

Paediatric, invasive pneumococcal disease in Switzerland, 1985-1994

Iwan Venetz, Kurt Schopfer, Kathrin Mühlemann and the Swiss Pneumococcal Study Group

- Background** Cost effective use of new vaccines against pneumococcal disease in children requires detailed information about the local epidemiology of pneumococcal infections.
- Methods** Data on 393 culture-confirmed cases of invasive pneumococcal infection in children (<17 years) hospitalized in Swiss paediatric clinics were collected retrospectively for the years 1985-1994.
- Results** Meningitis (42%) was most frequent, followed by pneumonia (28%) and bacteraemia (26%). The overall annual incidence was 2.7 cases per 100 000 children <17 years old and 11 cases per 100 000 children <2 years old. Annual incidence rates were stable over the study period. Lethality was high for meningitis (8.6%) and bacteraemia (8.9%). A history of basal skull fracture was reported in 3.3% of children with pneumococcal meningitis. Residence in a rural region was associated with an increased risk of pneumococcal infection (relative risk = 1.45, 95% confidence interval: 1.01-2.00).
- Conclusions** Paediatric, invasive pneumococcal disease seems to be less frequent in Switzerland than in other European and non-European countries. This may be due to differences in diagnostic strategies and lower frequency of risk factors such as the use of day care. Children with a history of basal skull fracture are at increased risk for pneumococcal meningitis. Further investigation of the association of invasive pneumococcal infection with rural residence and the use of antibiotics for upper respiratory tract infections might give new insight into the dynamics of *Streptococcus pneumoniae* infection and the development of antibiotic resistance.
- Keywords** *Streptococcus pneumoniae*, epidemiology, surveillance, vaccine, Switzerland
- Accepted** 24 March 1998

Streptococcus pneumoniae is an important cause of meningitis, pneumonia, bacteraemia and otitis media in young children. The increasing spread of antibiotic resistance world-wide and reports of increasing incidence trends of invasive pneumococcal infections from some countries make prevention of invasive pneumococcal disease a priority.¹ Available polysaccharide vaccines do not protect children <2 years of age, who are at high risk of pneumococcal disease. However, new conjugated vaccines are currently being evaluated in clinical studies. The cost efficient use and postlicensure evaluation of such new vaccines will need a detailed knowledge about the local epidemiology of pneumococcal infections.

Pneumococcal infections are not reportable in Switzerland. Here, we present the results from a 10-year retrospective surveillance of culture-confirmed, invasive pneumococcal infections in children <17 years of age residing in Switzerland. The

study provides a baseline for a future, nationwide surveillance programme and the planning of vaccination strategies.

Methods

Data on invasive pneumococcal infections were collected retrospectively for 1 January 1985 to 31 December 1994 from the records of 37 paediatric clinics. These study hospitals represent all paediatric clinics in Switzerland except for one teaching hospital (Geneva) and four small primary care units.² Cases were all children <17 years of age, hospitalized in any of the study clinics for invasive pneumococcal infection and residing in Switzerland at disease onset. Invasive pneumococcal infection was defined as a positive culture for *Streptococcus pneumoniae* from a sterile site including blood, cerebrospinal fluid (CSF), pleural fluid/biopsy, synovial or peritoneal fluid or a positive specific antigen test from CSF. The diagnosis of meningitis was based on the isolation of *S. pneumoniae* or a positive antigen test from CSF. Pneumonia cases had characteristic clinical symptoms and radiographic changes at admission and a positive culture from blood or pleural fluid/biopsy. Cases with a positive blood

Institute of Medical Microbiology, University of Bern, Bern, Switzerland.

