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Title page

Severe varicella complications in hospitalized children and adolescents in central Switzerland, 2010-2020

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Summary

AIM: Recent data on morbidity and mortality of hospitalized children of all age groups due to varicella are missing in Switzerland during a period where universal varicella vaccination (UVV) had not yet been introduced. The aim of the study therefore was to generate such data prior to a potential UVV recommendation by the Swiss national health authority.

METHODS: Retrospective case cohort study of children hospitalized with varicella between 2010 and 2020 at a tertiary children's hospital in central Switzerland, serving around 10 % of the Swiss population. Inclusion criteria were either acute varicella and/or related complications.

RESULTS: 95 patients were identified. The median age at onset was 4 years (range 2 months to 13 years) with a peak of patients between 1-4 years. 53 had mild or moderate and 42 patients had severe varicella-associated complications (8 had $\geq$ 2 severe complications). The most common severe complications were bacterial skin and soft tissue infections (n=28), invasive secondary bacterial infections (n= 18), and central nervous system related complications (n=12). Admission to the paediatric intensive care unit and surgical intervention were required in 11 and 16 patients, respectively. Two previously healthy school age children died due to secondary bacterial infections.

CONCLUSION: Our results demonstrate and confirm that varicella can cause severe and even fatal complications in children living in a highly developed country. This study provides valuable morbidity and mortality data from a large catchment area of Switzerland facilitating future data comparison of children before and after the introduction of UVV in Switzerland.

Abbreviations

CNS: Central nervous system · CSF: Cerebrospinal fluid · GAS: Group A β-hemolytic streptococci · ICD: International Statistical Classification of Diseases and Related Health Problems · MMRV: Measles Mumps Rubella Varicella · MRI: Magnetic resonance imaging · PCR: Polymerase chain reaction · PICU: Paediatric intensive care unit · SPSU: Swiss paediatric surveillance unit · UVV: Universal varicella zoster virus vaccination · VZV: Varicella zoster virus

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Introduction

Varicella (chickenpox) is a common and highly contagious infectious disease caused by varicella zoster virus (VZV). It manifests as a pruritic rash accompanied by fever and other systemic signs and symptoms that usually are mild to moderate. The rash is more intense on the trunk and head than on the extremities, and it typically evolves as a series of “crops” during 1 - 3 days in normal hosts. In the absence of universal varicella zoster vaccination (UVV), varicella occurs primarily in young children, i.e. 52 - 78% in children younger than six years and 89 - 96% of cases before adolescence. Occasionally, severe complications occur, leading to hospitalization, long-term sequelae, or death not only in immunocompromised but also in healthy, immunocompetent children [1]. Potential complications include secondary bacterial infections of the skin and soft tissue (e.g. impetigo, ecthyma, abscess, cellulitis, necrotising fasciitis), toxic shock syndrome, thrombocytopenia, pneumonia (viral and bacterial), hepatitis, arthritis, cerebellitis with ataxia, encephalitis with seizures and coma, as well as congenital varicella syndrome. In Europe, annual incidence rates for varicella vary between 300 - 1,291 per 100,000 population [2]. Data from international surveillance studies show hospitalization rates of 1.3 to 5.5 per 1,000 VZV cases [3-6]. Around 70,000 – 85’000 individuals contract varicella in Switzerland each year [7, 8]. In Switzerland the last national data on VZV hospitalizations of children were obtained during 2000-2003 through the Swiss Paediatric Surveillance Unit (SPSU) and this has been restarted by members of our group in 2021 and is currently ongoing. The calculated hospitalization rate during that 3-year period was 1.3 per 1,000 cases [9]. In USA and Germany, UVV was introduced in 1996 and 2004, respectively, for children from 11 months of age onwards. Thereafter the number of cases (all age groups) decreased by 84% in 2000 compared to 1995/96 in the USA [10]. In Germany, varicella case rates per reporting physician decreased by 84% from a total of 3.6 per month per year in 2005 to 0.6 per month per year in 2012 [11]. During the years of our described cohort, the Swiss Federal Commission for Immunization recommended VZV vaccination (2 doses, at least 4 weeks apart) as a basic vaccination for adolescents 11-15 years of age without a history of prior varicella. Furthermore VZV vaccination is recommended for high-risk individuals and health care workers [12). Only recently (January 2023) Switzerland introduced universal VZV vaccination. As no peer-reviewed paediatric varicella hospitalization data exists in Switzerland since 2003, our aim was to obtain such data, focusing on severe complications.

