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Back to Table of Contents
en es fr it pt
Previous

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IMPACT OF THE MENINGOCOCCAL C CONJUGATE VACCINE IN SPAIN: AN EPIDEMIOLOGICAL AND MICROBIOLOGICAL DECISION

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The new meningococcal C conjugate vaccine became available in Spain and was included in the infant vaccination schedule in 2000. A catch-up campaign was carried out in children under six years of age. As a consequence, the incidence of meningococcal disease caused by serogroup C has fallen sharply during the last three epidemiological years in Spain. The risk of contracting serogroup C disease in 2002/2003 fell by 58% when compared with the season before the conjugate vaccine was introduced. There was also an important decrease in mortality. Three deaths due to serogroup C occurred in the age groups targeted for vaccination in 2002/2003, compared with 30 deaths in the same age groups in the season before the launch of the vaccine campaign. In the catch-up campaign the vaccine coverage reached values above 92%. For the 2001, 2002 and 2003 routine childhood immunisation programme coverage values ranged from 90% to 95%. During the past three years a total of 111 cases of serogroup C disease have been reported in patients in the vaccine target group. Most of the vaccination failures occurred during the epidemiological year 2002/2003. Eight (53%) vaccine failures occurred in children who had been routinely immunised in infancy, and could be related to a lost of protection with time since vaccination. The isolation of several B:2a:P1.5 strains (ST-11 lineage) is noteworthy. These may have their origin in C:2a:P1.5 strains which, after undergoing genetic recombination at the capsular operon level, express serogroup B. These strains could have relevant epidemic potential.

Introduction

A change in the epidemiological pattern of meningococcal disease was observed in Spain and other European countries in the mid-1990s [1,2]. The median incidence of meningococcal disease was 2.9/100 000 for the five year period 1991-1996 and serogroup B was the most frequent among all the confirmed infections. In the epidemiological year 1996/1997, however, serogroup C became the predominant group (63%) in almost all Spanish regions, with a consequent increase in incidence and mortality. The incidence reached 5.8/100 000 with incidence due to serogroup C at 2.3/100 000. To reduce this incidence, a nationwide vaccination campaign (which included 16 out of the 19 autonomous Spanish regions) using anti-meningococcal A+C polysaccharide vaccine was launched in autumn 1997. The overall estimated coverage was 76.3%. This strategy reduced the national incidence of meningococcal disease by 45%. A reduction was seen in all age groups, and the most important reduction was found in 2 to 19 year olds, the target group of the intervention. In this group, the number of serogroup C cases fell by 76% in comparison with the year before vaccination was introduced. However, the incidence of meningococcal disease caused by serogroup C continued to increase in the years following vaccination [3], a foreseeable circumstance given the limitations in the immunogenicity of polysaccharide vaccine [4,5]. The new conjugate vaccine became available in Spain in 2000, and was included in the infant vaccination schedule. A catch-up campaign was carried out aimed at the most

vulnerable group: children under the age of six years. In three of the 19 national regions, this group was extended to include all those under 19 years of age over the next three years. This study analyses meningococcal disease surveillance data from the three epidemiological years from 2000/2001 and 2002/2003 following the introduction of the meningococcal serogroup C (MenC) conjugate vaccine in Spain, and includes data on incidence in the different age groups and on the characterisation of strains isolated in clinical cases. In this sense, the main interest in characterising these strains lies in verifying whether the vaccination with the MenC conjugate vaccine carried out during the last months of 2000 led to the selection of new antigenic variants as a result of recombination or shift of group B or C percentages, as well as an increase in the number of cases caused by serogroups other than B and C.

Methods

Epidemiological surveillance of meningococcal disease in Spain is based on a passive notification system. The weekly reporting of cases diagnosed is compulsory and physicians must complete a questionnaire for every case notified with the patient's demographic, clinical and epidemiological data. The epidemiologist updates the information on outcome and vaccination status a few days after the case is notified.

Data for the calculation of global and specific incidences by age during the years 1999/2000 to 2002/2003 were obtained from the cases notified to the Sistema de Enfermedades de Declaraci?n Obligatoria (EDO, Compulsory Disease Reporting System). For notification purposes, a probable case is defined as a patient who presents with clinical symptoms compatible with the disease and a presumptive analytical test (such as the presence of intracellular Gram negative diplococci in cerebrospinal fluid or other biochemistry analyses). In 2000, the definition of a confirmed case was modified to include both isolation of *Neisseria meningitidis* at a normally sterile site and the presence of meningococcal DNA or the detection of meningococcal antigen in the appropriate samples.

