Eur J Pediatr (2005) 164: 366–370
DOI 10.1007/s00431-005-1637-8

ORIGINAL PAPER

**Jan Bonhoeffer · Gurli Baer · Beda Muehleisen
Christoph Aebi · David Nadal · Urs B. Schaad
Ulrich Heininger**

Prospective surveillance of hospitalisations associated with varicella-zoster virus infections in children and adolescents

Received: 2 November 2004 / Accepted: 13 January 2005 / Published online: 4 March 2005

Abstract Our goal was to determine the epidemiology of severe varicella-zoster virus (VZV) infections in hospitalised paediatric patients. Admissions associated with VZV infection of patients aged 0–16 years were reported by all 38 paediatric units in Switzerland to the Swiss Paediatric Surveillance Unit (SPSU) during 3 consecutive years (4/2000–3/2003). We verified completeness of reporting by capture-recapture analysis with patient records identified by ICD-10 codes. Outcome of illness was assessed 6 months after hospitalisation. A total of 335 cases (235 identified by SPSU reports, 100 by ICD-10 code) were included in this study. Mean age of patients was 4.1 years (median 3.5 years, range 0–16 years); 54% were male. Some 293 (87%) patients presented with chickenpox, 42 (13%) with herpes zoster and 291 (87%) patients were not immunocompromised. A total of 319 complications occurred in 237 (71%) patients: secondary bacterial infections ($n=109$); central nervous system involvement ($n=76$); VZV pneumonitis ($n=7$); others ($n=127$). Eleven (3%) patients required intensive care and three died. On follow-up, 303 (96%) of 315 patients had completely recovered; sequelae were present in 12 (4%) patients. The calculated hospitalisation rate was 13 per 10^4 cases. *Conclusion*: This study describes a sizeable hospitalisation and complication rate of varicella-zoster virus infections and provides a solid basis for future immunisation recommendations in Switzerland.

Keywords Child · Complication · Epidemiology · Immunisation · Varicella zoster infection

Abbreviations SPSU: Swiss Paediatric Surveillance Unit · VZV: varicella-zoster virus

Introduction

In Switzerland, immunisation against varicella-zoster virus (VZV) has not been generally recommended and no specific recommendations for use of varicella vaccine existed in Switzerland when this study was performed, despite the availability of a safe and effective live attenuated vaccine for many years.

The range and severity of VZV infection complications in childhood have been described in several studies [3, 4, 9, 10, 11, 12, 16, 17, 18, 19, 22, 24,25]. However, there are considerable differences between studies regarding the frequency of complications and hospitalisation rates. This might be due to variability in methods of data collection and analysis, geographical settings, living conditions, and admission policies.

The goal of our study was to generate data on varicella-associated morbidity in Switzerland as a basis for national immunisation recommendations. We aimed to determine hospitalisation rate, complication rate, differences between immunocompromised and immunocompetent patients, and the role of bacterial pathogens in paediatric patients with active VZV infection by prospective data collection and validation of reporting completeness by use of a second independent data source.

This study was presented in part at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, September 27th–30th, 2002

J. Bonhoeffer · G. Baer · B. Muehleisen
U. B. Schaad · U. Heininger (✉)
Division of Paediatric Infectious Diseases,
University Children's Hospital,
P.O. Box, 4005 Basel, Switzerland
E-mail: Ulrich.Heininger@unibas.ch
Tel.: +41-61-6856528
Fax: +41-61-6856012

C. Aebi
Division of Paediatric Infectious Diseases,
University Children's Hospital, Bern, Switzerland

D. Nadal
Division of Paediatric Infectious Diseases,
University Children's Hospital, Zurich, Switzerland

Subjects and methods

Case definition

We defined active VZV infection as "typical varicella rash or herpes zoster diagnosed by a physician and occurring within 30 days prior to or during hospitalisation in a patient aged 0–16 years".

