Impact of a mass immunization campaign against serogroup C meningococcus in the Province of Quebec, Canada

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A mass immunization campaign was conducted in the Province of Quebec, Canada, during the winter of 1993, following an increase in the incidence of meningococcal disease, which was mainly caused by a virulent clone of Neisseria meningitidis, serogroup C, serotype 2a. About 1.6 million doses of the polysaccharide vaccine were administered, covering 84% of the target population aged between 6 months and 20 years; the overall cost was about 25.5 million Canadian dollars. Cases notified to the regional health authorities by clinicians, hospital laboratories, and the provincial reference laboratory from January 1990 up to March 1994 have been included in the analysis. In the first year following the campaign, the incidence of the disease dropped markedly among vaccinees as well as the unvaccinated fraction of the target population, while it remained unchanged among persons aged more than 20 years. This suggests the existence of herd immunity. The overall field efficacy of the vaccine was 79%, more in teenagers and less in under-5-year-olds. A minimum of 37 cases were prevented during the first year.

Introduction

The number of reported cases of meningococcal disease in Quebec has been increasing over recent years: from 37 in 1984, 62 in 1986, 107 in 1988, to 124 in 1990. This change was associated with the emergence of a virulent clone of Neisseria meningitidis, serogroup C, serotype 2a (1). Outbreaks caused by serogroup C organisms have also been observed in other parts of Canada and the USA (2, 3). Since 1990, the epidemiology of serogroup C meningococcal disease in Quebec has been characterized by an unusually high attack rate among teenagers and a high fatality rate (15%). The disease incidence was higher in some areas of Quebec Province (e.g., Hull) than others (Quebec city and Montreal). At regional level, there was a tendency for the cases to be clustered in time and space although few secondary cases were seen among direct contacts of patients.

In an attempt to control this outbreak, local and regional immunization programmes directed at school-age children were initiated in late 1991 and continued in 1992. In the autumn of 1992, approximately 300,000 doses of polysaccharide vaccine had been administered but the incidence remained high in unvaccinated groups and clusters appeared in previously unaffected areas. This provoked enormous anxiety in the population, fuelled by the media. As a result, it was decided to conduct a mass immunization programme and to offer the vaccine free of charge to all the 1.8 million persons living in the province who were aged between 6 months and 20 years. This intervention started in December 1992 and was completed by the end of March 1993, mainly through the local health units of the public health service.

This article describes the vaccination coverage achieved at the end of the programme and evaluates the costs and benefits in terms of cases prevented.

Study population and methods

The study population encompassed all persons living in the Province of Quebec. The size of the population and its age distribution were estimated from projections based on the 1991 census. During the mass immunization campaign, in early 1993, a central vaccination registry was created by linking the
provincial health insurance file with the individual vaccination forms returned by the local health units. The number of vaccinees in each single age category was extracted from the registry \((n = 1,174,957)\) and corrections were made for the forms not matching an individual in the health insurance file \((n = 2,362)\), for the vaccines provided by the private sector \((n = 12,003)\), and for vaccines administered in 1991–92 and not recorded \((n = 435,471)\), using a distribution proportional to age. The overall cost of the programme was calculated from the purchases of vaccines made by the Ministry of Health, including the doses given to the private sector, and the ordinary and extra resources used by the provincial, regional and local public health services to promote, organize, carry out and evaluate the immunization campaigns. The additional expenses incurred by the provincial health insurance plan for the participation of physicians was estimated as a three-day fee per 1000 persons vaccinated. Costs are expressed in 1993 Canadian dollars (CAD).

Since 1990, reportable diseases have been centrally registered at the provincial level and standard case definitions are provided (4). When a case of invasive meningococcal infection is reported by a clinician or a laboratory, an investigation is conducted by the regional health authority in order to collect additional information, including the date of occurrence of the disease, confirmation of the diagnosis, the serogroup of the bacteria, and the vaccination status of the patient. The sources of information include the hospital, the laboratory, and patients or their families. Cases occurring between 1 January 1990 and 31 March 1994 have been included in this analysis. Clinical cases and confirmed cases of unknown serogroup were ascribed to the different serogroups according to a proportion specific for the age, year, and vaccination status. The vaccination status of the patient was not systematically recorded in the central file, especially in the 1990–91 period when vaccines were not used. During the period from April 1993 to March 1994, however, the information was missing in only 7% of records \((7/101)\); all these patients were aged \(\geq 23\) years and therefore not eligible for vaccination. Accordingly, cases of unknown vaccination status were classified as not vaccinated.