Materials and methods

Study design

Retrospective case-cohort study of varicella associated hospitalizations. Inclusion criteria were children aged 0 to < 16 years, hospitalized at the Children's Hospital Lucerne between 2010 and 2020. An analysis was performed according to ICD-10- (code B01.-) with primary varicella diagnosis (primary

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diagnosis for hospitalization) or secondary varicella diagnosis (varicella as a concomitant disease during hospitalization). Exclusion criteria: Outpatients. Data collection was performed using a standardized clinical report form. Demographic data, medical history including vaccinations, risk factors, clinical symptoms, diagnostics, treatment, and associated complications were recorded from the case files and entered in an electronic database stored at the Children's Hospital.

Study setting

The study was conducted in the Children's Hospital Lucerne at the Cantonal Hospital Lucerne, which is a tertiary paediatric hospital, serving a catchment area of around 700,000 inhabitants from the entire canton of Lucerne and the other five central Swiss cantons, accounting for approximately 10% of the total Swiss population.

Analysis

Data was extracted using Microsoft Excel tables and statistical analysis was performed using IBM© SPSS© Statistics versions 26 and 29. Statistics were descriptive. Analyses were conducted by calculating the frequencies and percentages.

Definitions

We categorized complications as follows.

Severe:

- Death
- CNS related complications: cerebellitis, meningo-encephalitis, seizure, stroke (vasculitis)
- Invasive secondary bacterial infections: arthritis, meningitis, osteomyelitis, pneumonia, sepsis or toxic shock syndrome, endocarditis
- Bacterial skin and soft tissue infections

Mild:

- Clinical complications: dehydration, nausea, pain, kerato-conjunctivitis
- Laboratory abnormalities: coagulation disorder, elevated liver enzymes, thrombocytopenia

Ethical approval

The study (project number: 2020-01367) was approved by the Ethics Committee Northwestern and Central Switzerland (EKNZ).

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Results

Study Population

Screening for eligibility revealed 142 patients of which 47 had to be excluded (**Figure 1**). 4 children were re-hospitalized during the study period. Median age of the remaining 95 patients was 4 years (range 2 months - 13 years). **Figure 2** shows the distribution of hospitalized varicella cases by age groups including complication categories. There was no child with congenital VZV infection.