Swiss Paediatric Surveillance Unit surveillance

The Swiss Paediatric Surveillance Unit (SPSU) was established in 1995 to assess the epidemiology of selected childhood diseases leading to hospitalisation. The study period for VZV infections was April 1, 2000 to March 31, 2003. Each month a reporting form was mailed to all 38 paediatric units in Switzerland. Following each report of a case, one of the investigators (JB, GB, BM) visited the respective unit and completed a standardised questionnaire (available from the authors on request) together with the attending paediatrician. Six months after hospital admission, we sent a follow-up questionnaire to the initial reporter who reported on any subsequent hospitalisations and the final outcome of the VZV infection.

Performance of SPSU projects is in accordance with data protection guidelines of all participating paediatric units.

Patients identified by ICD-10 code

To evaluate completeness of SPSU reporting and to refine incidence estimates, we performed a capture-recapture analysis. The second independent data source was medical records of children admitted to 13 representative hospitals during the study period. Cases were identified by 46 ICD-10 codes (list available from the authors on request) for VZV infection, potentially VZV-associated complications, or both.

We reviewed all pertinent records and extracted data of hospitalisations that had not been reported via the SPSU and met the case definition for active VZV infection using the standardised questionnaire. The 6-month follow-up investigation was also performed as described above.

Analysis

Statistical analyses were performed with the SPSS 11.0.0 program (SPSS Inc., Chicago, IL, USA). Independent proportions were compared by the Pearson χ-squared test. P values <0.05 were considered significant. Data on the general population during the study period were obtained from the Federal Office of Statistics [20]. Capture-recapture analysis was calculated based on the Chapman-Wittes adjustment of the Lincoln-Petersen maximum likelihood estimate [7].

Results

General population

During the study period, the mean number of children and adolescents aged 0–16 years in Switzerland was 1,337,175. We calculated the annual number of varicella cases in this cohort to be 77,084 (based on the established VZV antibody prevalence of 98% at the age of 16 years) [1].

Hospitalisation rate

Compliance of paediatric units with returning postcards to the SPSU was 99% during the study period. A total of 335 patients fulfilled the case definition; 235 (70%) were reported to the SPSU and 100 additional patients (30%) were identified by ICD-10 codes (Fig. 1).

We performed a capture-recapture analysis on 261 cases identified from those units for which data of both independent sources were available (Table 1). The completeness of SPSU reporting and ICD code identification was 0.56 and 0.79, respectively ($P = 0.54$). Therefore, we assumed 44% underreporting to the SPSU and estimated the true number of all hospitalised patients in association with active VZV infection to be 420 (18 per 10^4 cases) and those caused by VZV infection to be 305 (13 per 10^4 cases). Of 420 estimated cases associated with active VZV infection, 296 (13 per 10^4 cases) were due to primary varicella and the remaining 124 cases were due to herpes zoster.

Age-specific hospitalisation rates of primary varicella were calculated and found to be highest in children up to 4 years of age (Table 2).

Study population

Of the 335 hospitalised patients identified in this study, 180 (54%) were male, 44 (13%) were immunocompromised, and none of them had been immunised against varicella. The mean age of the patients was 4.1 years (median 3.5 years; range 0–16 years) and infants 0 to 12 months old ($n = 61$; 18%) represented the largest single age group. Mean time from onset of rash to hospitalisation was 5 days (median 5 days; range -9 to 27 days) and mean duration of hospitalisation was 8 days (median 5 days; range:1–243 days). Herpes zoster was relatively more common in immunocompromised (41%) than in immunocompetent patients (8%; $P < 0.001$). Antiviral therapy had been administered to 43 (97%) of 44 immunocompromised and 52 (18%; $P < 0.001$) of 291 immunocompetent patients.

Overall, 319 complications attributable to VZV infection were noted. Notably, there was no significant difference in complication rates between the two data sources. Type and frequency of the 303 complications

occurring in those 253 patients (including 40 infants) who were hospitalised due to VZV infection (group 1 in Fig. 1) is shown in Table 3. The remaining ten and six complications occurred in 16 patients from group 2 and in 66 patients from group 3, respectively.

