

## Streszczenie w języku angielskim

**Title: Analysis of risk factors, clinical course and complications of diseases caused by varicella zoster virus in children with regard to the COVID-19 pandemic.**

### **Introduction**

The varicella-zoster virus (VZV) is a widespread virus that is a causative agent of chickenpox and shingles, diseases that have been described since ancient times. In the 1970s, the first vaccine against chickenpox was developed. It was introduced into many countries' immunisation schedules at the turn of the 20th and 21st centuries. Currently, the vaccination against chickenpox in Poland is only recommended (self-paid) (1). It is compulsory (free of charge) only in high-risk groups, e.g. children with immunodeficiencies and their siblings, children staying in care institutions, orphanages, etc. It is estimated that about 170,000 – 180,000 people, mainly children, get chickenpox in Poland every year (2, 3). Due to the long infectiveness period, the severity of potential complications, and the absence of caregivers from work, this disease represents a high financial burden for Poland's health care and social security systems. In addition, a history of chickenpox at a young age is one of the most important risk factors for an earlier onset of shingles. Although shingles is a relatively rare disease in children, it poses many diagnostic and therapeutic difficulties and often requires hospitalization.

### **Aims of the doctoral dissertation**

1. Assessment of the current epidemiological situation of varicella in children in Poland (Publication No. 1)
2. Description of the clinical course and complications of primary VZV infection in children, including a comparison of the situation before and after the COVID-19 pandemic (Publication No. 1, 2)
3. Analysis of the epidemiology, risk factors, clinical course and complications of herpes zoster in children (Publication No. 3)

4. Define difficulties in the diagnosis and treatment of shingles complications in children (Publication No. 3, 4, 5)

## **Material and methods**

The dissertation consists of a series of 5 publications. These are as follows:

1. An original study (a retrospective cohort study) on children hospitalized in the Department of Children's Infectious Diseases, Medical University of Warsaw/ the Pediatric Infectious Diseases Department of the Regional Hospital of Infectious Diseases in Warsaw in 2019 and 2022. The study compared the epidemiological status and the clinical course of varicella in children in the period before the COVID-19 pandemic and after the lifting of the pandemic restrictions. (Publication No. 1).
2. An original study (a retrospective cohort study) on children hospitalized in the Department of Children's Infectious Diseases, Medical University of Warsaw/ the Pediatric Infectious Diseases Department of the Regional Hospital of Infectious Diseases in Warsaw. The study compared the incidence and clinical course of hepatitis in children with primary VZV infection. (Publication No. 2).
3. Review paper on epidemiology, risk factors, clinical course and complications of herpes zoster in children. (Publication No. 3).
4. Letter to the editor describing a clinical case of zoster meningitis in an immunocompetent boy. (Publication No. 4).
5. Case report series of herpes zoster complicated by facial nerve palsy in immunocompetent children, including discussion on risk factors, clinical course and treatment (Publication No. 5).

## **Results**

**In Publication No. 1**, a group of 221 children was analyzed and an anticipated increase in the number of children hospitalized due to varicella (59 children in 2019 vs. 162 children in 2022) along with an increase in median age (3 years vs. 4 years,  $p = 0.02$ ) was shown. An atypical monthly distribution of cases throughout the year was observed with an increase in incidence in the summer and autumn months (13 patients in 2019 vs. 75 patients in 2022,  $p=0.0011$ ). Among hospitalized patients, 98-99% had not received a single dose of varicella vaccine.

Contacts at home and related to nursery and school attendance accounted for 68-71% of disease sources. In 2022, a more severe clinical course of chickenpox was observed with the worse general condition on admission, longer duration of fever (2 days vs. 4 days,  $p < 0.0001$ ) and longer hospitalization (4 vs. 5 days,  $p = 0.01$ ). The most frequently observed complication was bacterial superinfection of skin lesions, which not only occurred more frequently in 2022 (50.8% vs. 77.8%,  $p = 0.0001$ ), but also had a more severe course in the form of cellulitis (which occurred in 3.4% of patients in 2019 and in 13.6% in 2022,  $p = 0.03$ ). During this period, the incidence of sepsis was five times higher ( $p = 0.009$ ), and there was a significant increase in the use of antibiotics (from 71.2% to 85.2% of hospitalized patients). Patients were also more likely to require combined therapy with two antibiotics (increase from 3.4% to 15.4%,  $p = 0.01$ ).