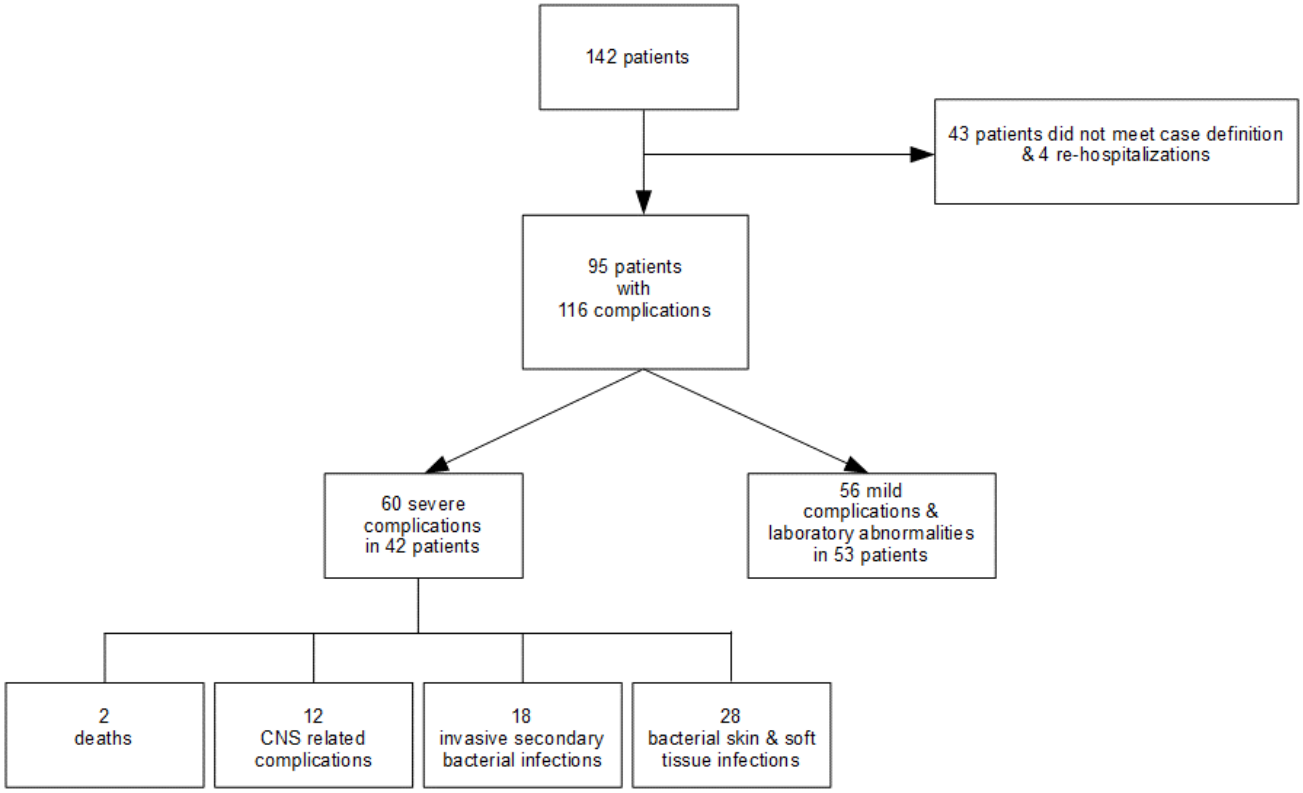

Figure 1: Study population

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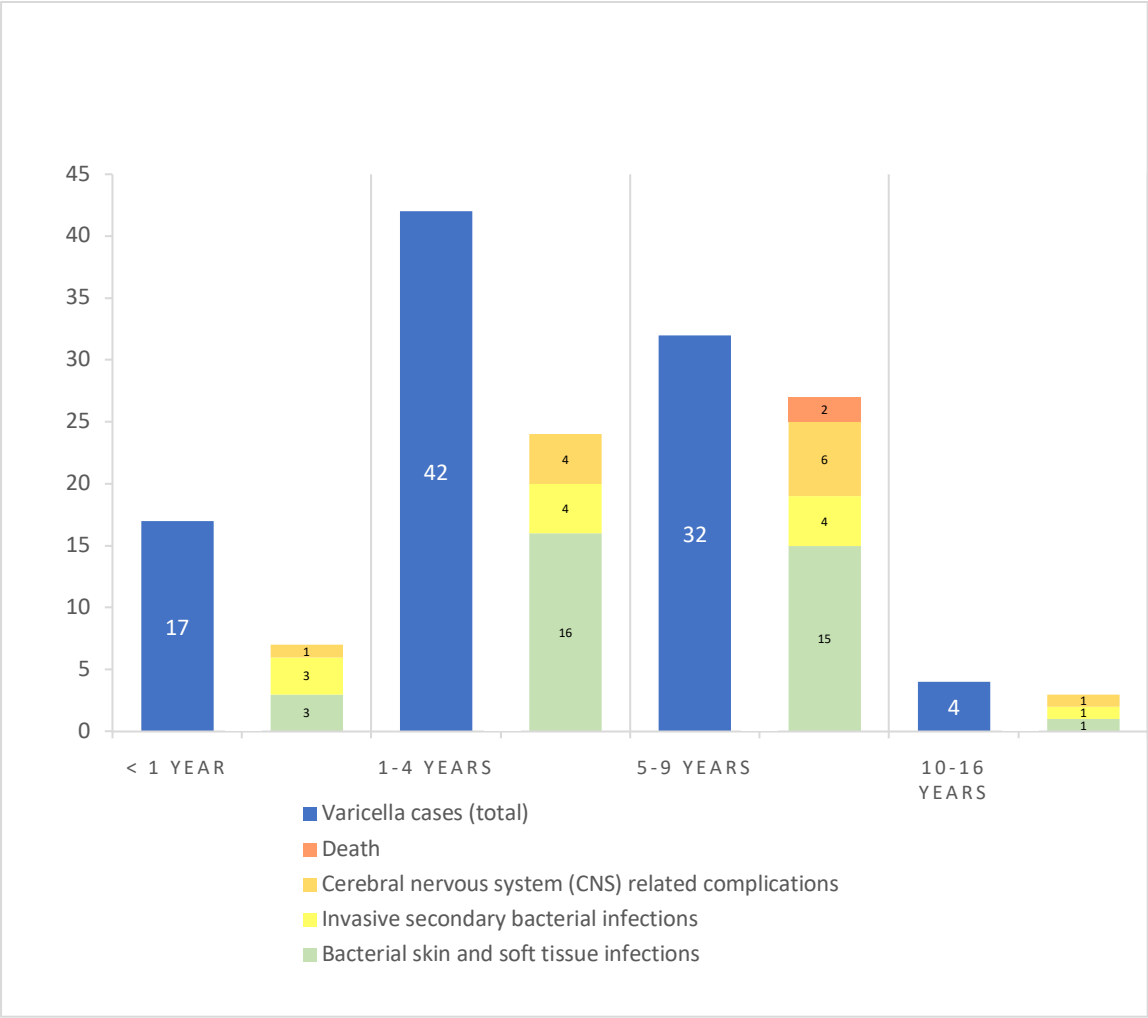

Figure 2: Severe varicella complications by age groups (n= 95 patients).

Of the 95 children, 80 were healthy without any comorbidities, 12 had atopic eczema, and 3 had an underlying oncologic disease. Vaccination status could be assessed in 84 patients: None had received VZV vaccination documented either by certificate or reported by parents. 79 had received universal general vaccinations according to age and the Swiss vaccination recommendations; two patients were incompletely vaccinated, and 3 children had no vaccinations, including two infants having not yet received vaccination due to their young age. Three oncology cases had been previously exposed to varicella and had received post exposure prophylaxis (VZV Immunoglobulin) at least 2 months prior to the current hospitalization. Where information was available, 32 children had been infected within the family and 12 infected within a public institution (e.g. nursery, kindergarten, or school).

Hospitalization duration

Eighty-six children presented to our emergency care unit and were admitted. The median time from onset of first symptoms to hospitalization was 10 days (range: 0 - 150 days). Nine patients had already been hospitalized for various reasons when varicella was diagnosed. The median hospitalization

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duration of 6 days was not different between previously healthy children and children with atopic eczema (range: 1 - 31 and 2-18 days, respectively). Oncological patients had a shorter median hospitalization period of 4 days (range: 3-5 days). Four children with varicella were discharged and had to be readmitted within 4 weeks because of newly occurring complications: Two were re-hospitalized with new pathologies (cerebral vasculitis; osteomyelitis) and two with worsening of a soft tissue infection (abscess; renewed inflammation and swelling pectoral).

Complications

A total of 60 severe complications occurred in 42 of the 95 patients **(Table 1**). Their median age was 4 years (range 7 months to 13 years) and 8 of them experienced more than one severe complication. No child with an underlying oncological disease experienced a severe complication.