Of 335 patients, 11 (3%) required intensive care treatment. All of them were immunocompetent, their median age was 5 years (mean 5.5 years, range 0–14 years), eight were hospitalised due to varicella infection (group 1), and three primarily for other reasons (group 3). Group 1 cases were admitted to the ICU due to severe haemorrhagic varicella ($n=1$), pneumonia ($n=1$), septic arthritis and toxic shock syndrome ($n=1$), congenital varicella with encephalitis ($n=1$), meningo-encephalitis ($n=2$), pneumococcal sepsis ($n=1$), and varicella pneumonitis ($n=1$). Group 3 cases were admitted for generalised seizures ($n=2$) and aspiration pneumonia ($n=1$).

Three (1%) patients died. Two deaths were attributable to VZV infection in immunocompetent patients (one due to pneumococcal sepsis and one due to encephalitis) and one death was caused by cerebral haemorrhage caused by a coagulation disorder in the light of an underlying leukaemia rather than VZV infection. Accordingly, the case fatality rate of hospitalised VZV infections was 0.5% and that of all VZV infections in Switzerland during the study period was calculated to be 1 in 100,000.

In 103 patients with 109 secondary bacterial infections, 65 blood cultures, 11 cerebrospinal fluid cultures, four urine cultures, and 43 tissue cultures were performed. A total of 51 cultures grew bacteria, of which 21 were group A beta-haemolytic streptococci and 17 were *Staphylococcus aureus*. Of note, one case of pneumococcal and two cases of meningococcal sepsis occurred.

Table 1 Capture-recapture analysis of hospitalisations associated with active VZV infection[a]

Identified by ICD-10	Reported by the SPSU		Total (n)
	Yes (n)	No (n)	
Yes	126	100	226
No	35	28[b]	63
Total	161	128	289

[a]Based on 261 cases from paediatric units for whom original source and analytical source data where available
[b]Undiscovered cases calculated by capture-recapture analysis

Follow-up

Follow-up information was available in 231 (98%) cases reported to the SPSU and in 84 (84%) of those identified by ICD-10 code. Seven patients required further hospitalisations due to VZV infections or complications thereof and 12 patients (4%), of whom 11 were immunocompetent, suffered from sequelae: disfiguring scarring ($n=9$), developmental retardation ($n=1$), joint cartilage destruction ($n=1$), and reduced lung capacity following pneumonia ($n=1$).

Discussion

We prospectively determined the spectrum and frequency of complications caused by VZV infections in children and adolescents in Switzerland during a 3-year period. While such data have been obtained by a similar approach in Germany and Canada [12,25], this

