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Clinical outcomes and severe complications of hospitalised children and adolescents with varicella in central Switzerland: a retrospective observational study

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Summary

AIM: Recent data on clinical complications and mortality among hospitalised children and adolescents due to varicella are unavailable in Switzerland. The aim of the study was to explore data on severe varicella complications in hospitalised children before the introduction of a universal varicella vaccination recommendation, which the Swiss Federal Office of Public Health implemented in January 2023.

METHODS: This was a retrospective observational study of children hospitalised with varicella between 01.01.2010 and 31.03.2020 at a tertiary children's hospital in central Switzerland serving approximately 10% of the Swiss population. The inclusion criteria were acute varicella and/or related complications.

RESULTS: A total of 95 patients were identified. The median age at onset was 4 years (range: 2 months to 13 years) and the peak age of patients was between 1 and 4 years. 53 had mild and 42 patients had severe varicella-associated complications (8 had >1 severe complication). 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 (12%) and 16 (17%) patients, respectively. Two previously healthy school-age children died because of secondary bacterial infections.

CONCLUSION: Our results demonstrate that varicella can cause severe and even fatal complications in children living in a highly developed country. This study provides valuable clinical data on severe varicella complications in hospitalised children from a large catchment area of Switzerland, facilitating future data comparison of the disease burden before and after the introduction of universal varicella vaccination in Switzerland.

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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" over 1 to 3 days in non-immunocompromised hosts. In the absence of universal varicella zoster vaccination, varicella occurs primarily in young children, specifically, 52–78% of cases occur in children younger than six years, and 89–96% of cases occur before adolescence [1]. Occasionally, severe complications occur – leading to hospitalisation, 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, and necrotising fasciitis), toxic shock syndrome, thrombocytopenia, pneumonia (viral and bacterial), hepatitis, arthritis, cerebellitis with ataxia, encephalitis with seizures and coma, and congenital varicella syndrome. In Europe, annual incidence rates for varicella vary between 300 and 1291 per 100,000 population [2]. Data from international surveillance studies show hospitalisation rates of 1.3 to 5.5 per 1000 VZV cases [3–6]. Approximately 70,000–85,000 individuals contract varicella in Switzerland each year [7, 8]. In Switzerland, the most recent national data on VZV hospitalisations of children were obtained in 2000–2003 through the Swiss Paediatric Surveillance Unit (SPSU). This national surveillance was restarted by members of our group in July 2021 and is currently ongoing. The calculated hospitalisation rate during that 3-year period was 1.3 per 1000 cases [9]. In the USA and Germany, universal varicella vaccination was introduced in 1996 and 2004, respectively, for children aged 11 months and older. Thereafter, in the USA, the number of cases (all age groups) decreased by 84% in 2000 compared with 1995/96 [10]. In Germany, varicella

case rates per reporting physician decreased by 84%, from 3.6 per month in 2005 to 0.6 per month in 2012 [11]. During the years of our described cohort, the Swiss Federal Commission for Immunisation recommended VZV vaccination (two doses, at least 4 weeks apart) as a basic vaccine for adolescents aged 11–15 years without prior varicella. Furthermore, VZV vaccination is recommended for high-risk individuals and healthcare workers [12]. Only recently (January 2023) did Switzerland introduce universal VZV vaccination. As no peer-reviewed paediatric varicella hospitalisation data have been collected in Switzerland since 2003, we aimed to explore data on severe varicella complications and clinical outcomes in hospitalised children from a large catchment area of Switzerland, facilitating future data comparison before and after the introduction of universal varicella vaccination in Switzerland.

Materials and methods

Study design

This retrospective observational study of varicella-associated hospitalisations included children aged 0 to <16 years with clinical signs and symptoms of varicella who were hospitalised at Children's Hospital Lucerne between 01.01.2010 and 31.03.2020. Microbiological confirmation of clinical varicella diagnosis was not a prerequisite. Screening for eligibility was conducted using ICD-10 code B01 for a primary varicella diagnosis (primary diagnosis for hospitalisation) or a secondary varicella diagnosis (varicella as a concomitant disease during hospitalisation or recent preceding disease). Outpatients were excluded. The output of this case capture was systematically reviewed and validated by the first author (JS) and last author (MB), and all double entries were removed. For this observational study, outcome measures were not differentiated into primary or secondary outcomes. The outcome measures included the exploration and description of varicella complications, clinical course, risk factors, microbiology, and treatment in hospitalised children and adolescents.

Data collection was performed using a standardised clinical report form. Demographic data (sex, age, and nationality), medical history (vaccination status, hospitalisation duration, place of infection, and family medical history), risk factors (immune status, co-morbidities, and atopic disease), clinical symptoms (rash, fever before hospitalisation and on admission, vomiting, diarrhoea, tachycardia, hypotension, dyspnoea, and others), diagnostics (microbiology: blood culture, polymerase chain reaction (PCR), cerebrospinal fluid, wound swab, radiology, and EEG), treatment (antipyresis, surgery, and antiviral and antibacterial therapy), and associated complications (see definitions below) were recorded from the case files and entered into an electronic database stored at the children's hospital.

Study setting

The study was conducted in the Children's Hospital of Central Switzerland (Lucerne) at the Cantonal Hospital of 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 were 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. No additional software libraries, frameworks, or packages were used in this study.

Definitions

Case definition used for varicella: Clinician diagnosis of an acute illness with a generalised vesicular or maculopapulovesicular rash with or without laboratory confirmation (e.g. for positive VZV PCR) or a positive VZV PCR detected in the diagnostic work-up (e.g. for cerebrospinal fluid or an atypical skin lesion) of a patient.

