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H. Jaccard Ruedin · B. Ninet · E. Pagano · P. Rohner

# Epidemiology of meningococcal disease in Switzerland, 1999–2002

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**Abstract** In Switzerland, immunisation against serogroup C meningococcal disease is recommended for persons at increased risk but is not included in the national vaccination programme. The aim of this study was to present the nationwide surveillance data on invasive meningococcal disease collected from 1999 to 2002, emphasising the evolution in the absence of extended vaccination. The number of reported cases of meningococcal disease peaked at 178 cases in 2000 (incidence rate of 2.5/100,000 person-years), with 61% of all cases attributed to serogroup C meningococci (incidence rate, 1.5/100,000 person-years). Since 2001, a spontaneous decrease in the reported cases was observed, resulting in an overall incidence rate of 1.4/100,000 person-years in 2002 (serogroup C cases, 0.8/100,000 person-years). On the other hand, the case-fatality rate of serogroup C cases increased to 18% in 2002, leading to an increase in the overall case-fatality rate from 8% to 14% ($P>0.05$). The small sample size reduces the interpretability of this observation. However, when the introduction of a generalised vaccination against serogroup C meningococcal disease is discussed, the fluctuations in the number of vaccine-preventable deaths should receive greater attention.

H. J. Ruedin (✉) · E. Pagano
Epidemiology and Infectious Diseases, Swiss Federal Office of Public Health,
3003 Bern, Switzerland
e-mail: helene.jaccardruedin@bfs.admin.ch
Tel.: +41-32-7136045
Fax: +41-32-7136654

*Present address:*
H. J. Ruedin
Swiss Health Observatory, Swiss Federal Statistical Office,
2010 Neuchatel, Switzerland

B. Ninet · P. Rohner
Laboratory of Bacteriology, National Center for Meningococci,
University Hospital,
1211 Geneva, Switzerland

## Introduction

Meningococcal disease remains one of the leading causes of bacterial meningitis and sepsis in infants and adolescents. These infections are endemic but also occur as outbreaks, affecting mostly young people and generating anxiety in the community [1–3]. Despite major advances in medical treatment, these infections remain associated with high rates of case-fatalities and complications [4–6].

The epidemiology of severe meningococcal disease varies greatly from country to country. Whereas New Zealand has been facing an epidemic of serogroup B since 1991, an increase in serogroup Y disease has been observed since 1995 in the USA [7–9]. After the Hajj pilgrimage of 2000, cases due to strains of serogroup W135 were described in various countries among returning pilgrims [10, 11]. Recently, this serogroup was identified among 38% of the strains analysed during the epidemic that occurred in Burkina Faso and Niger in 2001 [12]. By contrast, during the last decade, an increase in cases of serogroup C (SC) disease was observed in Canada, Australia, and some European countries, including the UK, Spain, the Czech Republic, and Greece [13–19]. This increase has been associated with a hypervirulent strain that expresses the phenotype C:2a:P1.2,5 and belongs to the ET-15 clone, which is part of the ET-37 clonal complex [16, 20, 21]. This clone has caused various outbreaks in these countries [13, 21, 22].

At the end of the 1990s, a new conjugated vaccine against SC strains (MenC), designed to provide long-term protection not only for adults and children but also for infants, became available. National recommendations for the use of this new vaccine differ from country to country, depending mainly on the local epidemiological situation. In Greece or in the Czech Republic, for example, no generalised immunisation has been recommended since a spontaneous decrease in the number of SC cases was observed [23, 24]. Other countries such as the UK or Spain introduced this vaccine into their national immunisation programme due to the increasing number of cases attributable to SC strains [25, 26]. Its widespread use led

to a successful reduction in the incidence of SC infections. In different Spanish communities, a reduction of 70–85% in the SC incidence rate was observed, and in the UK, a decrease of 80% for persons <19 years was noted within a 2-year period (from 1998–1999 to 2000–2001) [17, 27]. Estimates made for England in 2001 yielded a short-term vaccine efficacy of 91.5% in infants who received three doses and of 89.3% in toddlers after a single dose of MenC [28].

In Switzerland, the MenC vaccine is recommended only for microbiology laboratory workers and for patients with specific immune dysfunctions, such as asplenic patients or those with certain complement factor deficits [29]. Since the year 2001, it is also administered to military recruits. The present work describes the epidemiology of meningococcal disease in Switzerland from 1999 to the end of 2002. The main objective of this analysis was to assess the distribution of serogroups in a country where a large immunisation campaign was not recommended.