**In Publication No. 2**, 24 out of 216 analyzed children had an elevated level of alanine aminotransferase (ALT). In 79% of patients, ALT levels were less than twice of the upper limit of normal (ULN), in 16,7% of patients, ALT levels were elevated 2 to 3 times above the ULN, and in only one infant was ALT observed to be 9.4 times higher than the ULN according to age. The median age at the time of the diagnosis was significantly higher in the group of patients with elevated ALT: 5.5 years vs. 3 years in the group with normal ALT values ( $p = 0.02$ ). Gastroenteritis was diagnosed in 25% of the children with elevated ALT levels, which was statistically more frequent than in the group with normal ALT levels ( $p = 0.006$ ) and may have influenced the level of this aminotransferase independently of VZV infection. No gender influence on the ALT levels was found. The severity of the patient's clinical condition on admission did not influence transaminase levels. The median duration of fever and hospitalisation was 1 day longer in the group with elevated ALT. Similarly, varicella skin lesions lasted longer in this group, 7.5 days versus 6 days in the group with normal ALT levels ( $p = 0.01$ ). Despite the features of hepatitis, no effect on liver function as assessed by coagulation markers was observed. None of the patients developed liver failure.

**Publication No. 3** demonstrated that in countries where universal vaccination against chickenpox has been introduced, a decrease in the incidence of shingles in children was observed. Risk factors for developing shingles in childhood include a lack of vaccination against chickenpox, a primary VZV infection at the age of less than a year, Caucasian and Asian origins, adolescence, some chronic diseases such as asthma, and probably acute infections with lymphopenia. The most common locations of shingles in children are thoracic dermatomes. Pain is observed less often in children compared to adults (in about 28% of children up to 5 years of age and about 60% of adolescents, occasionally in children vaccinated against

chickenpox). Shingles complications might be more common in immunocompetent children. We also indicated that a thorough medical history and physical examination are sufficient to identify patients who require broader diagnostics e.g. for immunodeficiency and cancer. In countries with a high incidence of AIDS, HIV screening for every child presenting with shingles is recommended.

**In Publication No. 4**, a case of VZV meningitis in a child with ocular zoster was described. This paper highlights the potential for the appearance of general symptoms prior to the herpes zoster rash. Furthermore, we underlined the fact that features of meningitis may be overlooked in an immunocompetent child with ocular herpes zoster.

**In Publication No. 5**, two cases of Ramsay-Hunt syndrome (RHS) in children were described. This paper underlines that rare presentations of shingles in children pose significant diagnostic challenges, often resulting in delayed treatment initiation. We also underscored the possibility of shingles without a vesicular rash. In addition, attention was paid to the prognosis, which varies depending on the degree of facial nerve palsy. The role of the House-Brackmann scale as not only a descriptive but also a prognostic tool was analysed. It was stressed that in RHS, antiviral treatment and steroid therapy have a proven therapeutic effect. In contrast, other interventions such as physiotherapy, laser therapy, massage, etc., lack strong, substantial clinical evidence to support their use.

## Conclusions

1. In the period after the COVID-19 pandemic and the associated restrictions, an increase in varicella cases in older children was observed. The aforementioned restrictions and immigration due to the Russian aggression on Ukraine may have affected the non-standard distribution of varicella cases throughout the year, with an increase in the incidence during the summer and fall months. The study confirmed that the vaccination rate against chickenpox among hospitalized children was almost zero. Most cases of chickenpox (about 70%) were caused by contacts at home, in nurseries and in schools.
2. In the period after the lifting of the COVID-19 restrictions, a more severe clinical course of chickenpox was observed with a worse general condition on admission, longer

duration of fever and hospitalization, and more frequent septic course of the disease requiring treatment with multiple antibiotics. Bacterial superinfections of the skin remain the most common type of complication, although an increase in their incidence was observed in 2022. Elevated ALT was observed in some immunocompetent children, but no impairment of liver function was found in these patients.

3. The incidence of shingles in children is 1.6-2.2 per 1000 person-years. Risk factors for developing shingles in childhood include lack of varicella vaccination, primary VZV infection before the age of one year, Caucasian and Asian origins, adolescence, some chronic diseases such as asthma, and probably acute infections with lymphopenia. The most common localization of shingles in children include the thoracic dermatomes. Pain associated with the rash is less common in children than in adults. The most common complication is bacterial superinfection of the lesions.
4. Due to the relatively rare occurrence of shingles in children, the diagnosis of rare presentations is difficult and associated with a delay in diagnosis and thus in the initiation of adequate causative treatment. In addition, it also often leads to excessive and unnecessary diagnostic testing.
5. General conclusion resulting from the conducted research: In Poland, due to the lack of obligatory vaccination against varicella, diseases caused by VZV still pose a significant clinical problem. The COVID-19 pandemic has significantly affected the course of varicella, leading to a more severe clinical course of the disease and an increase in the frequency and severity of its complications, including the reactivation of the infection. Efforts to introduce routine vaccination against VZV infection for all children should therefore be supported.