Complications were categorised as follows.

Severe

- Death
- Central nervous system related complications: cerebellitis, meningoencephalitis, seizure, stroke (vasculitis)
- Invasive secondary bacterial infections of different organs: arthritis, endocarditis, meningitis, osteomyelitis, and pneumonia
- Sepsis (according to the Goldstein criteria) [13]
- Toxic shock syndrome (with clinical and laboratory changes caused by Gram-positive pathogens) [14]
- Bacterial skin and soft tissue infections (including all classes, not subdivided) [15]

Mild

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

Ethics approval

The study protocol was prepared by the first (JS) and last (MB) authors and was approved by the Ethics Committee of Northwestern and Central Switzerland (EKNZ) (project number: 2020-01367). General consent was not implemented in this tertiary hospital during the study period. According to article 34 a) HFG (swissethics.ch), the need for individual consent was waived by the ethics committee.

Results

Study population

Screening for eligibility by ICD-10 code resulted in 230 cases, 131 of whom had to be excluded due to not meeting the case definition; 88 patients had complications not related to varicella, and in 43 patients, varicella diagnosis was not confirmed (figure 1). Four children were re-hospitalised with new complications due to varicella during the study period; they were included in the analysis but counted as one case. The median age of the remaining 95 patients was 4 years (range: 2 months to 13 years). Figure 2

shows the distribution of hospitalised patients with varicella by age group. Between 2010 and 2020, 0.5 to 3.8 patients with VZV complications were identified per 1000 inpatient admissions (table 1) in Lucerne. Figure 3 provides an overview of patients with severe complications, including complication categories. No children had congenital VZV infection.

Of the 95 children, 80 (84%) had no comorbidities, 12 (13%) had atopic eczema, and 3 (3%) had an underlying oncologic disease. Vaccination status could be assessed in 84 patients; none had received VZV vaccination, as documented by a certificate or reported by the parents. A total of 79 had received other universal general vaccinations according to age and the Swiss vaccination recommendations; two patients were incompletely vaccinated; and three children had no vaccinations, including two infants who had not yet received vaccination due to their young age. Three oncology patients had been previously exposed to varicella and had received post-exposure prophylaxis (VZV Immunoglobulin) at least 2 months before the current hospitalisation. In 44 patients, exposure information was available: 32 children were exposed within their families, and 12 were exposed in a public institution (e.g. nurseries, kindergartens, or schools).

Figure 1: Study population meeting the inclusion criteria. The four patients with re-hospitalisation were counted as one case in the analysis. * Eight patients experienced more than one severe complication and are listed in more than one complication category. CNS: central nervous system.

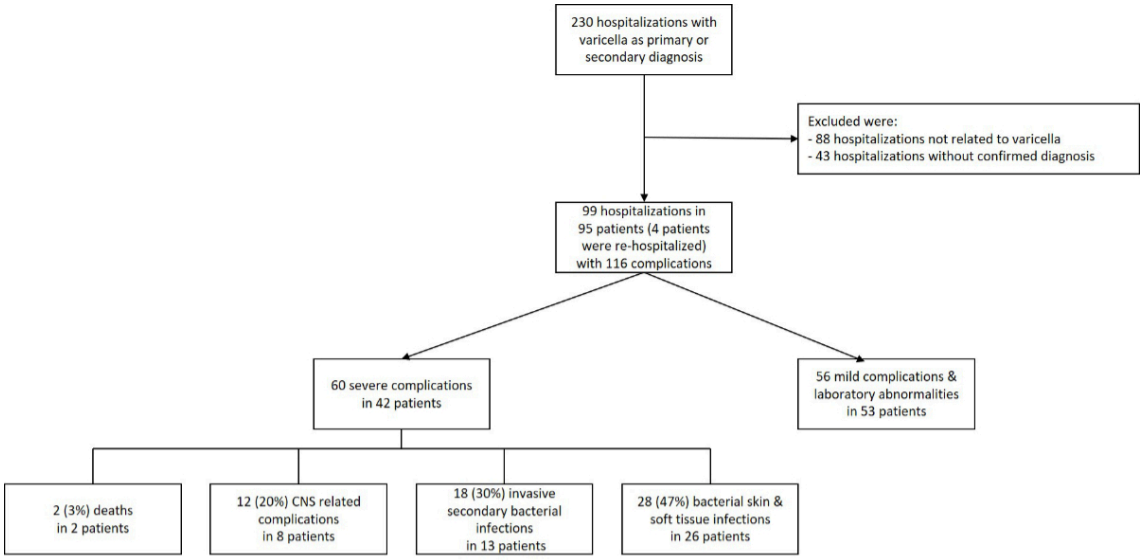
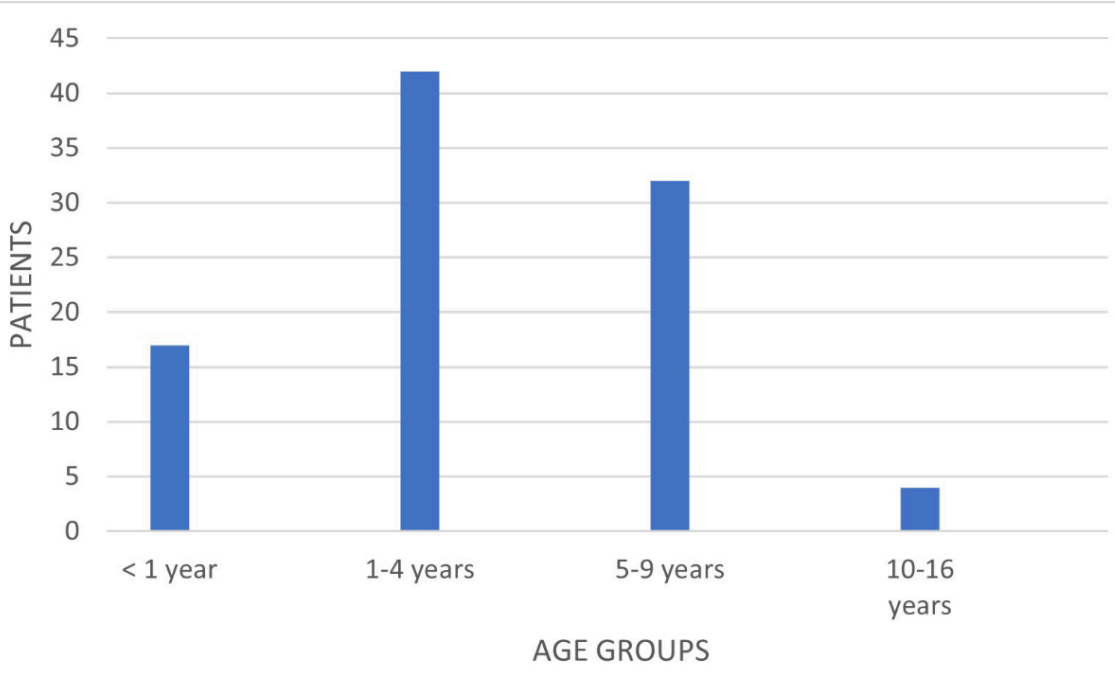