Reprint requests to: Kathrin Mühlemann, Institute of Medical Microbiology, University of Bern, Friedbühlstrasse 51, CH-3010 Bern, Switzerland

Table 1 Annual incidence and age distribution of invasive pneumococcal infections in Swiss children, 1985–1994

Diagnosis	No (%)	Median age (months)	% of cases less than specified age (y)		Cases/y per 100 000 less than specified age (y)		
			<2	<5	<2	<5	<17
Meningitis	165 (42.0)	16	55.8	71.5	5.64	3.13	1.19
Pneumonia	109 (27.7)	42	27.8	66.7	1.61	1.89	0.73
Bacteraemia	102 (26.0)	17	62.7	84.3	3.60	2.27	0.71
Total ^a	393 (100)	24	49.1	73.3	10.98	7.61	2.69

^a Including four cases with a clinical manifestation of septic arthritis, osteomyelitis, cellulitis or cerebellar abscess and 10 cases with unknown clinical presentation.

culture and no clinical focus were grouped as bacteraemia. Children with a positive blood culture and upper respiratory tract infection such as otitis media were also put into this category.

Cases were identified based on hospital statistics and clinical microbiological records and only included after review of the clinical chart done by the same investigator (IV). Sociodemographic and clinical characteristics were abstracted from clinical charts using a standardized questionnaire. Population data stratified by age (years), gender, and state were available from the Swiss Federal Statistical Office for the years 1985, 1990 and 1993. The population of the state of Geneva was excluded from the calculation of incidence rates, since no cases were ascertained from this region. Stratification in urban and rural areas was done according to the definition used by the Swiss Federal Statistical Office. A Poisson distribution was assumed in order to calculate 95% confidence intervals (CI) around incidence estimates.³ Statistical comparison of median ages was done with the Mann-Whitney test. Age-adjusted relative risk estimates (RR) and CI were calculated using the statistical software EGRET (SERC, Seattle, WA).

Results

During the 10-year study period 393 cases of invasive pneumococcal infections were identified. Meningitis was the most frequent diagnosis (42%), followed by pneumonia (28%) and bacteraemia (26%). Peritonitis was diagnosed in three (0.8%) patients and four cases presented with cellulitis, arthritis, cerebellar abscess or osteomyelitis. The clinical diagnosis was not known for 10 patients. *S. pneumoniae* was isolated from blood in 228 (58.1%) cases, from CSF in 154 (39.2%) cases, and in seven (1.8%) cases from a pleural biopsy. On 11 (2.8%) occasions the diagnosis of meningitis was based on specific antigen test in the CSF. Three (0.8%) of the cases had simultaneous, invasive *Haemophilus influenzae* infection. In an earlier study on the epidemiology of invasive *H. influenzae* infections in the same study population and using the same case ascertainment strategy completeness of the data was estimated to be around 90%.² This estimate was based on the proportion of cases listed in microbiology records that were also identified by hospital statistics in one teaching hospital.

Incidence rates for different age groups and clinical manifestations are given in Table 1. The overall annual incidence in children <17 years old was 2.7 cases per 100 000 and in children <2 years old 11 cases per 100 000. Almost half (49.1%) of all invasive pneumococcal infections occurred below age 2 years. The median age at pneumococcal pneumonia (42 months) was

significantly higher than for meningitis (16 months) or bacteraemia (17 months). Death occurred in 24 (6.1%) cases during the acute stage of infection (first 3 weeks after admission). Lethality for meningitis was 8.6%, for bacteraemia 8.8%, and 0.9% for pneumonia. Boys (n = 225) acquired invasive pneumococcal disease more often than girls (n = 164; RR = 1.37, CI: 1.01–1.69).

Invasive pneumococcal infections peaked in December and January (25.2% of all cases; $P < 0.001$) and there was a second peak between March and June (37.9% of all cases; $P = 0.02$) (Figure 1). Apart from seasonal variations, the annual incidence rates overall and for the different clinical manifestations did not show a significant time trend over the study period (data not shown).