## Materials and methods

In Switzerland, the reporting of meningococcal infections has been mandatory since 1914. The surveillance system currently applied was introduced in 1974 and relies on the notification of cases to the regional health authority and to the Swiss Federal Office of Public Health (SFOPH). Microbiology laboratories are requested to report any isolates of *Neisseria meningitidis* identified from normally sterile body fluids either by culture or by Gram stain, immunoagglutination, or PCR. Furthermore, physicians notify any case associated with the direct or indirect identification of *N. meningitidis* or Waterhouse-Friderichsen syndromes or polynuclear meningitis associated with coagulopathy.

Cases are considered as confirmed when the diagnosis relied on a positive culture or as probable when the diagnosis was based on other methods such as Gram stain, immunoagglutination, or PCR or on clinical findings as mentioned above. Since 1990, microbiology laboratories send their isolates on a voluntary basis to the National Centre for Meningococci (Centre National des Méningocoques [CNM]) at the University Hospital in Geneva, where the antibiotic susceptibility, phenotype, and genotype are determined.

On the basis of clinical information submitted by the physicians, cases were classified as meningitis when meningococci were identified in the CSF or when clinical signs of meningitis were mentioned. They were classified as sepsis in the absence of these features or if no localisation as arthritis or pneumonia was indicated.

The incidence rates were calculated on the basis of the resident population in Switzerland (Swiss Federal Statistical Office, 2000). To calculate serogroup-specific incidence rate estimates, the same age-specific serogroup distribution was attributed to the cases with unknown serogroup. For evaluation of the relationship between serogroup and clinical presentation or fatal outcome, only cases for which the serogroup was known were taken into account.

### Serotyping

Strains were typed with a dot-ELISA technique using monoclonal antibodies purchased from the National Institute for Biological Standards and Controls, Hertfordshire, UK [30].

### Genotyping

The multilocus sequence type (MLST) was also determined by sequencing the seven housekeeping-genes: *abcZ* (putative ABC transporter), *adk* (adenylate kinase), *aroE* (shikimate dehydrogenase), *fumC* (fumarate), *gdh* (glucose-6-phosphate dehydrogenase), *pdhC* (pyruvate dehydrogenase subunit), and *pgm* (phosphoglucomutase) [31]. The sequences determined were subsequently introduced into the website in order to obtain the MLST (http://mlst.zoo.ox.ac.uk).

### Sensitivity testing

Minimal inhibitory concentrations of penicillin, ciprofloxacin, chloramphenicol, cefuroxime, and ceftriaxone were determined with the *E*-test (AB Biodisk, Solna, Sweden) on Mueller-Hinton 5% sheep blood agar, and the values were interpreted according to available criteria proposed by the British Society for Antimicrobial Chemotherapy [32].

### Statistical analysis

The analysis was performed using SPSS 11.0 for Windows. Statistical significance was performed with the chi-square test for categorical variables. The association of age, serogroup, and clinical presentation with fatal outcome was tested using a multivariate logistic regression model. These variables were introduced together into the model and extracted stepwise. A two-sided *P*-value of <0.05 was considered statistically significant.