Figure 2: Distribution of all hospitalised patients with varicella by age group (n = 95).



Hospitalisation duration

Eighty-six children presented to our emergency care unit and were admitted. The median time from onset of first symptoms to hospitalisation was 10 days (range: 0–150 days). Nine patients had already been hospitalised initially for a "non-varicella" diagnosis; however, during the course, they had varicella as a further diagnosis. The median hospitalisation duration was 6 days in previously healthy children and in children with atopic eczema (range: 1–31 and 2–18 days, respectively). Oncology patients had a shorter median hospitalisation period of 4 days (range: 3–5 days).

Table 1:
Epidemiology of varicella zoster virus hospitalisations at the Children's Hospital of Central Switzerland, Lucerne (2010–2020).

Study year	Number of hospitalisations	Varicella-related hospitalisations	Varicella-related hospitalisations per 1000 hospitalisations
2010	3692	14	3.8
2011	3705	6	1.6
2012	3815	5	1.3
2013	3846	12	3.1
2014	4138	12	2.9
2015	3940	8	2
2016	4088	8	2
2017	4069	16	4
2018	4199	4	1
2019	4557	8	1.8
2020*	1112	2	1.8

* January to March 2020.

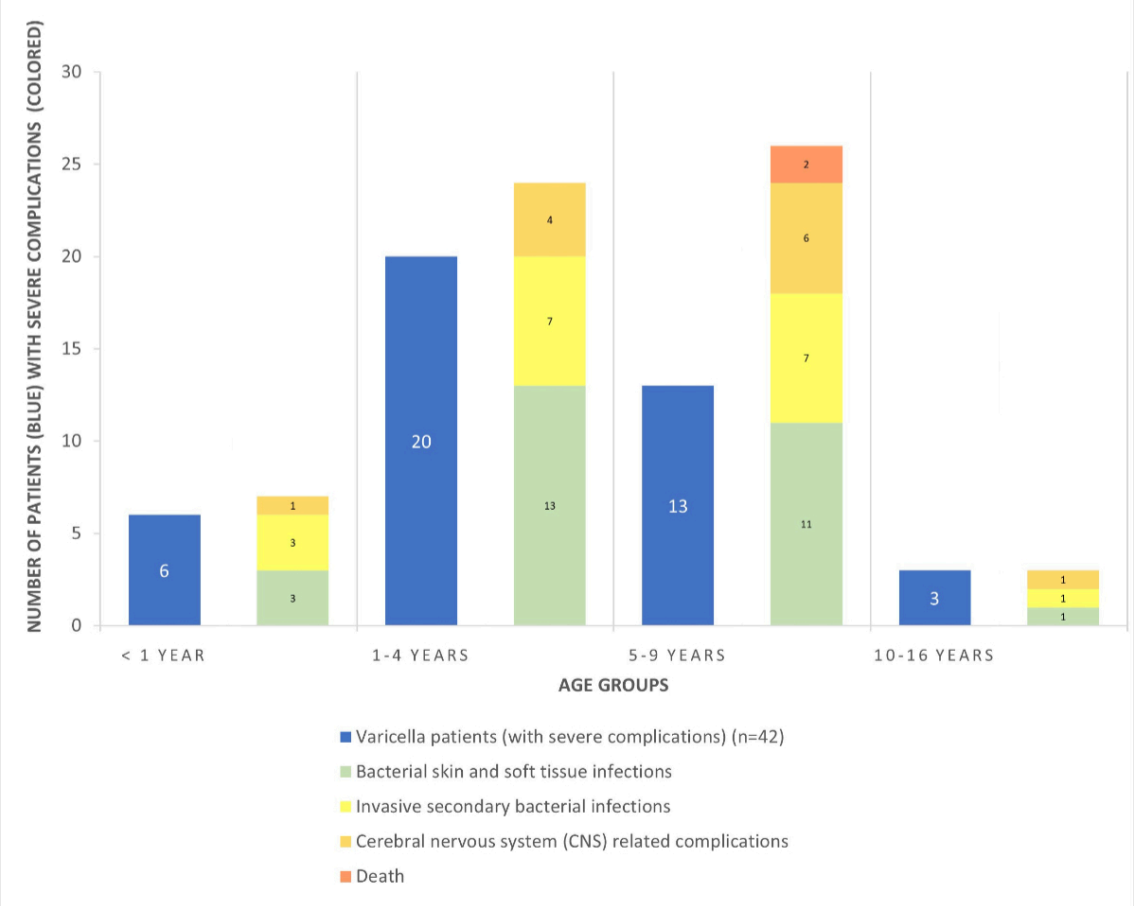
Complications

A total of 60 severe complications occurred in 42 (44%) of the 95 patients (table 2), including 8 (53%) of the 15 patients with comorbidities and 34 (42%) of the 80 patients without comorbidities. 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.

Four children with varicella were discharged and had to be readmitted within 4 weeks because of newly occurring complications: two were re-hospitalised with new pathologies (cerebral vasculitis (see case vignette 3) and osteomyelitis). Two had worsening soft tissue infections (abscess; renewed inflammation and pectoral swelling).

Secondary bacterial infections were the most common severe complications – both skin and soft tissue infections and invasive infections. The median time from the onset of the first symptoms to hospitalisation with a secondary bacterial infection was 6 days (range: 1–26 days). Of the 95 patients, 2 died from bacterial complications (see case vignettes 1 and 2).

Figure 3: Severe varicella complications by age group. The blue bars show the number of patients with severe varicella complications (n = 42); the coloured bars show the numbers and categories of severe complications (n = 60) in the respective age groups. Eight patients experienced more than one severe complication.



Case vignette 1: Fatal Listeria monocytogenes meningitis

A previously healthy 8-year-old boy died of *Listeria monocytogenes* meningitis. Fever and typical varicella skin lesions had occurred two days before hospitalisation, followed by vomiting, dehydration, neck pain, ataxia, somnolence, and convulsions. In 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. After a positive cerebrospinal fluid 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 apnoea) prompted magnetic resonance imaging (MRI), which revealed cerebellar swelling with transforaminal herniation. Despite an emergency bilateral craniectomy, the patient died within 24 hours of admission. No clinical or laboratory evidence indicated immunodeficiency, and no varicella zoster virus was detected in the cerebrospinal fluid or the brain.

