Dramatic decline of serogroup C meningococcal disease incidence in Catalonia (Spain) 24 months after a mass vaccination programme of children and young people

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Abstract

Study objectives—The objective of this study was to evaluate the effectiveness of a mass vaccination programme carried out in Catalonia (Spain) in the last quarter of 1997 in response to an upsurge of serogroup C meningococcal disease (SCMD).

Design—Vaccination coverage in the 18 month to 19 years age group was investigated by means of a specific vaccination register. Vaccination effectiveness was calculated using the prospective cohort method. Cases of SCMD were identified on the basis of compulsory reporting and microbiological notification by hospital laboratories. Vaccination histories were investigated in all cases. Unadjusted and age adjusted vaccination effectiveness referred to the time of vaccination and the corresponding 95% confidence intervals (CI) were estimated at 6, 12, 18 and 24 months of follow up.

Setting—All population aged 18 months to 19 years of Catalonia.

Main results—A total of seven cases of SCMD were detected at six months of follow up (one in the vaccinated cohort), 12 cases at 12 months (one in the vaccinated cohort), 19 cases at 18 months (two in the vaccinated cohort) and 24 at 24 months (two in the vaccinated cohort). The age adjusted effectiveness was 84% (95%CI 30, 97) at six months, 92% (95%CI 63, 98) at 12 months, 92% (95% CI 71, 98) at 18 months and 94% (95%CI 78, 98) at 24 months. In the target population, cases have been reduced by more than two thirds (68%) two years after the vaccination programme. In the total population the reduction was 43%.

Conclusion—Vaccination effectiveness has been high in Catalonia, with a dramatic reduction in disease incidence in the vaccinated cohort accompanied by a relevant reduction in the overall population. Given that vaccination coverage was only 54.6%, it may be supposed that this vaccination effectiveness is attributable, in part, to the herd immunity conferred by the vaccine.

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Meningococcal disease is endemic in Spain, with hyperendemic episodes taking place every 10–15 years, which lead to higher incidence rates, such as in the 1979 upsurge that reached a level of 17 per 100 000 inhabitants.[1]

In the past, serogroup B meningococcal disease was predominant, causing almost 80% of cases, with serogroups C and A next. However, this situation has changed. Serogroup A disappeared during the 1990s and from 1993 serogroup C meningococcal disease (SCMD) has increased, overtaking the declining number of serogroup B cases in 1996.[2]

A marked rise in SCMD was registered from mid-1996 with serogroup C becoming the main serogroup in virtually all the regions of Spain. This was accompanied by the appearance of a new serogroup C strain—C:2b:P1.2,5—which in some communities led to higher case fatality rates.[2]

Widespread media coverage of the upsurge caused considerable social alarm, which was heightened by the majority involvement of infants and adolescents.

The north western Spanish region of Galicia, where the upsurge first appeared, decided, in 1996, to respond with a campaign of mass vaccination of the 18 months to 19 years age group,[3] a strategy that was taken up by La Rioja and Cantabria in early 1997. The other regions, except Andalusia, Navarra and the Canary Islands, decided to adopt this policy and carry out mass vaccination during the last three months of 1997.

The campaign took place in the last quarter of 1997 in Catalonia, with free vaccination taking place in primary health and paediatric centres. In the 18 months to 19 years age group, overall coverage was 54.6%, reaching 65.2% in the 18 months to 4 years group, 77.8% in the 5–9 years group, 60.8% in the 10–14 years group and only 31.4 % among 15–19 year olds. The campaign was estimated to have cost around 4.5 million Euros.

Preliminary results after 6 and 12 months of follow up were presented at the 4th Europeance Conference on Vaccinology.[4]

In this article, mass vaccination effectiveness after 6, 12, 18 and 24 months of follow up is evaluated.

Methods

In Catalonia it is compulsory to report any suspected case of meningococcal disease to the health authorities. In all reported cases, cerebrospinal fluid and blood are cultivated to isolate the germ and identify the serogroup. In all confirmed cases of serogroup C, vaccination status is investigated.