The incidence of the disease among nonvaccinated persons aged 1–20 years and among those more than 20 years was calculated for 1990, 1991, and 1992. In 1992, approximately 291,000 persons were vaccinated in the course of nine local or regional campaigns. A vaccinee was considered to be immune 14 days after vaccination \((5)\) and the corresponding person–times were excluded from the denominator of the incidence for that year. The first quarter of 1993, during which the vast majority of vaccinations were carried out \((74\%)\), was excluded from the trend analysis. For the 12-month period from 1 April 1993 to 31 March 1994, the age-specific incidence was calculated for vaccinated and nonvaccinated persons.

The efficacy of the vaccine was calculated as 1 minus the ratio of attack rates among vaccinated and nonvaccinated persons during the 12-month period following the mass immunization campaign. The exact age at the time of vaccine administration was used instead of the age at disease occurrence; for those not vaccinated the age on 1 February 1993 \((\text{the median time of vaccinations})\) was used. Age-standardized attack rates were calculated using single-year categories and the population of Quebec in 1993 as a reference, to take into account the variability of the vaccination coverage and also the risk of disease according to age. The 95% confidence limits \((95\% \text{ CI})\) of the vaccine efficacy based on attack rates were computed according to Longini et al. \((6)\).

**Results**

**Vaccination coverage.** From December 1990 to March 1993, approximately 1625,000 doses of vaccine were administered, including a small number provided by the private sector. The tetravalent vaccine \((A, C, Y, W135; \text{Connaught Laboratories, North York, Ontario, Canada})\) \((24\%)\) of doses), the bivalent vaccine \((A, C; \text{SmithKline Beecham, Rixensart, Belgium})\) \((4\%)\), and the bivalent vaccine \((A, C; \text{Mérieux, Lyon, France})\) \((72\%)\) were used. Only 0.3% of the doses were given to persons aged \(>20\) years. The mean coverage of the target population \((\text{aged 6 months to 20 years})\) was 84%. The rate was >80% in preschool-age children and >90% in children aged 5 to 14 years attending kindergarten, primary, and secondary schools. Individuals no longer in school were difficult to reach, the rates decreasing from 83% among 17-year-olds to 36% in the 20-year-old group.

**Cost of the programme.** The cost of the vaccines, mostly available in 10-dose vials, was 10,437,000 CAD. Central coordination, promotion and evaluation of the programme cost 467,000 CAD and administration of the vaccines by the public health service cost 12,174,000 CAD. Fees for physicians were estimated at 2,400,000 CAD. The total was approximately 25.5 million CAD or 16 CAD for each vaccinee.
Incidence of meningococcal disease. The number of cases of meningococcal disease was 124 in 1990, 158 in 1991, 162 in 1992, 105 in 1993, and 31 in the first 3 months of 1994. In total, 285 cases were of serogroup C, 135 of serogroup B, 23 of other serogroups, and 137 of unknown serogroup (49 with confirmed meningococcal infection, 71 with a clinical diagnosis, and 17 for which the information was missing).

The distribution of cases by month is indicated in Fig. 1. The proportion of cases of unknown serogroup decreased from the beginning to the end of the study period, as a result of better forwarding of strains to reference laboratories for serogroup identification and of increasing use of diagnostic techniques based on the detection of antigens in the cerebrospinal fluid. An upward trend in incidence with a seasonal peak in winter was observed from January 1990 to January 1992 when 28 cases (unusually high) were reported. This led to the first large-scale interventions in regions with the highest incidence. After decreasing in the summer, the disease incidence started to increase in the autumn of 1992. During the mass campaign, from January to March 1993, the incidence of cases due to serogroup C decreased rapidly and remained low for the next 12 months. There was no indication of an increase in the incidence of cases due to other serogroups following the mass immunization campaign.

The evolution of the incidence of cases due to serogroup C, including the attributable fraction of cases of unknown serogroup, is indicated in Fig. 2. Among persons aged >20 years, the incidence increased from 2.1 per million in 1990, to 4.0 per million in 1991 and remained stable at 4.1 cases per million in 1992 and 4.6 per million from April 1993 to March 1994. Among nonvaccinated persons aged 1–20 years, the incidence increased from 31.5 per million in 1990 to 49.7 in 1991 and 47.3 in 1992, and decreased to 30.1 per million after the mass immunization campaign. In the immunized fraction of the target population, the incidence was much lower, 8.4 cases per million. The same pattern was seen when the analysis was restricted to persons aged 1–15 years, indicating that this was not an effect of a lower risk of disease in nonvaccinated adolescents.

Vaccine efficacy. The overall age-adjusted field efficacy of the vaccine in the target population was 79% (95% CI: 53–91%) when the analysis was restricted to confirmed cases of serogroup C, and 73% (95% CI: 42–87%) when clinical cases and confirmed
cases of unknown serogroup were included in the analysis. Efficacy rates in 5-year age categories are indicated in Table 1; rates above 90% were seen in children aged ≥10 years. The protection seemed to be less in younger children, five immunization failures being recorded in children vaccinated at the age of 4 years (2 cases), 3 years, 1 year, and 7 months.