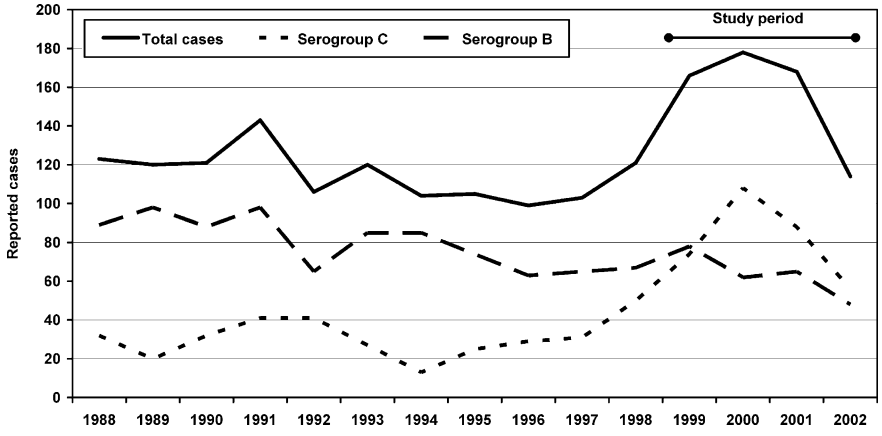


**Fig. 1** Reported cases of meningococcal disease in Switzerland, 1988–2002

## Results

Between 1 January 1999 and 31 December 2002, 626 cases were reported to the SFOPH, of which 519 (83%) were confirmed by positive cultures. The highest number of annual cases was reported in the year 2000, with 178 cases notified (Fig. 1). It was followed by a decrease to 168 cases reported in 2001 and 114 cases in 2002. The latter represents a 36% decrease compared to 2000. The global incidence rates varied between 2.5 cases/100,000 person-years in 2000 and 1.6/100,000 person-years in 2002. The distribution of the cases by age and serogroup is summarised in Table 1. The male-to-female ratio was 50.3:49.7. Median age of the patients was 16 years (range, 25 days–89 years; 25th percentile, 3 years; 75th percentile, 24 years).

### Microbiological analysis at the National Center for meningococci

Over the 4-year period, 482 strains (77% of all cases, 93% of culture-confirmed cases) were analysed at the CNM. Of these, 248 (51%) were serogroup C, 193 (40%) serogroup B, 20 (4%) serogroup W135, and 18 (4%) serogroup Y. For 3 (1%) strains, the serogroup could not be determined.

Serotypes 2b, 2a, 4, and 15 accounted for 28, 18, 14 and 10% of all strains, and subtypes P1.5, P1.2, P1.4 and P1.16 were identified in 43, 40, 11 and 9% of strains, respectively. Overall, 23% and 11% displayed the phenotypes C:2b:P1.2,5 (111 strains) and C:2a:P1.2,5 (51 strains), respectively. The most frequent MLSTs identified were the sequence types ST 8 (23%) and ST 11 (17%), followed by ST 41 (7%).

The antibiotic susceptibility was determined for 476 isolates: 432 (91%) were sensitive to penicillin (MIC≤0.12 μg/ml), with 106 (22%) showing an MIC value of 0.12. All strains were sensitive to ceftriaxone, cefuroxime, ciprofloxacin, and chloramphenicol, and one strain was resistant to rifampicin (MIC≥2 μg/ml).

### Evolution of serogroup C cases between 1999 and 2002

The distribution of annual cases according to the serogroups B and C and the serotypes 2a and 2b is illustrated in Fig. 2. The estimated proportion of SC cases peaked at 61% in 2000, leading to an estimated number of 108 SC cases (1.5/100,000 person-years). This proportion declined to 49% in 2002, corresponding to 56 SC cases (0.8/100,000 person-years), which represents a decrease of 48%.

Among the SC strains, the proportion of serotype 2b cases varied between 60% in 2000 and 38% in 2002 ($P>0.05$), and the proportion of serotype 2a cases increased from 29% in 1999 to 44% in 2002 ($P>0.05$). Similarly, the proportion of MLST 11 cases increased from 16% in 1999 to 44% in 2002 ($P=0.03$), and MLST 8 cases decreased from 54% in 2000 to 28% in 2002 ($P=0.05$).

The highest incidence of SC cases among children <1 year of age was observed in 1999 (10.9 cases/100,000 person-years). It declined to 5.2 cases/100,000 person-years in 2002. Among the age groups 1–4 years and 10–19 years, the highest incidence of SC cases was seen in 2000 (6.3 and 5.7, respectively), with a subsequent decline to 5.2 and 1.0, respectively, during 2002.

### Evolution of serogroup B cases between 1999 and 2002

The estimated number of serogroup B cases declined from 78 cases in 1999 (1.1/100,000 person-years) to 48 cases in 2002 (0.7 cases/100,000 person-years), corresponding to a decrease of 39%. The highest incidence was observed during the year 2000 among children <1 year of age (14.6 cases/100,000 person-years). Within this age group, the proportion of serogroup B strains increased from 47% in 1999 to 67% in 2002 ($P>0.05$), leading to an incidence of 10.3 cases/100,000 person-years during the last year of the

**Table 1** Meningococcal disease in Switzerland: distribution of the 626 cases reported to the SFOPH in 1999–2002, classified by age and serogroup

| Age group (years) | No. of cases (case-fatality rate) | | | |
|---|---|---|---|---|
| | Serogroup C[a] | Serogroup B[a] | Other or unknown | Total |
| <1 | 19 (5.3) | 28 (3.5) | 12 (16.7) | 59 (6.8) |
| 1–4 | 48 (10.4) | 30 (20.0[c]) | 41 (17.1) | 119 (15.1[b]) |
| 5–9 | 15 (6.7) | 10 (0) | 10 (0) | 35 (2.8) |
| 10–19 | 89 (5.6) | 49 (4.1) | 60 (1.7) | 198 (4.0) |
| 20–29 | 29 (10.3) | 33 (9.1) | 22 (18.2) | 84 (11.9) |
| ≥30 | 48 (12.5[c]) | 43 (9.3) | 40 (15.0) | 131 (12.2) |
| Total | 248 (8.5) | 193 (8.3) | 185 (10.8) | 626 (9.1) |

