

Targeted vaccination with meningococcal polysaccharide vaccine in one district of the Czech Republic

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SUMMARY

Vaccination against *Neisseria meningitidis* is not part of routine immunization schemes in any country; instead, targeted vaccination of groups at the highest risk is recommended during outbreaks and epidemics. After a long period of sporadic occurrence of meningococcal invasive disease, a new clone of *Neisseria meningitidis* C:2a:P1.2, ET-15/37, occurred in the Czech Republic, and caused local outbreaks in two neighbouring districts, Olomouc and Bruntal, in spring 1993. In Olomouc, a mass campaign was conducted during which 6191 students were vaccinated (5.6% of the total population of this locality and 96% of all students in the age group 15–19) within 2 weeks in June 1993. In Bruntal district, no such campaign was organized. In Olomouc, the incidence of invasive disease caused by *Neisseria meningitidis* C in the age group 10–24 decreased from 57 to 0 per 100 000 ($P < 0.001$) during the post-vaccination period (July 1993–August 1994), but no such decrease was observed in Bruntal. Although other factors can affect the frequency of disease, these results support the current recommendations of targeted vaccination in outbreaks of meningococcal disease.

INTRODUCTION

Infection by *Neisseria meningitidis* can result in serious invasive disease (meningitis, meningococcaemia, Waterhouse–Friderichsen syndrome) with high case-fatality rates and frequent sequelae [1–3]. In Europe, most cases of meningococcal invasive diseases occur sporadically and are caused by serogroup B, while outbreaks or epidemics are caused mainly by serogroup C or A. Local outbreaks of invasive disease caused by meningococcus group C, affecting mainly teenagers, have been recognized recently, although serogroup B can also cause outbreaks [4–8].

The serogroups are based on the capsular polysaccharide [9–15], and strains of *Neisseria meningitidis* can further be divided into serotypes and serosubtypes, based on non-capsular outer membrane proteins [16, 17]. Several kinds of vaccines against *Neisseria meningitidis* have been developed: polysaccharide (A, C, Y,

W135) and conjugated (combining the capsular and non-capsular antigens). The effect of meningococcal vaccines is antigen-specific and age-dependent [18–23]. Meningococcal polysaccharide vaccines are not used in routine immunization programmes and their use depends on epidemiological indications [24, 25]; most often, they are used for targeted vaccination of populations exposed during outbreaks, and in some countries for vaccination of military recruits [26, 27]. It has been reported that well organized vaccination campaigns have stopped epidemics of meningococcal invasive disease [28–33].

In the Czech Republic, meningococcal strains have been monitored since 1970. Meningococcal disease, caused mainly by *Neisseria meningitidis* B, occurred only sporadically for a long period [34], and the use of meningococcal polysaccharide vaccine was never indicated. This situation changed dramatically in 1993, when a previously unrecognized meningococcal clone appeared. This strain, identified as *Neisseria meningitidis* C:2a:P1.2, ET-15/37 [35, 36], caused disease with unusual epidemiological and clinical characteristics: a high age-specific morbidity in the age group of 15–19 years, a high case fatality rate (20%) and an atypical clinical course with a high incidence of Waterhouse–Friderichsen syndrome and meningococcal sepsis [37]. This agrees well with a recent report from Canada, where the identical clone of *Neisseria meningitidis* C appeared [7].

The incidence of invasive meningococcal disease caused by *Neisseria meningitidis* C (which was strain C:2a:P1.2 in 80% of cases) almost doubled in the Czech Republic from 0.4 to 0.7 per 100 000 ($P = 0.008$) over the period 1 January 1993–31 August 1994. The increase was most serious in two districts in the northeast of the country. A targeted vaccination campaign on a large scale was conducted in one of these two districts while no such measure was taken in the second. This has provided us with the opportunity to compare these two districts and to assess the effect of the vaccination campaign.

MATERIALS AND METHODS

Notification of meningococcal meningitis, meningococcaemia and Waterhouse–Friderichsen syndrome as well as of deaths from invasive meningococcal disease is required by law in the Czech Republic, and is considered to be virtually complete. In addition to routine notification, active surveillance of invasive meningococcal disease including deaths has been set up by the National Reference Laboratory (NRL) for Meningococcal Infections in Prague in collaboration with district Public Health Services and microbiological laboratories. Such surveillance provided the NRL with early and accurate data and enabled collection of *Neisseria meningitidis* strains from most cases. The diagnosis of invasive meningococcal disease was made on the basis of the clinical picture and laboratory examination, which included cultivation of *Neisseria meningitidis* from blood or cerebrospinal fluid, microscopic finding of Gram-negative diplococci in the cerebrospinal fluid, or detection of meningococcal exoantigens in cerebrospinal fluid or serum by direct methods. All cases of invasive meningococcal disease included in these analyses had at least one of the laboratory findings positive. Strains of *Neisseria meningitidis* were classified in serogroups based on capsular polysaccharides and sero/subtypes based on non-capsular outer membrane proteins. Electrophoretic types of

Neisseria meningitidis strains were designated on the basis of distinctive combinations of alleles over 13 enzyme loci, as previously described [38, 39].