Table 1 Distribution of confirmed cases of meningococcal disease in Catalonia, 1996–1999

	1996		1997		1998		1999	
	Cases (n)	%	Cases (n)	%	Cases (n)	%	Cases (n)	%
Serogroup B	123	63.4	102	54.6	77	70.6	113	74.8
Serogroup C total	64	33.0	77	41.2	28	25.7	33	21.9
Serogroup C <18 months	2	1.0	13	7.0	4	3.7	9	6.0
Serogroup C 18 months–19 years	49	25.3	50	26.8	13	11.9	16	10.6
Other serogroups	2	1.0	1	0.5	0	0	1	0.7
Non-groupable	5	2.6	7	3.7	4	3.7	4	2.6
Total	194	100	187	100	109	100	151	100

All confirmed cases from January 1996 to June 1999 have been included in the descriptive study.

Vaccination effectiveness (VE) was estimated using the cohort method applied to confirmed cases reported during the period 1 January 1998 to 31 December 1999. For the calculation the following formula was used[5]:

$$VE = \frac{Inv - Iv}{Inv} = 1 - RR \quad (1)$$

Where Inv is the incidence rate in the unvaccinated cohort, and Iv the incidence rate in the vaccinated cohort. The number of individuals in the target population was obtained from the last census returns (1996).[6] It was assumed that in these age groups the mortality is negligible.

For unadjusted vaccination effectiveness 95% confidence intervals (95% CI) were calculated by the Taylor series,[7] a method based on the asymptotic normality of the log transformation of the quotient of two proportions (see appendix).

The 95% CI of VE were calculated on the basis of the upper and lower limits of the relative risk (RR). Estimates of relative risk (RR) and 95% CI were calculated with and without stratification for the age at the time of vaccination.

To obtain lower and upper limits of VE the following formulas were used:

Lower limit of VE = $(1-RR_u) \times 100$, where RR_u is the upper limit of RR.

Upper limit of VE = $(1-RR_l) \times 100$, where RR_l is the 95% CI of the lower limit of RR.

The age adjusted vaccination effectiveness was obtained from the Mantel-Haenzel estimator and the 95% CI were calculated by the binomial likelihood method.[8]

For these calculations we have assumed that the unvaccinated population is identical to the vaccinated population in all characteristics that might affect both the transmission of the causal agent and the development of the disease.

The calculations have been made for 6, 12 and 18, and 24 months follow up periods.

Results

Table 1 shows the distribution of all confirmed cases of meningococcal disease according to the serogroup during the period 1996–1999.

A substantial reduction in the incidence of SCMD occurred during the follow up period. In total, during 1998, 28 cases of SCMD were reported, in comparison with the 77 reported during the preceding year. In the target vaccination age group, cases were reduced after 24 months of follow up by more than two thirds (16 cases in 1999 compared with 50 in 1997). The cases in this age group occurred almost exclusively in unvaccinated subjects (22 cases) with only two cases occurring in vaccinated children. It should be noticed that the incidence of unvaccinated cases was higher in older children, the age group with lower vaccination coverage. In the total population the reduction was also relevant (43%).

The target population according to the 1996 census returns was 1 273 348 and the global vaccination estimated vaccination coverage was 54.6, although this figure changed over age groups (see table 2). Thus, the vaccinated cohort was 694 814 subjects and the unvaccinated one 578 534. So, for the follow up period of 24 months, the number of persons year for each cohort was 1 389 628 and 1 157 068 respectively. The number of SCMD during the 24 months follow up period was 24 (two in the vaccinated cohort and 22 in the unvaccinated cohort). Thus, the incidence rate in the vaccinated cohort was 0.14 per 100 000 persons per year and in the unvaccinated one 1.90 per 100 000 persons per year. The unadjusted vaccination effectiveness was 92%; 95% CI, 68 to 98%.

These calculations by periods of follow up (6, 12, 18 and 24 months) are shown in table 3. No relevant differences have been observed in vaccination effectiveness according to the duration of follow up. Adjusted vaccination effectiveness shows similar results with narrower confidence limits.

Table 2 Distribution of cases of serogroup C meningococcal disease according to the period of follow up and the vaccination status

Age at the time of vaccination	Period of follow up							
	6 months		12 months		18 months		24 months	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
18 months–4 years	1	1	1	1	2	4	2	7
5–9 years	0	0	0	0	0	2	0	2
10–14 years	0	0	0	2	0	3	0	3
15–19 years	0	5	0	8	0	8	0	10
Total	1	6	1	11	2	17	2	22

Table 3 Meningococcal C vaccination effectiveness by periods of follow up. Catalonia, 1998–1999

| | Vaccinated cohort | | Unvaccinated cohort | | Vaccination effectiveness | | | |
| | | | | | Unadjusted | | Adjusted | |
Period of follow up	Person years	Cases	Person years	Cases	%	95% CI	%	95% CI
6 months	347 407	1	289 267	6	86	−15, 98	84	30, 97
12 months	694 814	1	578 534	11	92	41, 99	92	63, 98
18 months	1 042 221	2	867 801	17	90	58, 98	92	71, 98
24 months	1 389 628	2	1 157 068	22	92	68, 98	94	78, 98

Discussion

Age adjusted vaccination effectiveness according to the cohort method in the target population 24 months after the end of the vaccination programme is very high (94%).