[a]Includes the four strains for which the serogroup was determined by immunoagglutination, without confirmation at the National Center for Meningococci; $P>0.5$ for the age-specific variation in the serogroup distribution
[b]$P<0.05$ when compared to the lowest age-specific case-fatality rate (total cases)
[c]$P>0.05$ when compared to the lowest age-specific case-fatality rate (SC or serogroup B cases)

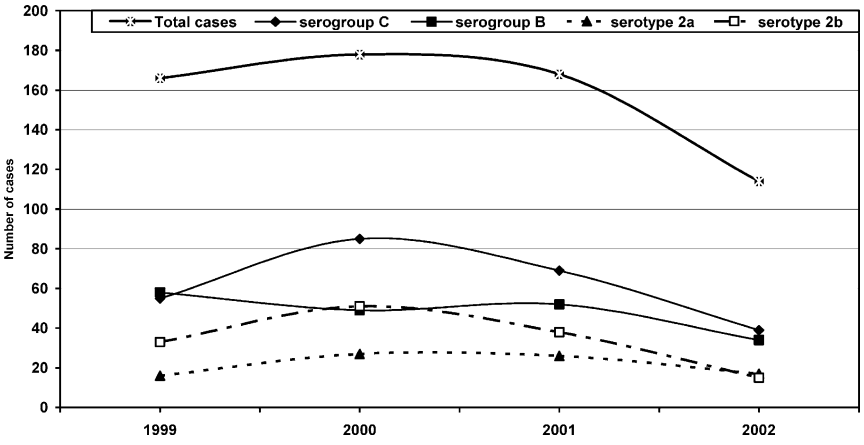


**Fig. 2** Annual distribution of cases of meningococcal infection in Switzerland caused by serogroup C, serogroup B, serotype 2a, and serotype 2b isolates

study. Within older age groups, less variation was observed.

### Clinical presentation

Sepsis with concomitant meningitis was reported for 55% of all cases, meningitis alone for 22%, and sepsis alone for 18%. The remaining 5% presented other symptoms such as arthritis. No statistically significant differences were noted for the number of cases presenting meningitis or sepsis alone in relation to the different age groups. The proportion of cases presenting sepsis with meningitis was highest in children aged 5–9 years and lowest among patients over 30 years of age (69% and 37%, respectively, $P<0.05$.

The proportion of cases attributed to serogroups C and B was comparable among cases of meningitis alone (19% and 26%, respectively, $P>0.05$) or among cases of meningitis and sepsis together (54% and 55%, respectively, $P>0.05$). Serogroup C was more frequent than serogroup B among cases of sepsis alone (23% vs 13%, $P<0.05$).

### Case-fatality rates

The overall case-fatality rate was 9% (95%CI, 7–11%). For the first 3 years, 1999–2001, the annual rate remained at 8% (95%CI, 6–10%). It increased to 14% (95%CI, 8–20%) in 2002. The case-fatality rate of confirmed serogroup B cases fluctuated around 8% (95%CI, 4–12%) each year, whereas the case-fatality rate of SC cases increased from 5% (95%CI, 1–12%) in 1999 and 7% (95% CI, 1–14%) in 2000–2001 to 18% (95%CI, 5–31%) in the year 2002 ($P>0.05$). Regarding the most frequent serotypes, the case-fatality rate associated with serotype 2a increased from 0% in 1999–2000 (0/16 and 0/27 cases) to 23% (4/17 cases) in 2002, whereas the case-fatality rate associated with serotype 2b fluctuated between 6% (2/33 cases in 1999) and 8% (3/38 cases in 2001). No significant association between a specific sequence type and a higher case-fatality rate could be identified.

In the univariate analysis, fatal outcome was associated with sepsis alone (OR, 2.99; 95%CI, 1.67–5.34) whereas meningitis alone was associated with higher survival (OR, 5.55; 95%CI, 1.75–20). In the multivariate analysis, which included age, serogroup, and clinical presentation, no significant association between fatal outcome and sepsis (OR, 6.95; 95%CI, 0.87–55.14) or meningitis (OR, 0.72; 95%CI, 0.07–7.35) was observed.