The districts compared in this study are two neighbouring districts in the north east of the Czech Republic: Olomouc and Bruntal. Population data on the two districts were obtained from the Czech Statistical Office. Olomouc district has a largely urban character with a population of 105893, and Bruntal is a rural district with a population of 110500.

Two periods were compared: pre-vaccination (1 January 1993–30 June 1993) and post-vaccination (1 July 1993–31 August 1994). To take into account different lengths of compared periods, incidence rates are expressed per 100000 person/years. Differences in the incidence rates of meningococcal invasive disease between pre- and post-vaccination periods within both districts and between the two districts in the post-vaccination period were assessed assuming a Poisson distribution of cases in the two populations. The comparisons were done both manually using formulae for the comparison of two rates [40] and using Poisson regression in EGRET [41] and gave identical results. All ages and the age group 10–24 years (the most susceptible group) were included in the comparisons. Analyses were made for (i) all invasive meningococcal disease (all), (ii) invasive disease caused by *Neisseria meningitidis* C (N.m.C) and (iii) a combined group of cases of invasive disease caused either by *Neisseria meningitidis* C or *Neisseria meningitidis* where serogroup was not done (N.m.C&ND).

RESULTS

Figures 1 and 2 show the dynamics of the outbreaks in the two districts. In Olomouc, there were eight invasive disease caused by N.m.C&ND in the period 2 February–8 May 1993. Two cases occurred in February (aged 17 and 12 years), 3 cases in March (1 case aged 10 years and 2 cases aged 15 years), 1 case in April (aged 16 years) and 2 cases in May (aged 2 and 15 years). In Bruntal, there were 6 cases of invasive disease caused by N.m.C&ND in the period 14 February–2 June 1993: 1 case in February (aged 18 years), 1 case in April (aged 17 years), 3 cases in May (2 cases aged 2 years and 1 case aged 17 years) and 1 case in June (aged 17 years). From these 14 invasive diseases, 8 N.m. strains were sent to NRL for typing/subtyping and ET-typing, and 7 of them were the new clone N.m.C:2a:P1.2, ET-type 15/37.

In May 1993, the highest age-specific incidence in Olomouc was in the age group 15–19 years (52.1 per 100000), while in Bruntal the two most affected age groups were 1–4 years (15.9 per 100000) and 15–19 years (27.4 per 100000). The respective age specific incidences for the whole Czech Republic were 1.9 per 100000 in both 1–4 and 15–19 years old.

The vaccination campaign started in Olomouc at the beginning of June 1993 and focused on the 15–19 year olds who had the highest incidence. During 2 weeks, 6191 students (defined as all persons enrolled in any form of secondary education or apprenticeship) aged 15–19 years attending schools/colleges in the city of Olomouc were vaccinated with polysaccharide meningococcal vaccine A+C (Merieux); this corresponded to 96% of all students in this age group, 72% of the population aged 15–19 years and 5.6% of the total population of this district. This group was selected as it was at the highest risk and the most easy to vaccinate over

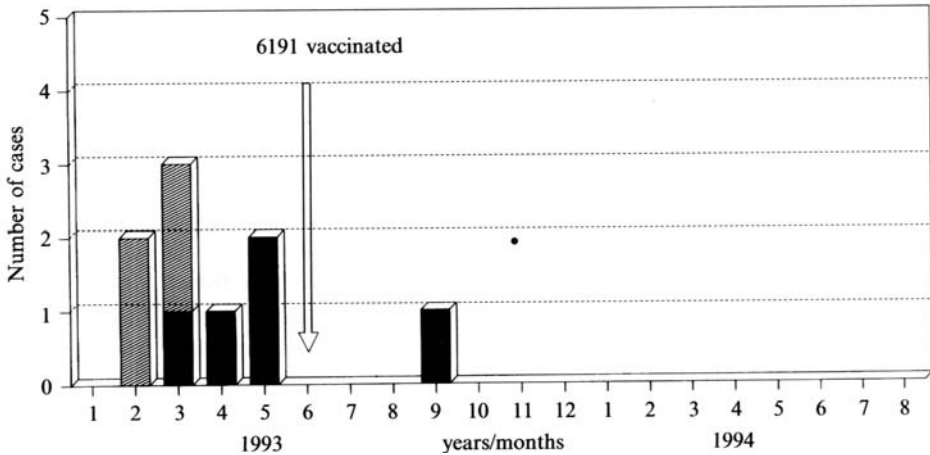


Fig. 1. Invasive meningococcal disease, 1993–4, Czech Republic, district Olomouc. ■, *Neisseria meningitidis* C; ▨, *Neisseria meningitidis* where serogroup was not done.