It is worth pointing out that effectiveness has remained stable (over 90%) during the last three periods analysed, and does not seem to diminish over the time since vaccination, although it must be remembered that the total follow up period is short and the number of cases is low.

The results of the mass meningococcal vaccination programme of children and young people in Catalonia measured after 24 months of follow up are encouraging and seem to confirm a high level of effectiveness of the vaccination programme in the control of SCMD, at least in the short-term. It is noteworthy that the reduction observed in SCMD after the intervention was not observed in serogroup B (table 1). A similar decrease of SCMD was not observed in the regions of Spain that decided not to carry out a mass vaccination.[4]

Given the social awareness of meningococcal disease we estimate that almost 100% of cases are notified, and that in most of them the serogroup is identified.

Although possible, we believe that the probability that information or misclassification bias has occurred is very low. The data on cases come from a comprehensive surveillance system, which includes compulsory notification of the disease by clinicians and the laboratory notification of positive cultures to the Microbiological Notification System of Catalonia. So, probably, all confirmed serogroup C meningococcal disease cases in Catalonia were included in the study. The information on the antecedents of the vaccination was collected by field epidemiologists in all cases, minimising the likelihood of misclassification bias. We do not think that the vaccination uptake rate was influenced by any other important factors because the vaccine was free to the point of delivery for all the children and young people living in Catalonia.

The results of the meningococcal serogroup C vaccination programme of Catalan children and young people carried out during the last three months of 1997 are better than those obtained in the six major studies of efficacy (results in optimal conditions) and effectiveness (results in real conditions of use) carried out in different countries during the past 20 years (table 4).[9–14]

Noteworthy is a reduction in cases among children under 18 months (only four cases in 1998 and nine cases in 1999 against 13 in 1997), which suggests the existence of herd immunity. This reduction has been achieved with relatively low levels of vaccination coverage (54.6%). Peltola et al[15] observed a similar phenomenon in a study of the effectiveness of the meningococcal A vaccination carried out in Finland in 1994, in the framework of a mass vaccination campaign of children in those areas with high disease incidence. A vaccination coverage of 38% was sufficient to reduce cases in unvaccinated subjects by 40%. Also in Finland, a vaccination coverage of 40% among military recruits was sufficient to contain an epidemic among the military, which however, continued unabated in the general population.[16]

These excellent epidemiological results have been achieved although studies of immunity in vaccinated children in different regions of Spain indicate that the proportion of vaccinated individuals who retain bactericidal titres ⩾1:8 decrease rapidly, especially in children under 6 years,[17–19] which is in agreement with the results obtained recently in the USA and Canada with current licensed vaccines.[20–22]

The decision to vaccinate was taken without a prior cost-benefit analysis. However, in light of the results obtained, a thorough economic

Table 4 Efficacy and effectiveness* of meningococcal C vaccine in published studies

| | | Study population | | | Follow up period | Efficacy/ effectiveness % | 95% CI |
Country (year) Author	Type of study	Number	Age	Design			
USA (1969) Artenstein et al[9]	Efficacy	68 000	Military recruits	Randomised controlled trial	2 months	87†	57, 100†
USA (1969/1970) Gold et al[10]	Efficacy	75 000	Military recruits	Randomised controlled trial	2 months	88†	52, 100†
Brazil (1972) Taunay et al[11]	Efficacy	135 000	6–36 months (24–36 months)	Randomised controlled trial	17 months	NS (67)†	(8, 89)†
Italy (1987/1989) Biselli et al[12]	Effectiveness	300 000	Military recruits	Incidence	12 months	91†	30, 99†
Quebec (1992/1993) De Walls et al[13]	Effectiveness	1.7 million	6 months–20 years (6 months–4 years)	Incidence	4 years	79 (72)	53, 91 (5, 91)
Gregg County (1993/1995) Rosenstein et al[14]	Case-control	17 cases 84 controls	2–29 years	Case-control		85	27, 97
Catalonia (Spain) 1998–99	Effectiveness	1.27 million	18 months–19 years	Incidence	12 months	92	63, 98
					18 months	92	71, 98
					24 months	94	78, 98

*Data in parentheses refer to specific population subgroups. †Recalculated by Rosenstein et al.[14]

analysis (cost-benefit and cost effectiveness) is currently underway to investigate the efficiency of the programme.