Complication categories and causes	**TOTAL PATIENTS (n=42) 60 complications**	**HEALTHY (n=34) 52 complications**	**ATOPIC ECZEMA (n=8) 8 complications**
Death	**2**	**2**	**-**
Listeria monocytogenes meningitis	*1*	*1**	
GAS fulminant sepsis	*1*	*1**	
CNS related complications	**12**	**12**	**-**
Meningo-encephalitis	*4*	*4*	
Cerebellitis	*4*	*4*	
Febrile seizure	*2*	*2*	
Stroke (vasculitis)	*2*	*2**	
Invasive secondary bacterial infections	**18**	**15**	**3**
Endocarditis	*1*	*1**	*-*
Pneumonia	*5*	*4*	*1*
Sepsis or toxic shock syndrome	*9*	*8*	*1*
Arthritis	*2*	*1*	*1*
Osteomyelitis	*1*	*1*	*-*
Bacterial skin and soft tissue infections	**28**	**23**	**5**
Skin	*6*	*4*	*2*
Ecthymata	*1*	*1*	*-*
Others	*5*	*3*	*2*
Soft tissue	*22*	*19*	*3*
Abscess	*4*	*3*	*1*
Necrotising fasciitis	*3*	*2**	*1*
Cellulitis/phlegmon	*11*	*11*	*-*
Others	*4*	*3*	*1*

Table 1: Summary of severe complications in healthy and atopic eczema patients. ** Short case reviews; GAS: Group A β-hemolytic streptococci; fatal Listeria monocytogenes meningitis had multiple complications (case vignette*

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1): sepsis, meningo-encephalitis, cerepellitis, febrile seizure; fatal GAS fulminant sepsis hat multiple complications (case vignette 2): skin infection, sepsis, toxic shock syndrome.

Secondary bacterial infections were the most common severe complications, both skin and soft tissue infections and invasive infections. The median time from onset of first symptoms to hospitalization with a secondary bacterial infection was 6 days (range 1 - 26 days); median age was 4 years (range 7 months - 13 years). Of the 95 patients, two died from bacterial complications (see case vignettes 1 and 2).

Case vignette 1: Fatal Listeria monocytogenes meningitis

A previously healthy eight-year-old boy died of *Listeria monocytogenes* meningitis. Two days prior to hospitalization, fever and initial skin manifestations had occurred, followed by vomiting, dehydration, neck pain, ataxia, somnolence and convulsions. At the emergency room, varicella encephalitis was suspected; immediate intravenous therapy with acyclovir and ceftriaxone (standard local regimen for suspected bacterial meningitis) was initiated and the patient was admitted to the paediatric intensive care unit (PICU). After positive CSF culture for listeria monocytogenes was received within 20 hours, antibiotic therapy was immediately extended to intravenous amoxicillin and amikacin. Rapid neurological deterioration (fixed pupils and apnea) prompted magnetic resonance imaging (MRI) which showed cerebellar swelling with transforaminal herniation. Despite emergency bilateral craniectomy, the patient died within 24 hours of admission. There was no clinical or laboratory evidence of immunodeficiency; and no varicella zoster virus was detected in the cerebrospinal fluid and the brain.

Case vignette 2: Fatal group A β-hemolytic streptococcus (GAS) sepsis

A previously healthy 5-year-old girl presented to the emergency room with septic shock and multiorgan failure, followed by immediate intubation and admission to PICU. Typical skin lesions had evolved three days earlier. Intravenous antibiotic therapy included ceftriaxone, clindamycin and amoxicillin. Blood culture revealed GAS. The patient deteriorated rapidly with cardiac, respiratory and renal failure and was transferred to a university hospital for renal support (hemofiltration) and extracorporeal membrane oxygenation (ECMO). However, the child died 5 days later secondary to brain swelling and herniation.