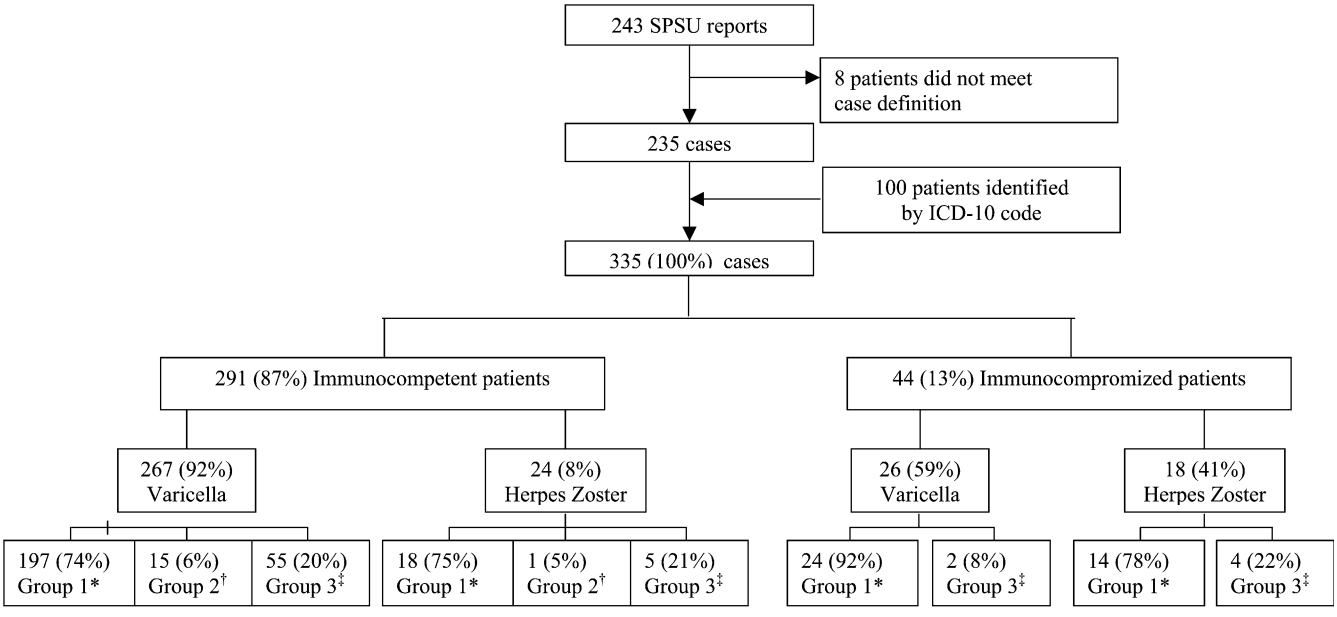

Fig. 1 Profile of study population.*Group 1 ($n=253$; 76%): patients admitted only due to VZV infection. †Group 2 ($n=16$; 5%): patients admitted due to combination of VZV infection and concomitant other diseases. ‡Group 3 ($n=66$; 20%): patients primarily admitted for diseases other than the VZV infection

Table 2 Age-specific numbers of primary VZV infections leading to hospitalisation (group 1) during the 3-year study period

Age group (years)	Sero-prevalence increase[a] (%)	Number of cases (estimated)	Number of cases hospitalised	Number of cases hospitalised (capture-recapture estimate)	Age-specific hospitalisation rate[b]
<1	11	25,957	38	55	21
1–4	27	63,712	117	148	23
5–9	49	115,626	58	80	7
10–16	11	25,957	8	13	5
Total	98	231,252	221	296	13

[a]From age group to age group; based on age-specific anti VZV-IgG seroprevalence in Switzerland [1]
[b]Per 10^4 cases, based on capture-recapture estimates from this study

is the first prospective nation-wide study where source completeness was validated by two independent data sources.

We trust that we determined the true hospitalisation rate and spectrum of complications amongst hospitalised patients, since (1) the active surveillance system involved all paediatric units in Switzerland, (2) every single report was thoroughly validated, (3) the data set was supplemented by a search of further cases using a broad range of ICD-10 codes in a sample of 13 representative paediatric units, (4) comparison of the two data sources showed no significant difference in complication rates between the two sources (i.e. no evidence for reporting bias of severe cases to the SPSU), and (5) capture-recapture analysis showed that both data sources were independent because the product of the probabilities of being reported to the SPSU and being identified by an ICD-10 code was equal to the probability of appearing in both sources (0.43).

Hospitalisation rates are widely used as surrogate measures for disease severity [3, 4, 10, 11, 12, 16, 17, 19, 24, 25]. We aimed to improve this estimate by capture-recapture analysis and performed this analysis by use of a representative sample of paediatric units, therefore potential selection bias should be minimal. The estimated hospitalisation rate for primary varicella was 13 per 10^4 cases. Whereas this is in the range of reported rates, it is considerably higher than those in the only two other prospective studies, i.e. 1 and 5 per 10^4 cases, respectively [12, 25].

Age-specific hospitalisation rates vary between studies and generally peak in children of 1–4 years of age as they did in our study [3, 4, 5, 6, 14, 24, 25]. Also, 50% of all cases occurred in this age group. This underlines the importance of early immunisation if prevention of varicella complications is the goal. Interestingly, 18% of patients were infants and 4% were younger than 3 months of age. This suggests insufficient levels of

Table 3 Type and frequency of complications in 253 patients[a] admitted due to VZV infection (group 1)