Twenty-eight cases (7.1%) had a known predisposing condition: splenectomy due to hereditary spherocytosis (n = 1), malignancy (n = 7), human immunodeficiency virus (HIV) infection (n = 2), immunodeficiency (n = 5), or skull fracture (n = 13). Thirteen children (3.3%) had two and one child (0.3%) had three episodes of invasive pneumococcal infections during the study period. Meningitis was the clinical manifestation in nine of the children with two episodes and the one child with three infections. Pneumonia and bacteraemia occurred twice in two children. The median age of the patients at the time of the second or third episode was 5.5 years (range 12 months to 10 years). The interval between the first and second episode ranged between 9 days and 7 years. Four children had relapsing infection (interval <3 weeks) and 10 recurrent episodes (interval >3 weeks). Two patients with repeated meningitis had a history of basal skull fracture. No other predisposing factors, such as asplenia, malignancies or HIV

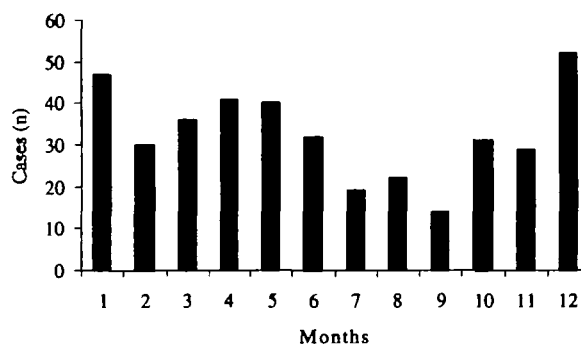


Figure 1 Seasonal distribution of invasive pneumococcal infections among Swiss children, 1985–1994

infection was present in any of the cases with more than one episode.

Basal skull fracture was mentioned in the history of 13 cases (3.3%), one of which had a known persisting traumatic CSF fistula. The median interval between the head trauma and infection was 11 months (range 0 days to 4 years; the time interval was unknown for six cases) and the average at disease was 7 years.

The incidence of invasive pneumococcal infection was higher among children living in a rural region than among those living in an urban area (annual incidence per 100 000: 3.15 for rural regions and 2.70 for urban regions, RR = 1.38, CI: 1.12–1.70). Also, the median age at disease onset was significantly higher in children residing in rural regions (30 months) than in children in urban areas (20.5 months; Mann-Whitney test $P < 0.05$).

Children of non-Swiss nationality had a significantly higher rate of pneumococcal pneumonia between the age of 2 and 4 years than Swiss children (annual incidence per 100 000: in non-Swiss 2.11, in Swiss 1.34, RR = 2.11, CI: 1.01–4.36). Also, non-Swiss children had pneumococcal pneumonia at a significantly younger age (34 months) than Swiss children (47 months; Mann-Whitney test $P = 0.02$). The frequency of meningitis and bacteraemia was not significantly different for Swiss and non-Swiss children (data not shown).

Discussion

This study investigated the epidemiology of invasive pneumococcal infection in Swiss children between the years 1985 and 1994 in order to establish a baseline for a nationwide surveillance programme and the planning of vaccination strategies against *S. pneumoniae*. The overall incidence of invasive, paediatric pneumococcal infection was lower than that reported from other European and non-European countries. For example, estimated annual incidence rates per 100 000 children <2 years old were 26 in Sweden, 45 in Finland, 104 in Israel, 145 in California, USA and 1195 in Alaska.^{4–8} The considerably higher rate of bacteraemias observed in other countries might explain some of these differences. For example, in Finland and Israel the proportion of bacteraemia among invasive pneumococcal infection was 69% and 37%, respectively, as compared to 26% in Switzerland.^{5,6} Finnish paediatricians have been encouraged to take blood cultures, which leads to a higher proportion of diagnosed bacteraemias.⁵ Also, it might be that in Switzerland children with pneumococcal pneumonia or bacteraemia are more often treated as outpatients due to their higher age at disease than in other countries. The incidence rates for pneumococcal meningitis are similar in Switzerland and in Finland. Factors that might also contribute to a comparably low incidence of invasive pneumococcal infections in Swiss children are the infrequent use of day care and less crowding.^{9,10} Other non-specific risk factors such as nutrition are less likely to play a role due to the uniformly high living standard in Switzerland. The higher age at infection in Swiss children indicates lower exposure to *S. pneumoniae*. In most other countries or populations the proportion of infections below age 2 years is higher than 50%, e.g. in Sweden, Finland, the US, and Alaskan Natives.^{4,5,7,8}