Case vignette 2: Fatal group A Streptococcus 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 the paediatric intensive care unit. Typical skin lesions had evolved three days earlier. Intravenous antibiotic therapy included ceftriaxone, clindamycin, and amoxicillin. Blood culture revealed group A *Streptococcus*. 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

Case vignette 3: Cerebral vasculitis and stroke

A previously healthy 6-year-old girl presented to the emergency room with left hemiparesis and choreoathetoid movement disorder. Immediate cranial MRI showed vascular stenosis secondary to vasculitis of the right cerebral artery around segment M1. The patient had experienced uncomplicated varicella 4 months prior. A positive VZV PCR in the cerebrospinal fluid and a positive VZV immunoglobulin G (IgG) cerebrospinal fluid / serum index were consistent with postinfectious varicella-associated vasculitis. The girl recovered rapidly under high-dose intravenous methylprednisolone therapy and acyclovir. Doppler sonographic and MRI angiographic control 4 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-hospitalised for repeated steroid therapy over 4 days. Currently (5 years later), the neurological status is unremarkable; the vasculitis changes on MRI have resolved completely on secondary antithrombotic prophylaxis with acetylsalicylic acid.

Case vignette 4: Group A Streptococcus – 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 interven-

Table 2:
Summary of severe complications in healthy patients and those with atopic eczema.

Complication categories			**Total patients**	**No comorbidities**	**Atopic eczema**
			n = 42	**n = 34**	**n = 8**
Including specified pathologies			**60 complications**	**52 complications**	**8 complications**
Death			**2**	**2**	–
	Listeria monocytogenes meningitis		1	1*	
	Group A *Streptococcus* fulminant sepsis		1	1*	
Cerebral and nervous system-related complications			**12**	**12**	–
	Meningoencephalitis		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
		Ecthyma	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

* Short case vignettes (see below). The patient with fatal *Listeria monocytogenes* meningitis had multiple complications (case vignette 1): meningoencephalitis, cerebellitis, febrile seizure, and sepsis; the patient with fatal group A *Streptococcus* fulminant sepsis had multiple complications (case vignette 2): sepsis, toxic shock syndrome, and skin infection.

tion and administration of intravenous antibiotics with clindamycin and cefuroxime. Blood culture and wound swabs grew group A *Streptococcus*. Two further surgical interventions were required. On day 6 of hospitalisation, 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 centre for reconstruction with intraoperative evidence of bacterial endocarditis. Re-operation 2 years later for a new rupture of the chordae tendineae was necessary. Currently (6 years later) the boy has normal exercise tolerance, requires no medication, and has a residual defect of moderate mitral regurgitation.

Microbiology

In the 42 patients with severe complications, 35 blood samples, 5 cerebrospinal fluid samples, and 21 wound swab or tissue biopsy samples were analysed. Bacterial growth or viral PCR was detected in 8 blood, 3 cerebrospinal fluid, and 16 tissue samples. Table 3 shows the distribution of pathogens by specimen and severe varicella complication category. The most frequently detected pathogen was group A *Streptococcus*.