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Case vignette 3: Cerebral vasculitis and stroke

A previously healthy 6-year-old girl presented to the emergency room with left hemiparesis and choreoathetotic movement disorder. Immediate cranial MRI showed vascular stenosis secondary to vasculitis of the right cerebral artery in the area of segment M1. The patient had experienced uncomplicated varicella 4 months ago. Positive VZV polymerase chain reaction (PCR) in CSF and positive VZV immunoglobulin G (IgG) CSF/serum index was consistent with postinfectious varicella-associated vasculitis. The girl recovered rapidly under high-dose intravenous methylprednisolone therapy and acyclovir. Doppler sonographic and MRI angiographic control four weeks later showed a new stenosis of the right anterior cerebral artery without clinical symptoms in the presence of focal cerebral arteriopathy. The girl was re-hospitalized for repeated steroid therapy over 4 days. Currently (5 years later), the neurological status is unremarkable, the vasculitic changes on MRI have resolved completely on secondary antithrombotic prophylaxis with acetylsalicylic acid.

Case vignette 4: GAS – necrotising fasciitis and endocarditis

A previously healthy 5-year-old boy presented to the emergency room with severe gluteal pain. Typical skin lesions had evolved 2 days earlier. Gluteal necrotising fasciitis was suspected, followed by immediate surgical intervention and administration of intravenous antibiotics with clindamycin and cefuroxime. Blood culture and wound swabs grew GAS. Two further surgical interventions were required. On day 6 of hospitalization, the patient developed a systolic murmur and respiratory and cardiac deterioration. Echocardiography revealed rupture of the chordae tendineae with severe mitral valve prolapse. Antibiotic therapy was switched to intravenous gentamycin and ceftriaxone, and the patient was transferred to a cardiac surgery center for reconstruction with intraoperative evidence of bacterial endocarditis. Re-operation two years later for a new rupture of the chordae tendineae was necessary. Currently (6 years later) the boy has normal exercise tolerance, no medication and a residual defect of moderate mitral regurgitation.

Microbiology

In the 42 patients with severe complications, 35 blood samples, 5 CSF samples, and 21 wound swab or tissue biopsy samples were analyzed. Bacterial growth or viral PCR was detected in 8 blood, 3 CSF and 13 tissue samples. **Table 2** shows the distribution of pathogens by severe VZV complication category. The most frequently detected pathogen was group A β-hemolytic streptococcus (GAS).

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	Specimen		
	Blood	CSF	Wound swab, tissue biopsy
Death	**2**	**1**	**2**
Listeria monocytogenes	*1*	*1*	*1*
GAS	*1*	-	-
GAS & S. aureus	-	-	*1*
CNS related complications	**5**	**3**	**1**
VZV	4	2	-
Listeria monocytogenes	1	1	1
Invasive secondary bacterial infections	**3**	**1**	**7**
GAS	2	-	3
S. aureus	-	-	1
GAS & S. aureus	-	-	1
Listeria monocytogenes	1	1	1
S. aureus & E. faecalis	-	-	1
Bacterial skin and soft tissue infections	**2**	**0**	**13**
GAS	2	-	5
S. aureus	-	-	3
GAS & S. aureus	-	-	2
GAS & P. aeruginosa	-	-	1
S. aureus & Stenotrophomonas maltophilia	-	-	1
S. aureus & P. aeruginosa & E. faecalis	-	-	1

Table 2: Detected pathogens by complication category and source of specimen

Patients and results may appear in more than one complication category, 4 cases with both invasive secondary bacterial infections and bacterial skin or soft tissue infection, both fatal cases with multiple complications see table 1. CSF = cerebrospinal fluid; *GAS = Group A β-hemolytic streptococcus; S. aureus = Staphylococcus aureus; P. aeruginosa = Pseudomonas aeruginosa; E. faecalis = Enterococcus faecalis*

Treatment

In 34 (88%) of 42 patients with severe complications, intravenous antibiotic treatment was administered for a median duration of 6 days (range: 1-16 days). Surgery was performed in 16 cases, including wound debridement in three because of cervical (n =1) or gluteal (n=2) necrotising fasciitis. Six children with soft tissue infection developed an abscess located in the retro-auricular, periorbital, cheek, neck, lower abdomen or thigh area; all abscesses were surgically drained. The further 7 surgical interventions included 2 punctures and one craniectomy, lymph node extirpation, thoracic drainage, nail extraction and wound debridement, respectively.