By restricting this study to hospitalized cases the overall number of invasive and non-invasive infections that might possibly

be prevented by an efficient vaccine has been underestimated.⁷ Reliable assessment of pneumococcal pneumonia and bacteraemia and otitis media in outpatients over time is difficult. Therefore, in Switzerland and probably in other countries the surveillance of pneumococcal disease must be based on incidence trends of invasive infections that require hospitalization. However, increased awareness and more frequent diagnostic work up of pneumococcal infections makes such a surveillance strategy susceptible to reporting bias.

This study could not provide data on the distribution of pneumococcal serotypes causing invasive paediatric disease, since *S. pneumoniae* isolates are not routinely typed in Switzerland. Based on the results from a recent Swiss multicentre study on antibiotic resistance and serotype distribution of *S. pneumoniae* about 90% of invasive strains are covered by the currently used 23-valent polysaccharide vaccine.¹¹ A conjugate vaccine including the six most common serotypes would cover 61% of invasive isolates in Switzerland. This is lower than estimated for Finland.⁵

Interestingly, invasive pneumococcal infections were more frequent in rural than urban areas of Switzerland. This correlates with a higher frequency of invasive *H. influenzae* infections in rural areas, which we found in an earlier study (Mühlemann, unpublished data). This observation is unlikely to be due to a diagnostic or reporting bias, since access to health care is generally high. The higher age at disease in rural cases suggests that exposure to pneumococcus is less frequent or intense in rural than urban regions. In fact, factors that promote exposure such as high population density, use of public transportation, day care usage etc. are more frequent in urban than rural areas. However, one might then expect a lower and not a higher incidence of disease in rural children. It might be that children in urban areas are treated more frequently with antibiotics for upper respiratory tract infection and might therefore get some protection from invasive infection despite higher exposure. This might promote antibiotic resistance of *S. pneumoniae* among the urban population. We have currently no data to support this hypothesis. Further investigation of the association of invasive pneumococcal infection with rural residence and the use of antibiotics for upper respiratory tract infections might give new insight into the dynamics of *S. pneumoniae* infection and the development of antibiotic resistance.¹²

Data on the frequency of repeated pneumococcal infections are scarce in the literature.¹³ In our study the number of children with more than one invasive episode was surprisingly high. Especially, meningitis was more frequent than in earlier reports.^{5,13,14} Our patients less often had a known predisposing condition and they were on the average older. It might be that a relatively long observation time and a relatively low proportion of bacteraemia in our study population can explain some of the differences.

Skull fracture is a known risk factor for bacterial meningitis.¹³ However, data on the incidence of meningitis after skull fracture are scarce and vary between 0 and 36%.¹³ Among our patients, 3.3% had a history of basal skull fracture. To our knowledge there are no data available about the ability of the available pneumococcal vaccines to protect from meningitis after skull fracture. The pathogenesis of such a meningitis may not involve bacteraemia but proceed directly from the colonized upper respiratory tract. Only conjugated pneumococcal vaccines (once

available) might therefore have the potential to lower the risk of meningitis after skull fracture by reducing nasopharyngeal carriage of *S. pneumoniae*¹⁵