Complication	Total		Immunocompetent		Immunocompromised	
	N	%	*N*	%	*N*	%
Secondary bacterial infections	109	36	104	37	5	26
Skin infection	65	21	62	22	3	16
Soft tissue infection	8	3	8	3	0	0
Invasive infections	36	12	34	12	2	10
Bacterial pneumonia	12		11		1	
Sepsis	9		8		1	
Acute osteomyelitis	6		6		0	
Septic arthritis	6		6		0	
Meningitis	2		2		0	
Nephritis	1		1		0	
Central nervous system involvement	75	25	72	25	3	16
Meningo-encephalitis	21	7	18	6	3	16
Cerebellitis	33	11	33	12	0	0
Febrile seizure	21	7	21	7	0	0
Dehydration	35	12	35	12	0	0
Severe pain	21	7	14	5	7	37
Coagulation disorder	19	6	16	6	3	16
Kerato-conjunctivitis	11	4	11	4	0	0
Pneumonitis	7	2	6	2	1	5
Parental distress	4	1	4	1	0	0
Congenital VZV infection	3	1	3	1	0	0
Hepatitis	2	1	2	1	0	0
Nephropathy	2	1	2	1	0	0
Other complications	15	5	15	5	0	0
Total	303	100	284	100	19	100

[a]Patients may have experienced more than one complication

maternally derived anti-VZV IgG in these cases, an important factor to be considered when designing a VZV immunisation strategy [15, 23].

Our data confirm that immunocompetent children are at risk for severe complications of varicella leading to hospitalisation and deaths with secondary bacterial infections, mainly caused by group A beta-haemolytic streptococci and *S. aureus*. Of particular note are two cases of severe meningococcal sepsis which occurred in one unit during the study period and have been published elsewhere [21].

The spectrum and outcome of complications in immunocompromised patients was similar to those in immunocompetent individuals. This is most likely due to increased risk awareness and prompt administration of antivirals, which were administered to all but one of the immunocompromised patients.

Whereas cost-benefit analyses of varicella immunisation have been performed in the United States and Germany, such data are not available for Switzerland [2, 8, 13]. The present study provides a reliable basis for the assessment of the burden of disease and the potential benefits of a universal varicella immunisation programme in Switzerland: a considerably high complication rate, varicella-related long-term sequelae and fatal outcome in 4% and 0.5% of hospitalised patients, respectively, challenge the preconception of varicella as a benign disease.

Acknowledgements A research grant was provided by GlaxoSmithKline, Switzerland.

We would like to thank Daniela Beeli, SPSU secretariat, for coordinating the report forms; Esther Schilling, study secretariat, for keeping track of reports and managing follow-up. We also would like to particularly thank the SPSU representatives of the respective paediatric units in Switzerland: A. Blumberg, J-L. Micheli, C. Aebi, E. Antonelli, P. Baeckert, W. Bär, J. P. Berclaz, J. P. Bossi, H-U. Bucher, L. Buetti, U. Bühlmann, E. Bussmann, O. Carrel, P. O. Cattin, J-M. Choffat, A. Corboz, G. Délèze, P. Diebold, P. Dolivo, F. Farron, M. Gehri, C. A. Haenggeli, J. Hentschel, P. S. Hüppi, P. Imahorn, C. Kind, B. Knöpfli, S. König, O. Lapaire, B. Laubscher, C. Le Coultre, M. Maherzi, A. Malzacher, W. Pezzoli, G. P. Ramelli, B. M. Regazzoni, F. Renevey, P. Rimensberger, C. Rudin, C. Stüssi, A. Superti-Furga, R. Tabin, J. Wisser, M. Wopmann, G. Zeilinger, and U. Zimmermann for their continuous and invaluable support as well as all the dedicated paediatricians taking care of the patients and helping us to complete the questionnaires.