PICU admission for a median stay of 3 days (range: 1-7 days) was required for 11 of 42 patients with 23 severe complications (10 secondary invasive bacterial infections; 7 CNS related complications; 3 bacterial skin infections; 2 bacterial soft tissue infections; 1 multiorgan failure). 7 PICU patients experienced more than one severe complication, two of them had 5 and 4 severe complications at the same time, respectively. The median age of all PICU patients was 6 years (range: 2 to 12 years).

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Discussion

This comprehensive retrospective case analysis spanning an 11-year period (2010-2020) reviewed all varicella associated pediatric hospitalizations at a large tertiary hospital in central Switzerland, serving approximately 10% of the Swiss paediatric population. The study encompassed 95 patients, with nearly half of the affected children manifesting severe complications. Most of the hospitalized children where 0- 9 years old with a peak in preschool age which is in accordance with the overall age distribution of all varicella cases in Switzerland during the pre-vaccination era [13]. This pattern was also true for the severe complications, PICU stay and surgery interventions. Our observation is in accordance with a former Swiss Paediatric Surveillance study [9], as well as studies in other countries [11, 14-16]. None of the patients had been vaccinated against varicella. At the time of this study there was no universal varicella immunization recommendation in Switzerland. However, there was a recommendation to vaccinate children from 11 years of age onwards who did not have varicella by then. This means, that one of our patients (12 years old) should have been vaccinated but was not. Consequently, these findings accentuate the vulnerability of this specific age cohort and advocate for the preemptive implementation of immunization strategies, ideally instigated preceding the first birthday. Since January 2023, universal varicella immunization has been recommended in Switzerland with 2 doses at 9 and 12 months of age and a catch-up program for older children [17].

Analysis of our cohort showed that most patients with severe VZV complications were previously healthy, except a small subgroup of patients with atopic eczema. Furthermore only 3% of cases were children with an underlying oncological disease. This observation has also been made in studies from Germany and New Zealand, which showed that most patients with complicated varicella are primarily healthy. However, they were older during onset of varicella complications and the duration of hospitalization compared to immunocompetent children was similar [10, 18, 19]. Possible reasons for this observation in the oncology cases may be a faster presentation to the health care system, a lower threshold for hospitalization, and use of anti-viral medications.

Generally, in secondary bacterial infections in both previously healthy and children with underlying atopic eczema the most prominent pathogen was Group A streptococcus (GAS), causing a considerable amount of morbidity necessitating surgical interventions and PICU admission. The GAS pathogen was also the cause of one fatal case in our study. The association of GAS as secondary bacterial infection in varicella is well described [20-22] and was responsible for one-third of the bacterial skin and soft tissue infections in our cohort. Invasive bacterial infections affecting skin and soft tissue accounted for one third of admissions in our cohort and the most common invasive complications were sepsis and pneumonia.

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Varicella has been shown in various studies to be the most important risk factor for developing invasive infection with GAS (including necrotising fasciitis), with the risk estimated to be 58-60-fold higher than in the general population [20-22]. Children may be colonized with virulent GAS strains and transfer these to different body areas by scratching varicella skin lesions further breaking the skin barrier facilitating invasive GAS infections and complications [23].

Furthermore, children with atopic dermatitis may be at increased risk for bacterial infections. Negative influencing factors are chronic inflammation, a dysfunctional skin barrier due to altered skin pH values and lower epidermal antimicrobial peptins, and anti-inflammatory medication (topical steroids) used in atopic dermatitis [24, 25). VZV infection may lead to transient virus-induced alterations in the innate immune response [26].

