularly significant in the context of early diagnosis, treatment and prevention of influenza infections.
A more profound comprehension of the clinical characteristics and risk factors associated with severe cases has the potential to enhance the outcomes and optimise the clinical care for paediatric patients.

It is therefore important that clinicians pay increased attention to influenza as a cause when children present with acute respiratory or neurological symptoms during the influenza season.
As demonstrated in our study, even previously healthy children can be affected by severe cases. This further emphasises the importance of early diagnosis in children presenting with suspicious symptoms as well as vaccination in non high-risk groups. Due to the high sensitivity and specificity of the method, PCR is considered the gold standard for diagnosis [5,41,45].

As both our study and the existing literature demonstrate, children with pre-existing neurological conditions are particularly at risk of severe disease complications [5,31,45]. This should be considered in the context of preventive vaccination campaigns and when deliberating the early administration of antiviral medication. Furthermore, it is suggested that these children be subjected of more extensive monitoring.

Current guidelines and literature on treatment recommend early administration of antiviral drugs to high-risk groups in order to reduce complications [5,8,45]. In our study, just under 61% of children were treated with antiviral medication. This suggests that this medication may be underused in clinical settings. In high-risk children, empirical antiviral medication could be considered even before a laboratory-confirmed diagnosis.

As a preventative measure, there is a clear need to enhance coverage rates for vaccination in this age group. The present study reveals that none of the patients with documented vaccination status had been immunised. This finding highlights an existing gap in preventive care.

It is recommended that healthcare professionals routinely evaluate the vaccination status of children, using patient interactions as an opportunity to educate parents or guardians on the importance of vaccination and to inform them about ongoing vaccination initiatives [58].

In summary, it can be stated that a severe course of influenza infection has the capacity to affect both healthy children and those with pre-existing conditions. It is therefore crucial for clinicians to pay particular attention to the corresponding clinical manifestations in children, especially during the influenza season. It follows that increased awareness, early diagnosis, adequate drug therapy and appropriate preventive measures can play a key role in alleviating the burden of influenza in children.

4.4 Public health and preventive strategies

The study under discussion highlights not only issues relevant to everyday clinical practice, but also problems and difficulties for the public health system. While cases of severe influenza infection in children are rare, they present a significant challenge to public health systems and clinicians. The low vaccination coverage among the young population in particular demonstrates the importance of the government focusing on public health prevention measures in this area.

In general, Austria has shown a persistent tendency to have a low influenza vaccination coverage rates. A study of vaccination coverage in Austria from 1982 to 2015 revealed that the highest number of vaccine doses distributed per 1,000 population was 142 doses/1,000 in 2006. The vaccination rate in this year was 15.4%. In the following years, there was a significant reduction in the number of vaccine doses. In the 2015/16 season, there were only 62 doses per 1,000 inhabitants with a vaccination rate of 6.1% [59]. A similar situation has been observed in Austria in subsequent seasons. Until the 2020/21 season, the vaccination coverage rate remained at a similarly low level (5.35-7.93%). The onset of the Coronavirus pandemic resulted in a substantial increase in the vaccination coverage rate among the general population. During the 2020/21 period, the highest recorded vaccination rate was 22.13%. This was followed by a slight decline, but far from returning to the previous level: in 2021/22 it was 16.87%, in 2022/23 13.62% and in 2023/24 13.35% [54].

In order to determine the most recent statistics regarding the vaccination coverage rate amongst children and adolescents, the most recent data set (week 30 of 2025 to week 41 of 2025) available for the year 2025 from Austria was analysed. And these shows that the age groups 0-4 years (8.72%), 5-14 years (9.49%) and 15-29 years (3.40%) together account for a small total of 21.60% of all vaccinations documented in the electronic vaccination record. This low vaccination rate is reflected in the data presented in this study. The European Commission has issued a recommendation for a vaccination coverage rate of 75% in vulnerable groups [55].

Consequently, public health system strategies should prioritise the enhancement of vaccination coverage rates. A significant development in this regard was the incorporation of influenza vaccination for children within the scope of the free vaccination programme in Austria. The present situation requires greater popular awareness to be raised through increased publicity.

Another possibility is increased education and vaccination campaigns in schools and educational institutions, as well as medical consultations during routine paediatric check-ups. The key to increasing vaccination rates lies in providing parents and guardians with accurate information regarding the benefits of risks of vaccination [58]. The objective of these campaigns is twofold: firstly, to establish a foundation of trust between medical professionals and guardians; and secondly, to address any misinformation or concerns surrounding vaccination, thereby improving the population's level of knowledge.

A further important tool for reducing the burden of influenza on the population is the maintenance of up-to-date, efficient epidemiological surveillance systems.
It is important to note that these measures enable the continuous monitoring of the effectiveness of therapeutic interventions and vaccinations. Furthermore, they facilitate the capacity of health systems to prepare for disease outbreaks at an early stage.
In Austria, a new reference centre, the 'Reference Centre for Respiratory Viruses', started operating at the Medical University of Vienna on 1 October 2025. The objective of this centre is precisely such continuous monitoring, with the aim of facilitating a faster and more targeted response to waves of infection. The manner in which this centre will contribute to the reduction of the burden of disease will become apparent in the coming years [60].