Treatment

In 35 (84%) of 42 patients with severe complications, intravenous antibiotic treatment was administered for a median duration of 6 days (range: 1–16 days). No antibiotic treatment was administered to five patients with non-bacterial central nervous system-related complications (one with encephalitis, two with cerebellitis, one with febrile seizure, and one with stroke) or two patients with bacterial soft tissue infections (of the abdomen and knee). The two soft tissue infections did not require antibiotics, as one was a superficial abscess that was locally disinfected and rinsed during the treatment course, and the other was a knee joint effusion without evidence of a pathogen after rinsing.

Surgery was performed in 16 patients, including wound debridement in three because of cervical (n = 1) or gluteal (n = 2) necrotising fasciitis. Six children with soft tissue infection developed abscesses in the retro-auricular, periorbital, cheek, neck, lower abdomen or thigh area; all abscesses were surgically drained. The other seven surgical

Table 3:
Pathogens detected and complication categories.

Patient ID	Specimen	Pathogen	Complication category			
			Death	Central nervous system-related complications	Invasive secondary bacterial infections	Bacterial skin and soft tissue infections
10-01	Swab	Group A *Streptococcus*			X	X
10-02	Swab	Group A *Streptococcus* and *Pseudomonas aeruginosa*				X
11-02	Blood (PCR)	Varicella zoster virus				X
	Swab	Group A *Streptococcus* and *Staphylococcus aureus*				
11-06	Swab	*Staphylococcus aureus* and *Stenotrophomonas maltophilia*				X
13-01	Swab	*Staphylococcus aureus* and *Enterococcus faecalis*			X	
13-03	Blood (PCR)	Varicella zoster virus		X		
	Cerebrospinal fluid	Varicella zoster virus				
13-11	Swab	*Staphylococcus aureus*				x
13-12	Blood	*Listeria monocytogenes*	X	X	X	
	Cerebrospinal fluid	*Listeria monocytogenes*				
	Swab	*Listeria monocytogenes*				
14-07	Blood	Group A *Streptococcus*	X		X	X
	Swab	Group A *Streptococcus* and *Staphylococcus aureus*				
14-11	Blood (PCR)	Varicella zoster virus		X		
16-07	Blood (PCR)	Varicella zoster virus		X		
17-02	Blood	Group A *Streptococcus*			X	X
	Swab	Group A *Streptococcus*				
17-05	Swab	*Staphylococcus aureus*			X	X
17-07	Swab	Group A *Streptococcus*			X	
17-09	Swab	*Staphylococcus aureus* and *Enterococcus faecalis* and *Pseudomonas aeruginosa*				X
17-10	Swab	Group A *Streptococcus*				X
17-14	Swab	Group A *Streptococcus*				X
17-15	Cerebrospinal fluid	Varicella zoster virus		X		
18-02	Swab	*Staphylococcus aureus*				X
19-01	Blood	Group A *Streptococcus*				X
20-01	Swab	Group A *Streptococcus*				X

PCR: polymerase chain reaction.

Blood n = 8; cerebrospinal fluid n = 3; swab (swab means either a wound swab or a tissue biopsy) n = 16. Some patients had positive tests in more than one specimen.

interventions included two joint punctures (knee and shoulder) and one craniectomy (case vignette 1), lymph node extirpation, thoracic drainage, nail extraction, and wound debridement, respectively.

Paediatric intensive care unit admission for a median stay of 3 days (range: 1–7 days) was required for 11 (26%) of 42 patients with 23 severe complications (10 secondary invasive bacterial infections, 7 central nervous system-related complications, 3 bacterial skin infections, 2 bacterial soft tissue infections, and 1 multiorgan failure). Seven patients in the paediatric intensive care unit experienced more than one severe complication; two of them had five and four severe complications at the same time, respectively. The median age of all paediatric intensive care unit patients was 6 years (range: 2 to 12 years).

Discussion

In this comprehensive retrospective observational study conducted over 10 years and 3 months (2010–2020), we reviewed all varicella-associated paediatric hospitalisations at a large tertiary hospital in central Switzerland serving approximately 10% of the Swiss paediatric population. The study included 95 patients, nearly half of whom had severe complications. Most of the hospitalised children were 0–9 years old, with a peak in preschool age, which aligns with the overall age distribution of all varicella cases in Switzerland during the pre-vaccination era [16]. This pattern was also observed for severe complications, paediatric intensive care unit stay, and surgery interventions. Our observation is consistent with a former Swiss Paediatric Surveillance Unit study [9], as well as studies from other countries [11, 17–19]. At the time of this study, no universal infant varicella immunisation recommendation was in place in Switzerland. However, vaccination was recommended for children aged 11 years and older with no history of varicella. In our cohort, one patient (13 years old) should have been vaccinated but was not.

Since January 2023, universal varicella immunisation has been recommended in Switzerland, with two doses at 9 and 12 months of age and a catch-up program for older children [20].

Analysis of our cohort revealed that most patients with severe varicella zoster virus (VZV) complications were previously healthy without pre-existing comorbidities, except for a small subgroup with atopic eczema. Additionally, only 3% of patients hospitalised for varicella were children with underlying oncological conditions. This is consistent with previous studies conducted in Germany and New Zealand, which also reported that most patients with complicated varicella were otherwise healthy. However, patients with oncological diseases were older at the onset of varicella complications, and the duration of hospitalisation was similar to that of immunocompetent children [10, 21, 22]. Potential explanations for this observation in oncology patients include earlier presentation to healthcare services, a lower threshold for hospitalisation, and non-reluctant use of anti-viral medications.