The seroprevalence study carried out in Cantabria 10 months after the mass vaccination campaign supports the hypothesis that in this vaccination, there seems to exist no clear correlation between immunogenicity (at least, as it is currently measured) and the protective efficacy of the vaccine; in this study only 6.9% of vaccinated children between 18 months to 5 years retained bactericidal titres 10 months after vaccination. In the 6–11 years age group, this percentage was 51.3%.[17] However, no cases of SCMD were observed in vaccinated children in these age groups during 1998 in this region.

So, the distinction between immunogenicity and effectiveness should be taken into account, because results are not always coincident. In this case, challenging current thinking on this issue,[20–22] results in the field are superior to those that could have been expected from immunogenicity studies.

The conjugation with proteins of the capsular polysaccharide converts it into T dependent antigen and makes the vaccine immunogenic in breast feeding babies and also generates immunological memory, thus ensuring long term protection. This has stimulated the obtention of serogroup A and C capsular polysaccharide meningococcal vaccines conjugated with proteins.[23] These vaccines have been tested in Africa and the UK, with promising results.[24–29]

The excellent results obtained in Catalonia in controlling the SCMD upsurge by mass vaccination supports both the recently taken decision of the UK Medicines Control Agency to license production of the new conjugated meningococcal C polysaccharide vaccine without implementing field trials of efficacy and the English Government's decision to begin mass vaccination of children and young people.[30]

Appendix

As suggested by Kleinbaum *et al*[7] and Ewell[31]

Y_1 e Y_0 denote the number of person years of follow up in vaccinated and non-vaccinated respectively in whom C, and c_1 y c_0 cases of infection have been observed in the corresponding groups. It is supposed that the incidence in the respective groups are independent. In this case, the relative risk (RR) is calculated by:

$$RR = \frac{c_1/Y_1}{c_0/Y_o} \tag{a1}$$

Firstly, the natural log transformation of the relative risk is calculated, as we assume the asymptotic normality of this transformation.

The variance of this new variable ($\ln\_RR$) is obtained

$$\text{var}(\ln\_RR) = \text{var}\left(\ln\left(\frac{c_1/Y_1}{C_0/Y_o}\right)\right)$$
$$= \text{var}(\ln(c_1/Y_1) - \ln(c_0/Y_0))$$
$$= \text{var}(\ln(c_1/Y_1)) + \text{var}(\ln(c_0/Y_0)) \tag{a2}$$

and approximating $\text{var}(\ln(c_i/Y_i)), i = 0, 1$, by Taylor's series we obtain

$$\text{var}(\ln(c_i/Y_i)) \sim \left(\frac{1}{c_i/Y_i}\right)^2 \text{var}(c_i/Y_i)$$
$$= \frac{1-(c_i/Y_i)}{c_i} \quad i = 0,1 \tag{a3}$$

Substituting (a3) for (a2), we obtain

$$\text{var}(\ln\_RR) \sim \frac{1-(c_1/Y_1)}{c_1} + \frac{1-(c_0/Y_0)}{c_0} \tag{a4}$$

According to the hypothesis of asymptotic normality of the transformation mentioned above, the confidence intervals calculated at $(1-\alpha)\%$ for the variable $\ln\_RR$ are obtained by the following equation

$$\ln\_RR \pm Z_{1-\alpha/2}\sqrt{\text{var}(\ln\_RR)} \tag{a5}$$

and thus, the lower and upper limits of the relative risk, named RR_l y RR_u respectively are obtained by the equation

$$RR \times \exp\left(\pm Z_{1-\alpha/2}\sqrt{\text{var}(\ln\_RR)}\right)$$
$$= RR \times \exp\left(\pm Z_{1-\alpha/2}\sqrt{\frac{1-(c_1/Y_1)}{c_1} + \frac{1-(c_0/Y_0)}{c_0}}\right) \tag{a6}$$

Finally, the confidence intervals of vaccine effectiveness are calculated in function of the intervals obtained for the relative risk using the expression (a6):

$(VE_l, VE_u) = (1-RR_u, 1-RR_l)$

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