Among cases of meningococcal disease due to the non-C and non-B serogroups, no statistical differences were observed between age groups and clinical presentation. The annual case-fatality rate fluctuated between 14% in 1999 (95%CI, 4–24%) and 9% in 2001 (95%CI, 1–19%).

## Discussion

In Switzerland, a peak incidence of meningococcal disease was observed in the year 2000, which was due to an important increase in SC cases. The decline described in 2002 concerned both serogroups B and C strains, but it was more pronounced for the latter serogroup. During the years with a high incidence of SC cases (2000 and 2001), the phenotype most frequently identified was C:2b:P1.2,5. The serotype 2b was frequently reported in Spain at the end of the 1990s [15]. In Switzerland, the conjugated vaccine against SC meningococci became available in 2001. However, its introduction as a generalised vaccination was postponed because, at that time, a decline in the number of preventable SC cases was noted. The exact number of doses of the conjugated vaccine administered in Switzerland is unknown, but about 60,000 doses have been sold since its registration (personal communication, Wyeth Lederle & Baxter), in a country with about seven million inhabitants. This amount is certainly insufficient to induce herd immunity, which could explain the decreased incidence of SC cases. No changes in the surveillance system have occurred recently, and therefore under-reporting may be neglected as an apparent reason for the observed decline. On the contrary, the vigilance of physicians to diagnose and report meningococcal disease may be higher, since the potential benefits of the conjugate vaccine are currently being debated.

A similar decrease in the incidence of SC cases was described previously in Greece and in the Czech Republic, whereas a decrease in serogroup B cases was observed in Denmark in 2002 [24, 32, 33].

A detection bias due to undiagnosed cases with negative cultures is possible. National guidelines insist on early antibiotic treatment of any patient with symptoms of meningococcal infection, a policy that can lead to an increasing number of cases with negative cultures. Nucleic acid amplification techniques such as PCR are useful in these situations and have become an important procedure. In Switzerland, however, only 11 cases were diagnosed by PCR (2% of total cases and 10% of probable cases) during the study period. This proportion is much lower than in other countries, where up to 45% of all cases are diagnosed by this amplification method [24, 34]. In order to get a more accurate assessment of the burden of this disease, efforts will be made to reinforce the diagnosis and reporting of cases with negative cultures.

The reasons for the changing proportions of serotype 2a and 2b or of MLST 8 and 11 in the year 2002 compared to the preceding seasons remains unknown, and the small number of cases complicates its interpretation. During the years with a high incidence of SC cases, serotype 2b was predominant. However, in the beginning of 2001, a cluster of seven cases occurred in a region with 40,000 inhabitants, and serotype 2a was identified in four of five strains.

The higher case-fatality rate associated with SC cases among older patients is in agreement with observations reported previously in England [5]. An association between septicaemia and SC has also been observed elsewhere [4, 35]. Similarly, a lower case-fatality rate has been described among patients presenting with meningitis alone, whereas a higher case-fatality rate of SC cases than of serogroup B cases was reported [27, 36]. In our dataset, the association between sepsis and death disappeared after controlling for age and serogroup, but misclassification due to scarce clinical information cannot be excluded.

The increase in the case-fatality rate of SC cases was surprising. A similar observation has been reported in Spain, where the case-fatality rate of SC cases increased from 9% in 1997–1999 to 16% in 2000–2001, whereas the case-fatality rate of serogroup B cases remained stable, leading the authors to suspect the introduction of a more virulent serotype 2b [27]. In our population, the case-fatality rate associated with serotype 2b remained stable, whereas for serotype 2a, it varied from year to year. A high case-fatality rate associated with phenotype C:2a:P1.2,5 was also described previously in Denmark [4]. The interpretation of these differences is limited by the small sample size. However, it seems that serotype 2a has a greater potential for variation in virulence factors than serotype 2b.

In conclusion, a spontaneous decrease in the number of SC cases was observed in Switzerland between 2000 and 2002. However, the number of fatal cases caused by isolates belonging to this serogroup remained stable. This fact underscores the subtle changes observed with the epidemiology of meningococcal infections. When the introduction of the conjugated vaccine against SC meningococci into the national immunisation programme is discussed, the potential variation in the rate of vaccine-preventable deaths should receive greater attention.

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