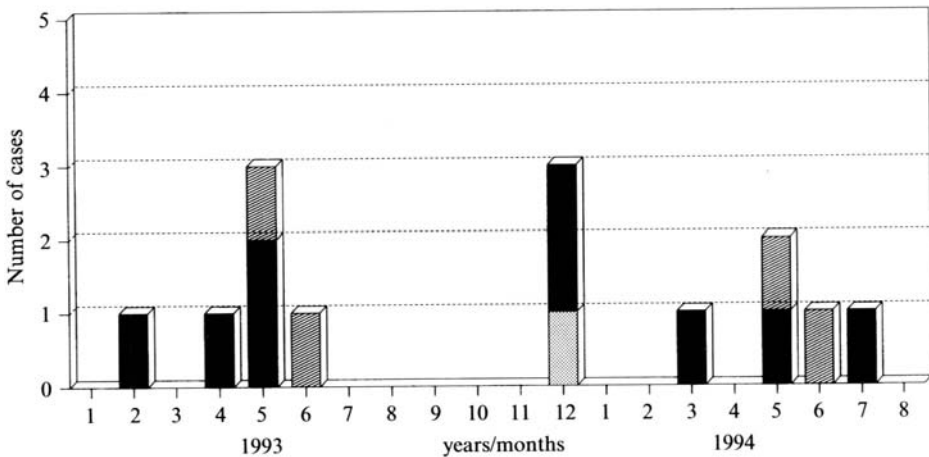


Fig. 2. Invasive meningococcal disease, 1993–4, Czech Republic, district Olomouc. ▤, *Neisseria meningitidis* B; ■, *Neisseria meningitidis* C; ▨, *Neisseria meningitidis* where serogroup was not done.

a short time period. In the second district, only contacts of cases (137 persons) and those requesting vaccination (908 persons) were vaccinated, corresponding to 0.9% of the total population of the district.

There were 8 cases of invasive disease caused by *N.m.C&ND* in Olomouc during the prevaccination period (1 January–30 June 1993) (Fig. 1), and 6 cases in Bruntal (Fig. 2). Five of the 8 cases in Olomouc occurred in the age group 15–19 years, while in Bruntal 2 age groups were affected: 1–4 years (3 cases) and 15–19 years (3 cases). After the vaccination campaign conducted in Olomouc, the incidence of invasive meningococcal disease decreased in Olomouc dramatically: only one case caused by *N.m.C* occurred in the post-vaccination period (Fig. 1) in the age group 1–4. In Bruntal, 7 cases of invasive disease caused either by *N.m.C&ND* occurred in the same period: (Fig. 2) in age groups 1–4 years (3 cases) and 15–19 years (4 cases).

Table 1. Incidence rate per 100 000 persons-years (number of cases) in pre- and post-vaccination periods

| | Type* | Pre-vac. | Post-vac. | P (between pre- and post-) |
|------------------|------------|----------|-----------|-------------------------------------|
| All ages | | | | |
| District Olomouc | N.m.C | 7.6 (4) | 0.8 (1) | 0.041 |
| District Bruntal | N.m.C | 7.2 (4) | 3.9 (5) | 0.36 |
| | <i>P</i> † | | 0.153 | |
| District Olomouc | C&ND | 15.1 (8) | 0.8 (1) | < 0.001 |
| District Bruntal | C&ND | 10.9 (6) | 5.4 (7) | 0.277 |
| | <i>P</i> † | | 0.075 | |
| District Olomouc | All | 15.1 (8) | 1.6 (2) | 0.002 |
| District Bruntal | All | 10.9 (6) | 6.2 (8) | 0.321 |
| | <i>P</i> † | | 0.089 | |
| Age 10–24 years | | | | |
| District Olomouc | N.m.C | 24.5 (3) | 0.0 (0) | 0.033 |
| District Bruntal | N.m.C | 13.9 (2) | 11.9 (4) | 0.334 |
| | <i>P</i> † | | 0.090 | |
| District Olomouc | C&ND | 57.1 (7) | 0.0 (0) | < 0.001 |
| District Bruntal | C&ND | 27.8 (4) | 11.9 (4) | 0.264 |
| | <i>P</i> † | | 0.090 | |
| District Olomouc | All | 57.1 (7) | 3.5 (1) | < 0.001 |
| District Bruntal | All | 27.8 (4) | 14.9 (5) | 0.363 |
| | <i>P</i> † | | 0.185 | |

* N.m.C, invasive disease caused by *Neisseria meningitidis* C; C&ND, invasive disease caused by *Neisseria meningitidis* C and *Neisseria meningitidis* where serogroup was not done; All, all invasive meningococcal disease.