Generally, in secondary bacterial infections in previously healthy children and those with underlying atopic eczema, the most prominent pathogen was group A *Streptococcus*, which caused considerable morbidity and required surgical interventions and paediatric intensive care unit admission. Group A *Streptococcus* was also the cause of one fatal case in our study. The association of group A *Streptococcus* as a secondary bacterial infection in varicella is well described [23–25]. In our cohort, group A *Streptococcus* was the most common pathogen (10 out of 24). Invasive bacterial infections affecting the skin and soft tissue accounted for one-third of admissions in our cohort, and the most common invasive complications were sepsis and pneumonia. Varicella has been shown in various studies to be the most important risk factor for developing invasive infection with group A *Streptococcus* (including necrotising fasciitis), with the risk estimated to be 58–60-fold higher than in the general population [23–25]. Children may be colonised with virulent group A *Streptococcus* strains in their oropharynx and transfer them to different body areas by scratching varicella skin lesions, further breaking the skin barrier and facilitating invasive group A *Streptococcus* infections and complications [26]. Notably, one case of mitral regurgitation and papillary muscle rupture due to a varicella complication with invasive group A *Streptococcus* infection occurred during the study period and has been published elsewhere [27].

Furthermore, children with atopic dermatitis are at increased risk for bacterial infections. The risk factors are chronic inflammation, a dysfunctional skin barrier due to altered skin pH values and lower epidermal antimicrobial peptides, and anti-inflammatory medication (topical steroids) used for atopic dermatitis [28, 29]. VZV infection may lead to transient virus-induced alterations in the innate immune response [30].

The other fatal case in our study had a combination of varicella with concurrent *Listeria monocytogenes* meningitis. However, risk factors such as immunosuppression or associated underlying diseases (HIV, post-transplant status, and 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.Despite a lack of evidence of immunodeficiency, 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[31, 32]. Thus, it can be assumed that invasive infection with *Listeria monocytogenes* can occur as a complication of VZV infection. Therefore, it may be prudent to broaden the empirical treatment by including an antibiotic that also covers *Listeria monocytogenes* (such as aminopenicillin) in children presenting with varicella and meningitis.

Central nervous system complications were the second most common complication leading to hospitalisation. Central nervous system complications have been described for varicella, and their proportion among all complications varies between studies (9–61%) [33–36]. Bonhoeffer et al. described a large paediatric varicella cohort in Switzerland and reported that 25% of complications involved the central nervous system (9). Encephalitis was the most frequent manifestation [33].

Weeks to months after varicella, patients are at an increased risk of vasculopathy and ischemic stroke or transient cerebral arteriopathy. The pathogenesis of varicella zoster virus vasculopathy involves viral invasion of blood

vessels, in which the virus spreads transaxonally from the ganglia to the vascular walls [37]. After reactivation from the trigeminal or upper cervical ganglia, the virus travels along neurites and infects the adventitia of the cerebral arteries, causing vasculopathy [38].

Various studies have reported an average duration of hospitalisation due to varicella of 4–8 days, and the results of our study are within this range [9, 22, 35, 36]. 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 who were admitted to the paediatric intensive care unit was 6 years, slightly higher than the average age of the overall study population (4 years). The results of Bonhoeffer et al. regarding the mean age of admission to paediatric intensive care unit support this observation [9]. The proportion of patients that required admission to the paediatric intensive care unit was slightly higher in our study (12%) than in the literature (3–9%) [9, 17, 22].

Although often regarded as a benign illness, varicella imposes significant financial and societal burdens. The direct healthcare costs range from €1000 to €25,000 per hospital admission depending on the duration of stay and complications (with an average cost of €1625), as demonstrated by a European study. Moreover, the socioeconomic impact is considerable, as caregivers and parents often face extended absences from work during their children's illness [35]. When comparing the costs of universal varicella vaccination (universal varicella vaccination) (as recommended in Switzerland since 2023) with the previous vaccination strategy (vaccination at ages 11–40 in those with no history of varicella), the direct costs – preventive vaccination versus healthcare expenditures due to the disease – are comparable, at CHF 1.75 million and CHF 1.5 million, respectively. However, considering indirect costs, universal varicella vaccination results in an annual savings of approximately CHF 620,000. The reduced morbidity and complication rates further support the implementation of universal varicella vaccination in Switzerland [39].

With an average of nine paediatric hospitalisations per year (95 patients over 11 years), our cohort in central Switzerland represents approximately 6% of the 146 annual varicella complication-related hospitalisations in Switzerland [7]. Most of the complications in our catchment area occurred in children younger than 11. These children were not vaccinated, as per the national recommendations at that time. This observation calls for the early introduction of universal varicella vaccination, ideally before a child's first birthday. However, without knowing the total number of varicella cases in the whole population and the respective age groups, we cannot use our study data to draw firm conclusions and suggest a strategy for the optimal age to introduce varicella vaccination. The recent recommendation in Switzerland for universal varicella vaccination before a child's first birthday is based on the experience and evidence from other countries, in which the introduction at an early age reduced the disease burden and morbidity in subsequent age groups, including vulnerable patient groups (young infants, non-immune pregnant women, and immunocompromised individuals) [39].

To the best of our knowledge, none of the patients in our cohort had received the varicella vaccine. The documentation concerning varicella vaccination status was incomplete and likely not explicitly addressed in the medical history in many cases, as it was not among the routinely recommended vaccinations at that time. Consequently, our data provide limited utility for accurately comparing vaccination rates before and after the implementation of the universal varicella vaccination.