Members of the Swiss Pneumococcal Study Group

K Baerlocher and C Baumgartner (St Gallen), J-P Bossi (Martigny), LG Buetti (Locarno), U Bühlmann and H Bucher (Zürich), O Carrel (Vevey), D Chessex (Pompaples), J-M Choffat (Morges), V D'Appuzzo (Mendrisio), MA Panchard, B Voudaux, J Bille and A Calome (Lausanne), G Délèze (Sion), P Diebold (Monthey), P Dolivo and K Eggenberger (Yverdon), A Fanconi, U Lips and D Nadal (Zürich), R Favre (La Chaux-de-Fonds), H Fricker (Chur), B Friolet (Delémont), H Gaze (Neuchâtel), M Gianinazi (Lugano), H-P Gnehm (Aarau), E Gugler (Bern), RM Haller (Münsterlingen), U Hunziker (Winterthur), F Lattion (Payerne), D Lauffer (Nyon), J Lütschg (Bruderholz), J-R Panchaud (Clarens), F Renevey and F Besson (Fribourg), H Roten (Visp), G Schubiger (Luzern), H Schwestermann (Brig), P Sigg (Zürich), R Tabin (Sierre), F Taminelli (Bellinzona), A Tschumi (Schaffhausen), RP Zurbrugg and A Blumberg (Biel).

References

- ¹ Kaythy H, Eskola J. New vaccines for the prevention of pneumococcal infections. *Emerg Infect Dis* 1996;**2**:289-95.
- ² Mühlemann K, Alexander ER, Pepe M, Schopfer K. Invasive *Haemophilus influenzae* disease among Swiss children 1980-1993—Evidence for herd immunity among older age groups? *Scand J Infect Dis* 1996;**28**:265-68.
- ³ Haenszel W, Loveland D B, Sirken M G. Lung cancer mortality as related to residence and smoking histories 1. White males *J Natl Cancer Inst* 1962;**28**:947-1001.
- ⁴ Burman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors and prognosis. *Rev Infect Dis* 1985;**7**:133-42.
- ⁵ Eskola J, Takala AK, Kela E, Pekkanen E, Kalliokoski R, Lemonen M. Epidemiology of invasive pneumococcal infections in Finland. *JAMA* 1992;**268**:3323-27.
- ⁶ Dagan R, Englehard D, Piccard E. The Israeli Pediatric Bacteremia and Meningitis Group, Epidemiology of invasive childhood pneumococcal infections in Israel. *JAMA* 1992;**268**:3328-32.
- ⁷ Zangwill KM, Vadheim CM, Vannier AM, Hemenway LS, Greenberg DP, Ward JI. Epidemiology of invasive pneumococcal disease in Southern California: Implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. *J Infect Dis* 1996;**174**:752-59.
- ⁸ Davidson M, Schraer CD, Parkinson AJ *et al*. Invasive pneumococcal disease in an Alaskan Native population, 1980 through 1986. *JAMA* 1989;**261**:715-18.
- ⁹ Takala AK, Jussi J, Kela E, Rönnerberg P, Koskenniemi E, Eskola J. Risk factors for primary invasive pneumococcal disease among children in Finland. *JAMA* 1995;**273**:859-64.
- ¹⁰ Mühlemann K, Alexander ER, Weiss N, Pepe M, Schopfer K. Risk factors for invasive *Haemophilus influenzae* disease among children 2-16 years of age in the vaccine era, Switzerland 1991-1993. *Int J Epidemiol* 1996;**25**:1280-85.
- ¹¹ Wust J, Huf E, Kayser FH. Antimicrobial susceptibilities and serotypes of invasive *Streptococcus pneumoniae* strains in Switzerland. *J Clin Microbiol* 1995;**33**:315-63.
- ¹² CDC. Defining the public health impact of drug-resistant *Streptococcus pneumoniae*: Report of a Working Group. *MMWR* 1996;**45**,RR-1:1-20.
- ¹³ Kline MW. Recurrent bacterial meningitis. *Antibiot Chemother* 1992;**45**:254-61.
- ¹⁴ Orlicek SL, Herrod HG, Leggiadro RJ, Luedtke G, English BK. Repeated invasive pneumococcal infections in young children without apparent underlying immunodeficiency. *J Pediatr* 1997;**130**:284-88.
- ¹⁵ Obaro SK, Adegbola RA, Banya WA, Greenwood BM. Carriage of pneumococci after pneumococcal vaccine. *Lancet* 1996;**348**:271-72.