† Between districts in post-vaccination.

In the pre-vaccination period, incidence rates of disease caused by N.m.C&ND in Olomouc and Bruntal were 15.1 and 10.8 per 100 000, respectively, for all ages, and 57.0 and 27.8 per 100 000, respectively, in the age group 10–24 years (Table 1); these differences were not statistically significant. After vaccination, the incidence rate remained high in Bruntal (6.3 per 100 000), but decreased in Olomouc (0.9 per 100 000). This decrease was highly significant ($P < 0.001$) and the difference between the two localities became marginally significant ($P = 0.075$). The difference between the two districts in post-vaccination period was more pronounced in the age group 10–24 years: 13.9 vs. 0 per 100 000 and particularly in the student group (15–19 years): 36.6 vs. 0 per 100 000. Changes in the all age incidence rates were mostly due in the age group 10–24 and followed the pattern described above. The incidence of disease caused by N.m.C or all *Neisseria meningitidis* followed the same pattern (Table 1).

DISCUSSION

Introduction of a new clone of *Neisseria meningitidis* has apparently caused an increase of invasive disease in the Czech Republic, mostly due to outbreaks in two districts. After a large scale vaccination campaign focused on the most affected

age group, 15–19 years, in Olomouc the spread of the disease stopped, while it continued in the district where no such measure was taken. This suggests that the intervention was effective.

The vaccination strategy in the Czech Republic is as follows: contacts of cases are not vaccinated (within the possible incubation period of the meningococcal disease). They are under intensive medical care and in indicated cases prophylactic treatment with penicillin is started [42]. Epidemiologists monitor the situation in their region with the aim of recognizing as soon as possible the part of population at highest risk for invasive disease caused by *Neisseria meningitidis* C in which targeted vaccination should be started. In addition, vaccination is available on request, together with explanation of the real risk for the infection (reflecting the age group, the locality, etc.).

The optimal way to assess effectiveness of any intervention is a randomized placebo-controlled trial. However, such trials are expensive and impractical for rare diseases such as meningococcal disease, and it is often necessary to rely on observations made during outbreaks. Such observations can be influenced by a large number of other, mostly unmeasured, factors. The two districts in our study differed in other respects than just vaccination, and these factors can be related to occurrence of disease. Our results should therefore be interpreted with caution and in the context of other reports.

Our observation that the targeted campaign can help to stop outbreaks or epidemics of meningococcal disease is consistent with the literature. Vaccination campaigns against meningococcal disease are mainly organized as mass vaccinations in selected subgroups of the population. In Finland, where a group A meningococcal epidemic developed in 1973 and peaked in 1974, its rapid decline and end was attributed to large scale vaccination in 1975–6, involving approximately one quarter of the total population [32]. In Denmark, selective vaccination in the most affected school was conducted (with 780 students vaccinated) during a localized outbreak of meningococcal disease (serogroup C). This small scale selective vaccination did not prevent further spread of the disease in the area; therefore, a large scale vaccination campaign covering nearly 100% of students aged 10–19 years (13300 students) was organized which did stop further spread of the disease [33]. Further evidence that selective vaccination may be cost-effective in the control of meningococcal disease was observed in Nigeria [29] where vaccination was conducted in villages (total population 10000) suffering from outbreaks of meningococcal disease; this selective vaccination stopped the spread of meningococcal disease in vaccinated villages, while it continued in control villages. Another example of successful intervention in an outbreak caused by *Neisseria meningitidis* group A by targeted vaccination was reported from Auckland, New Zealand [43]. A city-wide vaccine campaign was conducted in children 3 months–13 years of age. Overall 130000 doses were delivered with the coverage of approximately 90%. After 2.5 years of active surveillance there were no cases of invasive group A meningococcal disease in children appropriately vaccinated for age (100% efficacy).

Despite the reservation made above, our observations made during the recent increase of invasive meningococcal disease in the Czech Republic suggest that the targeted vaccination contributed to termination of the outbreak of the disease. In

the context of other reports, our data suggest that targeted vaccination is an effective measure to control outbreaks of invasive meningococcal disease.

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