Of note, our analysis focused exclusively on inpatient VZV cases, excluding data from outpatient consultations during the same period. As a result, we could not make comparisons with complication-free outpatient cases. Furthermore, patients with herpes zoster were not included in this study, which could have provided valuable comparisons after universal varicella vaccination implementation. In addition, the retrospective nature of the data collection may have led to incomplete case identification due to potential misdiagnoses or inadequate documentation. Nevertheless, the long observation period and large cohort allowed us to gather comprehensive clinical data on the complications and clinical outcomes associated with cases of VZV requiring hospitalisation.

Conclusion

This retrospective study provides a comprehensive description of the age, hospitalisation duration, disease characteristics, severity of complications, and treatment of children and adolescents hospitalised with varicella over 10 years and 3 months before the introduction of universal varicella vaccination in Switzerland. These data will be supplemented by current ongoing, prospective nationwide surveillance and can be used in future for evaluations of the impact of universal varicella vaccination introduction, particularly the reduction in VZV-associated hospitalisations and severe complications.

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Anonymised study data can be shared on request by contacting the corresponding author.

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Potential competing interests

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References

1. Piazza MF, Amicizia D, Paganino C, Marchini F, Astengo M, Grammatico F, et al. Has Clinical and Epidemiological Varicella Burden Changed over Time in Children? Overview on Hospitalizations, Comorbidities and Costs from 2010 to 2017 in Italy. Vaccines (Basel). 2021 Dec;9(12):1485. http://dx.doi.org/10.3390/vaccines9121485.
2. Wutzler P, Bonanni P, Burgess M, Gershon A, Sáfadi MA, Casabona G. Varicella vaccination - the global experience. Expert Rev Vaccines. 2017 Aug;16(8):833–43. http://dx.doi.org/10.1080/14760584.2017.1343669.
3. Galil K, Brown C, Lin F, Seward J. Hospitalizations for varicella in the United States, 1988 to 1999. Pediatr Infect Dis J. 2002 Oct;21(10):931–5. http://dx.doi.org/10.1097/00006454-200210000-00009.
4. Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect. 2001 Oct;127(2):305–14. http://dx.doi.org/10.1017/S0950268801005921.
5. Boëlle PY, Hanslik T. Varicella in non-immune persons: incidence, hospitalization and mortality rates. Epidemiol Infect. 2002 Dec;129(3):599–606. http://dx.doi.org/10.1017/S0950268802007720.
6. Ratner AJ. Varicella-related hospitalizations in the vaccine era. Pediatr Infect Dis J. 2002 Oct;21(10):927–31. http://dx.doi.org/10.1097/00006454-200210000-00008.
7. Bundesamt für Gesundheit EKfIE. Windpocken (Varizellen)/ MMRV: Basisimpfung für Säuglinge. Bern: Bundesamt für Gesundheit; 2023.
8. Lienert F, Weiss O, Schmitt K, Heininger U, Guggisberg P. Acceptance of universal varicella vaccination among Swiss pediatricians and general practitioners who treat pediatric patients. BMC Infect Dis. 2021 Jan;21(1):12. http://dx.doi.org/10.1186/s12879-020-05586-3.
9. Bonhoeffer J, Baer G, Muehleisen B, Aebi C, Nadal D, Schaad UB, et al. Prospective surveillance of hospitalisations associated with varicella-zoster virus infections in children and adolescents. Eur J Pediatr. 2005 Jun;164(6):366–70. http://dx.doi.org/10.1007/s00431-005-1637-8.
10. Seward JF, Watson BM, Peterson CL, Mascola L, Pelosi JW, Zhang JX, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. JAMA. 2002 Feb;287(5):606–11. http://dx.doi.org/10.1001/jama.287.5.606.
11. Siedler A, Hecht J, Rieck T, Tolksdorf K, Hengel H. [Varicella vaccination in Germany. A provisional appraisal in the context of MMR vaccination]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2013 Sep;56(9):1313–20. http://dx.doi.org/10.1007/s00103-013-1789-z.
12. Bundesamt für Gesundheit EKfI. Kantonales Durchimpfungsmonitoring Schweiz. BAG-Bulletin. 2018. Bull BAG. 2018;(24):13.
13. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2005;6(1). http://dx.doi.org/10.1097/01.PCC.0000149131.72248.E6.
14. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. Lancet Infect Dis. 2009 May;9(5):281–90. http://dx.doi.org/10.1016/S1473-3099(09)70066-0.
15. Eron LJ, Lipsky BA, Low DE, Nathwani D, Tice AD, Volturo GA. Managing skin and soft tissue infections: expert panel recommendations on key decision points. The Journal of antimicrobial chemotherapy. 2003;52 Suppl 1. http://dx.doi.org/10.1093/jac/dkg466.
16. A I, C A, K B, M B, AM S, U H. Prospective surveillance of varicella-zoster virus infections in an out-patient setting in Switzerland. Hum Vaccin. 2009;5(12).
17. Blumental S, Sabbe M, Lepage P; Belgian Group for Varicella. Varicella paediatric hospitalisations in Belgium: a 1-year national survey. Arch Dis Child. 2016 Jan;101(1):16–22. http://dx.doi.org/10.1136/archdischild-2015-308283.