Moreover, it is necessary to uphold generally accepted hygiene standards during the influenza season in order to disrupt the chain of infection. These include non-pharmacological measures such as maintaining proper hand hygiene, adhering to proper respiratory etiquette, and refraining from using public facilities when experiencing symptoms of an infection [20]. The efficacy of these measures during the course of the pandemic has been well documented, and it is recommended that they be applied universally during the upcoming cold season.

To reduce the burden of influenza infections, particularly among children, a combination of non-pharmaceutical preventive measures, increased vaccination coverage, early diagnosis, education and monitoring of epidemiological surveillance centres is required.
Investing continuously in preventive measures within the public health system is significantly more cost-effective than intensive care treatment and can save lives [61].

4.5 Strengths of the study

A significant benefit of the study is its extensive 15-year investigation period. Additionally, the study is confined to a single centre, ensuring the uniformity of data collection.

A detailed analysis was performed, with the focus exclusively on patients receiving intensive care. This enabled the collective evaluation of clinical, epidemiological and microbiological data.

The cohort studied is drawn from the largest childrens hospitals in Austria, thus providing representative results for Austria in severe cases of paediatric influenza infections.

4.6 Limitations

The present study also has certain limitations.
The study is of retrospective nature and was conducted at a single centre, resulting in a relatively small study cohort of only 57 patients. This reduces the statistical significance of the analyses.

In the early years of the study period, documentation was not yet fully digitalised, therefore incomplete documentation regarding comorbidities, co-infections and clinical manifestations must be taken into account.
In addition, during the initial years of the study period, the options for diagnostic procedures were also more limited. However, the increasing availability of faster point-of-care PCR diagnostics is resulting in a more rapid and accurate diagnosis of the virus. Consequently, it can be concluded that the number of unreported cases of influenza infection was higher in the early years of the study period.

The vaccination status was not documented in approximately 50% of patients, thus severely limiting the significance of the association between severe influenza infection and lack of vaccination. In addition, there is very limited documentation on the vaccination coverage rate of the Austrian population and these figures refer to doses administered and recorded in electronic vaccination records, rather than to population coverage. It is reasonable to assume that the actual number of vaccinations is higher than the reported figure.

Moreover, there is an absence of long-term follow-up data, which precludes the drawing of any conclusions about the subsequent consequences of influenza infection.

4.7 Conclusion and outlook

In summary, this study shows that, although severe cases of influenza are rare, they can affect both healthy children and those with pre-existing conditions, particularly children with neurological disorders. The vaccination rate was extremely low. This highlights the persistent gap in preventive measures, as well as the need to improve early diagnosis and treatment of influenza infections.

It is important for doctors to consider influenza as a possible cause when treating children with respiratory infections or neurological symptoms. In addition, children's vaccination status should be checked during regular check-ups to improve vaccination coverage. Paying more attention to influenza could lead to earlier diagnosis and treatment, resulting in better outcomes.

Future efforts should focus on prevention, such as increasing vaccination rates, establishing epidemiological surveillance centres, improving education and raising awareness.

The study's limitations lie in its retrospective, single-centre design and small cohort size. In addition, undocumented vaccination status prevents more accurate correlation between vaccination status and disease severity. Future studies should be prospective, multicentre and focus on recording vaccination status and long-term follow-up data.

The following hypotheses could be considered for future studies: a comparative study of intensive care influenza cases in Austria with the case rate in countries with higher vaccination rates would be a valuable addition to the research, as it would further investigate the effects of increased vaccination rates. Sweden, Ireland or Spain, for example, could be used for this purpose. Regarding the coverage of vaccinations in the population aged over 65, these countries were at the top of the European rankings in 2024 [62]. Furthermore, a more detailed examination of countries with higher vaccination rates would be beneficial to understand the role of vaccination campaigns, public education, integration of vaccination programmes in schools, general vaccination availability, and vaccination costs in increasing vaccination rates. A profound examination of these elements would thereby furnish measures to enhance the vaccination rate in Austria.

A similar research study should be conducted within Austria. A comparative study of the federal states regarding vaccination rates and measures taken to increase vaccination coverage can provide insightful methods for increasing vaccination rates in other federal states. This would assist in reducing the impact of seasonal influenza. The analyses should be divided into age groups so that they can be examined separately.

Furthermore, a comparison of the vaccination rate and the incidence of illness requiring intensive care across various age groups within the federal states is advised, with a view to re-establishing the correlation between vaccinations and severe cases.

With regard to the subject of vaccination rates in the paediatric population, a study on the relationship between vaccination rates and parents' educational standards could provide relevant information for targeted vaccination campaigns and measures within the population.

Boosted vaccination rates, early identification of the illness, and close cooperation between medical and public health services are fundamental to stopping avoidable illness and death. On-going awareness and financial support for prevention measures are required to ensure the safety of high-risk children during future influenza outbreaks.

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Appendix

The following tool was used to optimize the language of the text:

- Chat GPT
- Chat GPT 4o
- Chat GPT 5.2

Provider: Open AI

Date: April 2024 – December 2025

URL: https://chatgpt.com