**Discussion**

There are relatively few studies on the clinical efficacy of the polysaccharide vaccine against *N. meningitidis* serogroup C, especially in children. Three controlled trials were carried out with American army recruits in 1968–70 (7). In all, 14482 individuals received the monovalent serogroup C vaccine at the time they enlisted, while 60172 individuals did not. Vaccinal efficacy during the 8 weeks of basic training was 80%. The only efficacy study in a paediatric population was carried out in Brazil in 1972–74 (8). During a serogroup C meningococcal outbreak, 67299 children aged 6–36 months were given bivalent A + C vaccine, while an equal number received a placebo. The protection conferred by the vaccine during the 18-month period following administration was 55% among the 24–36-month age group, while there was a nonsignificant reduction of 12% among the 6–12-month age group. The Quebec experience is therefore of interest.

The present study is based on the number of cases reported to regional health authorities by clinicians, hospital laboratories, and the provincial laboratory serving as a reference centre for *N. meningitidis*. There are good reasons to believe that a high notification level was achieved during the study period. The outbreak caused much anxiety in the population, and the medical profession was continuously informed of the epidemiological situation. Tracing high-risk contacts of patients and prescribing chemoprophylaxis are the responsibilities of the public health services, and clinicians tended to report very quickly any suspected case.

The measure of the direct efficacy of the vaccine is based on the hypothesis that nonimmunized and immunized individuals are comparable in terms of their baseline risk of disease. An increased risk among nonimmunized individuals would cause an overestimation of the direct efficacy of the vaccine. The existence of a reduced risk in the nonimmunized would have the opposite effect on estimations. The vaccination rates in the different age groups were rather uniform in the different regions of the province and the risk of disease was not heavily associated with any particular socioeconomic variable. There is a possibility that adolescents not attending school (and therefore not vaccinated) were also less exposed, but this is certainly not true for children aged <15 years.

In this study, the estimates of the short-term clinical efficacy of the serogroup C polysaccharide vaccine were greater than 90% in teenagers but seemed to be less in young children. The number of cases is too small to allow a meaningful analysis of single-year age categories. There is, however, no indication that vaccination of 6–24-month-olds was not beneficial or even harmful. A case–control study is currently being carried out in Quebec and should produce data on the long-term efficacy of the vaccine.

During the 12 months following the mass immunization campaign, 11 cases caused by serogroup C bacteria were observed among vaccinees. On the basis of the rate observed among nonvaccinated persons of the same age, 48 cases were expected. Therefore, the estimated number of cases prevented as a result of the direct efficacy of the vaccine was 37, or 34 when the analysis included clinical cases and confirmed cases of unknown serogroup. Analysis of surveillance data indicated that the frequency of severe adverse effects of vaccination was very low and neither death nor sequelae were reported (9).

Whether a mass immunization campaign against serogroup C meningococcus can have an indirect protective effect as a consequence of a reduced transmission of the pathogenic bacteria (herd immunity) in the entire population is unknown. Three pro-
Mass immunization against meningococcus in Quebec

In conclusion, a mass immunization campaign is an effective intervention for controlling outbreaks of invasive serogroup C meningococcal infections. In Quebec, close to 1.6 million persons were immunized at a cost of approximately 25.5 million CAD. The efficacy of the serogroup C polysaccharide vaccine in children has been confirmed and an estimated 37 cases of meningococcal disease were prevented by the vaccine in the first year following the campaign. This estimate does not include the probable benefits of cases avoided by herd immunity.

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Résumé

Impact d'une campagne de vaccination de masse contre le méningocoque du sérogroupe C dans la Province de Québec, Canada

Une campagne de vaccination de masse a été menée dans la Province de Québec (Canada) pendant l'hiver 1993, à la suite d'une augmentation de l'incidence des méningocoques, principalement dues à un clone virulent de Neisseria meningitidis sérogroupe C, sérotype 2a. Environ 1,6 million de doses du vaccin polysaccharide ont été administrées, ce qui représente une couverture de 84% de la population cible, âgée de 6 mois à 20 ans. Le coût global de l'opération a été d'environ 25,5 millions de dollars du Canada. Les cas notifiés aux autorités sanitaires régionales par les médecins, les laboratoires hospitaliers et le laboratoire provincial de référence de janvier 1990 à mars 1994 ont été inclus dans l'analyse. La première année suivant la campagne, l'incidence de la maladie a fortement baissé chez les sujets vaccinés ainsi que chez la fraction non vaccinée de la population cible, et est restée inchangée chez les personnes de plus de 20 ans. On peut donc penser qu'il existe une immunité collective. L'efficacité globale du vaccin sur le terrain était de 79%, plus forte chez les adolescents et plus faible chez les enfants de moins de cinq ans. Au cours de la première année, la vaccination a permis d'éviter au minimum 37 cas.

References