18. Turel O, Bakir M, Gonen I, Hatipoglu N, Aydogmus C, Hosaf E, et al. Children Hospitalized for Varicella: Complications and Cost Burden. Value Health Reg Issues. 2013;2(2):226–30. http://dx.doi.org/10.1016/j.vhri.2013.05.003.
19. Chang LY, Huang LM, Chang IS, Tsai FY. Epidemiological characteristics of varicella from 2000 to 2008 and the impact of nationwide immunization in Taiwan. BMC Infect Dis. 2011 Dec;11(1):352. http://dx.doi.org/10.1186/1471-2334-11-352.
20. Bundesamt für Gesundheit EKfI. Schweizerischer Impfplan 2023. Richtlinien und Empfehlungen. Bern: Bundesamt für Gesundheit; 2023.
21. Hagemann C, Krämer A, Grote V, Liese JG, Streng A. Specific Varicella-Related Complications and Their Decrease in Hospitalized Children after the Introduction of General Varicella Vaccination: Results from a Multicenter Pediatric Hospital Surveillance Study in Bavaria (Germany). Infect Dis Ther. 2019 Dec;8(4):597–611. http://dx.doi.org/10.1007/s40121-019-00273-6.
22. Wen SC, Best E, Walls T, Dickson N, McCay H, Wilson E. Prospective surveillance of hospitalisations associated with varicella in New Zealand children. J Paediatr Child Health. 2015 Nov;51(11):1078–83. http://dx.doi.org/10.1111/jpc.12937.
23. Abuhammour W, Hasan RA, Unuvar E. Group A beta-hemolytic streptococcal bacteremia. Indian J Pediatr. 2004 Oct;71(10):915–9. http://dx.doi.org/10.1007/BF02830836.
24. Laupland KB, Davies HD, Low DE, Schwartz B, Green K, McGeer A; Ontario Group A Streptococcal Study Group. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Pediatrics. 2000 May;105(5):E60. http://dx.doi.org/10.1542/peds.105.5.e60.
25. Imöhl M, van der Linden M, Reinert RR, Ritter K. Invasive group A streptococcal disease and association with varicella in Germany, 1996-2009. FEMS Immunol Med Microbiol. 2011 Jun;62(1):101–9. http://dx.doi.org/10.1111/j.1574-695X.2011.00788.x.
26. Coleman S. The association between varicella (chickenpox) and group A streptococcus infections in historical perspective. SAGE Open Med. 2016 Jul;4:2050312116658909. http://dx.doi.org/10.1177/2050312116658909.
27. Savoia P, Heininger U, Buettcher M. *Streptococcus pyogenes* Endocarditis Associated With Varicella-Case Report and Review of the Literature. Front Pediatr. 2019 Dec;7:500. http://dx.doi.org/10.3389/fped.2019.00500.
28. Kienast AK, Kreth HW, Höger PH. Varicella vaccination in children with atopic eczema. J Dtsch Dermatol Ges. 2007 Oct;5(10):875–80. http://dx.doi.org/10.1111/j.1610-0387.2007.06488.x.
29. Han JH, Yoon JW, Yook HJ, Bang CH, Chun JH, Lee JY, et al. Evaluation of Atopic Dermatitis and Cutaneous Infectious Disorders Using Sequential Pattern Mining: A Nationwide Population-Based Cohort Study. J Clin Med. 2022 Jun;11(12):3422. http://dx.doi.org/10.3390/jcm11123422.
30. Gerada C, Campbell TM, Kennedy JJ, McSharry BP, Steain M, Slobedman B, et al. Manipulation of the Innate Immune Response by Varicella Zoster Virus. Front Immunol. 2020 Jan;11:1. http://dx.doi.org/10.3389/fimmu.2020.00001.
31. Tim MW, Jackson MA, Shannon K, Cohen B, McCracken GH Jr. Non-neonatal infection due to Listeria monocytogenes. Pediatr Infect Dis. 1984;3(3):213–7. http://dx.doi.org/10.1097/00006454-198405000-00006.
32. Wright H, MacGregor A. A case of meningitis due to Bacterium monocytogenes. J Pathol Bacteriol. 1939;48(2):48. http://dx.doi.org/10.1002/path.1700480220.
33. Science M, MacGregor D, Richardson SE, Mahant S, Tran D, Bitnun A. Central nervous system complications of varicella-zoster virus. J Pediatr. 2014 Oct;165(4):779–85. http://dx.doi.org/10.1016/j.jpeds.2014.06.014.
34. Ziebold C, von Kries R, Lang R, Weigl J, Schmitt HJ. Severe complications of varicella in previously healthy children in Germany: a 1-year survey. Pediatrics. 2001 Nov;108(5):E79. http://dx.doi.org/10.1542/peds.108.5.e79.
35. Bernal JL, Hobbelen P, Amirthalingam G. Burden of varicella complications in secondary care, England, 2004 to 2017. Euro Surveill. 2019 Oct;24(42):1900233. http://dx.doi.org/10.2807/1560-7917.ES.2019.24.42.1900233.
36. Gowin E, Wysocki J, Michalak M. Don't forget how severe varicella can be—complications of varicella in children in a defined Polish population. Int J Infect Dis. 2013 Jul;17(7):e485–9. http://dx.doi.org/10.1016/j.ijid.2012.11.024.
37. Guedes M, Filipe R, Costa A, Soares C, Sarmento A, Tavares M. Central nervous system varicella zoster vasculopathy in an immunocompromised patient. IDCases. 2018 Dec;15:e00483. http://dx.doi.org/10.1016/j.idcr.2018.e00483.
38. Nagel MA, Niemeyer CS, Bubak AN. Central nervous system infections produced by varicella zoster virus. Curr Opin Infect Dis. 2020 Jun;33(3):273–8. http://dx.doi.org/10.1097/QCO.0000000000000647.
39. Banz K, Iseli A, Aebi C, Brunner M, Schmutz AM, Heininger U. Economic evaluation of varicella vaccination in Swiss children and adolescents. Hum Vaccin. 2009 Dec;5(12):847–57. http://dx.doi.org/10.4161/hv.9898.