References

1. Aebi C, Fischer K, Gorgievski M, Matter L, Mühlemann K (2001) Age-specific seroprevalence to varicella-zoster virus: study in Swiss children and analysis of European data. Vaccine 19: 3097–3103
2. Banz K, Wagenpfeil S, Neiss A, Goertz A, Staginnus U, Vollmar J, Wutzler P (2003) The cost-effectiveness of routine childhood varicella vaccination in Germany. Vaccine 21: 1256–1267
3. Choo PW, Donahue JG, Manson JE, Platt R (1995) The epidemiology of varicella and its complications. J Infect Dis 172: 706–712
4. Galil K, Brown C, Lin F, Seward J (2002) Hospitalisations for varicella in the United States, 1988 to 1999. Pediatr Infect Dis J 21: 931–935
5. Gil A, Oyaguez I, Carrasco P, Gonzalez A (2001) Epidemiology of primary varicella hospitalisations in Spain. Vaccine 20: 295–298
6. Guess H, Broughton D, Melton L, Kurland LT (1986) Population based studies of varicella complications. Pediatrics 78[Suppl]: 723–727
7. Hook EB, Regal RR (1995) Capture-recapture methods in epidemiology: methods and limitations. Epidemiol Rev 17: 243–264
8. Huse DM, Meissner HC, Lacey MJ, Oster G (1994) Childhood vaccination against chickenpox: an analysis of benefits and costs. J Pediatr 124: 869–874
9. Iff T, Donati F, Vassella F, Schaad UB, Bianchetti MG (1998) Acute encephalitis in Swiss children: aetiology and outcome. Eur J Paediatr Neurol 2: 233–237
10. Jackson MA, Burry VF, Olson LC (1992) Complications of varicella requiring hospitalisation in previously healthy children. Pediatr Infect Dis J 11: 441–445
11. Jaeggi A, Zurbruegg R, Aebi C (1998) Complications of varicella in a defined central European population. Arch Dis Child 79: 472–477
12. Law B, MacDonald N, Halperin S, Scheifele D, Dery P, Jadavji T, Lebel MH, Mills E, Morris R, Vaudry W, Gold R, Marchessault V, Duclos P (2000) The Immunization Monitoring Program Active (IMPACT) prospective five year study of Canadian children hospitalised for chickenpox or an associated complication. Pediatr Infect Dis J 19: 1053–1059
13. Lieu TA, Cochi SL, Black SB, Halloran ME, Shinefield HR, Holmes SJ, Wharton M, Washington AE (1994) Cost-effectiveness of a routine varicella vaccination program for US children. JAMA 271: 375–381
14. Lin F, Hadler JL (2000) Epidemiology of primary varicella and herpes zoster hospitalisations: the pre-varicella vaccine era. J Infect Dis 181: 1897–1905
15. Linder N, Waintraub I, Smetana Z, Barzilai A, Lubin D, Mendelson E, Sirota L (2000) Placental transfer and decay of varicella-zoster virus antibodies in preterm infants. J Pediatr 137: 85–89
16. Manfredi R, Chiodo F, Titone L, Vierucci A, Catania S, Ghirardini G, Assanta N, Caramia G, Marcucci F, Loizzo B, Muscolino F (1997) Chickenpox complications among immunocompetent hospitalised children in Italy. Pediatr Med Chir 19: 99–104
17. Peterson CL, Mascola L, Chao SM, Lieberman JM, Arcinue EL, Blumberg DA, Kim KS, Kovacs A, Wong VK, Brunell PA (1996) Children hospitalised for varicella: a prevaccine review. J Pediatr 129: 529–536
18. Preblud SR (1981) Age-specific risks of varicella complications. Pediatrics 68: 14–17
19. Preblud SR, Orenstein WA, Bart KJ (1984) Varicella: clinical manifestations, epidemiology and health impact in children. Pediatr Infect Dis 3: 505–509
20. Swiss Ministry of Statistics. Statistics of population structure and development (2002) Available athttp://www.statistik.admin.ch
21. Travaglini M, Gubler J, Buhlmann U, Goetschel P (2001) Varicella zoster virus infection complicated by *Neisseria meningitidis* bacteraemia in two children. Eur J Pediatr 160: 399
22. Varughese PW (1988) Chickenpox in Canada, 1924–87. Can Med Assoc J 138: 133–134
23. WHO Vaccines, Immunizations and Biologicals. Country profiles. Available at:http://www-nt.who.int/vaccines/globalsummary/Immunization/
24. Yawn B, Yawn R, Lydick E (1997) Community impact of childhood varicella infection. J Pediatr 130: 759–765
25. Ziebold C, von Kries R, Lang R, Weigl J, Schmitt HJ (2001) Severe complications of varicella in previously healthy children in Germany: a 1-year survey. Pediatrics 108: E79