In the other fatal case found in our study, there was a combination of varicella with a concurrent *Listeria monocytogenes* meningitis. Risk factors such as a weakened immune system or associated underlying diseases (HIV-AIDS, post-transplant status, cancer) were not present in this child. A previous literature review yielded only two case reports of patients who developed *Listeria monocytogenes* meningitis within 6 weeks of varicella. Although there was no evidence of immunocompromise, a transient T-cell abnormality due to VZV infection could not be excluded as a risk factor for invasive listeriosis which can be a serious and life-threatening condition [27, 28]. Thus, it can be assumed that invasive infection with *Listeria monocytogenes* can occur as a complication of VZV infection. Nevertheless, it may be prudent in children presenting with varicella and meningitis to broaden the empirical treatment by including an antibiotic covering also *Listeria monocytogenes* (such as an aminopenicillin).

CNS complications were the second most common complications which led to hospitalization. CNS complications have been described for varicella and their proportion among all complications varies in different studies (9 - 61 %) [29-32]. Bonhoeffer et al described a large pediatric varicella cohort in Switzerland and reported 25% CNS involvement in the complications they studied [9]. Encephalitis, being the most frequent manifestation [29] of CNS complications, may occur because of direct viral invasion or as a postinfectious immunological late reactivation of a latent or subclinical infection. Weeks to months following varicella, there is an increased risk of vasculopathy and ischemic strokes or transient cerebral arteriopathy. Reason for VZV vasculopathy is vascular invasion when the virus spreads transaxionally from the ganglia to vessel walls [33]. After reactivation from trigeminal or upper cervical ganglia it travels along neurites and infects the adventitia of cerebral arteriae causing vasculopathy [34]. Of particular note, one case of mitral regurgitation and papillary muscle rupture due to varicella complication with GAS occurred during the study period and has been published elsewhere [35].

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The average duration of hospitalization due to varicella has been reported in various studies to be 4-8 days, and the results of our study are also within this range [9, 19, 31 - 32]. Most of the children requiring intensive care were previously healthy, i.e., immunocompetent (8 patients), which is in accordance with other international studies [2, 9]. The average age of the children with admission to PICU was 6 years, slightly higher than the average age of the overall study population (4 years). This is plausible because the risk of severe disease appears to increase with age. The results of Bonhoeffer et al. considering mean age of admission to PICU support this observation as well [9]. The proportion of cases that had to be admitted to the PICU is slightly higher in our study (12%) compared to the literature (3-9%) [9, 14, 19].

Often considered a harmless disease, varicella causes high costs and burden for the society. Not only the direct health costs caused by the disease, which can, depending on the length of stay and complications, sum up only for the hospital admission up to between 1,000 - 25,000 euros (average 1,625 euros). But also, the socio-economic costs caused by the sometimes-long absences from work for caregivers and parents during the illness of their children [31]. If we compare the costs of an UVV, as recommended in Switzerland since 2023, with the vaccination recommendation that was valid during our study (vaccination at the age of 11-40 years in the absence of a history of varicella), we see that the direct costs (costs of preventive vaccination vs. healthcare costs caused by the disease) differ only slightly (CHF 1.75 to 1.5 million, respectively). Looking at the indirect costs, however, there is a saving of around CHF 620,000 per year with UVV. In addition to the lower morbidity and complication rate, these are arguments in favor of introducing UVV in Switzerland [36].

Conclusion

This retrospective study provides a comprehensive description of age, hospitalization duration, disease characteristics, severe complication rate, and treatment of children and adolescents hospitalized with varicella over a period of 10 years before the introduction of UVV in Switzerland. These data will be supplemented by a current ongoing, prospective nationwide surveillance and can be used in the future for evaluations of the impact of UVV introduction, in particular the reduction of VZV-associated hospitalizations and severe complications.

Statement on funding sources and conflicts of interest

This study did not receive any funding. The authors declare no competing interests.

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