In this study, the epidemiological year (also known as 'season') runs from week 27 of a particular year until week 26 of the next. Calculation of national and age-specific meningococcal disease incidences was made using population estimates made mid-year by the National Statistics Institute (Instituto Nacional de Estadística). The risk of suffering from the disease during the previous epidemiological year in the study was calculated, (using relative risk and a 95% confidence interval,) by comparing the current season with each of the previous epidemiological seasons.

Vaccine failure cases were studied from 1 January 2001 to 31 December 2003. A confirmed vaccine failure was defined as a confirmed case of serogroup C disease with onset more than 14 days after the last dose of vaccine scheduled for that age group.

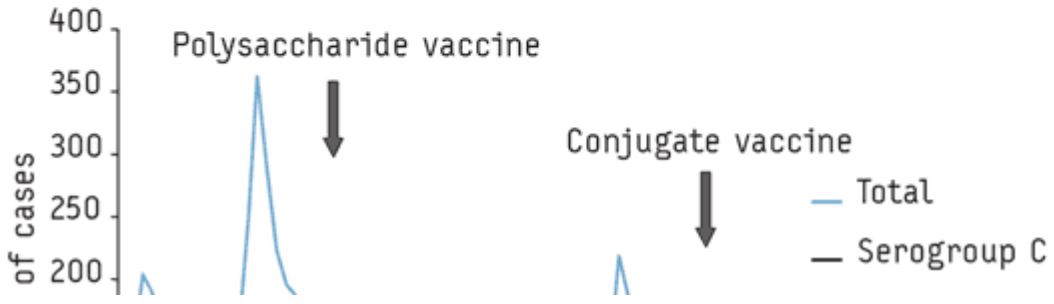
To analyse the specific characteristics of the meningococcal strains in all isolates, serogroup, serotype and serosubtype were determined using specific monoclonal antibodies according to techniques described elsewhere [6]. Furthermore, in order to study the possible appearance of capsular genetic interchange phenomena, multilocus sequence typing (MLST) [7] was used to define precisely the clone lines to which the suspected strains belonged.

Results

In the epidemiological year 2002/2003, 948 cases of meningococcal disease were reported (2.3/100 000), of which 76% were confirmed cases. The percentage of confirmed cases during the study's final season was higher than that of the previous three seasons (71% on average), and 468 serogroup B (1.2/100 000) and 175 serogroup C cases (0.4/100 000) were notified [TABLE 1]. The number of serogroup C cases notified fell during the three seasons after the introduction of the vaccine, except for a slight increase in the rates both for this serogroup and for the others in the season 2001/2002 [FIGURE 1, TABLE 1].

FIGURE 1

Meningococcal disease. Total number of cases and serogroup C cases notified at four-week periods, Spain, 1996-2003



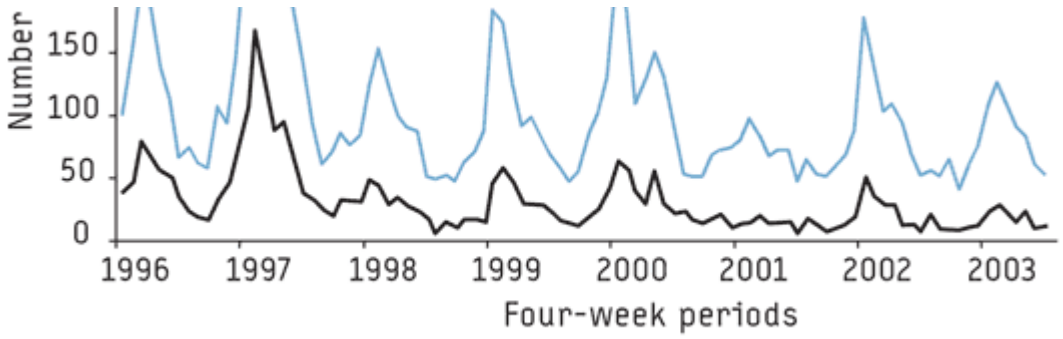


TABLE 1

Meningococcal disease. Cases and incidence per 100 000 inhabitants. Spain, epidemiological years 1999–2000 to 2002–2003

Case classification	1999/2000		2000/2001		2001/2002		2002/2003	
	Cases	incidence	Cases	incidence	Cases	incidence	Cases	incidence
Serogroup B	607	1.52	467	1.16	551	1.36	468	1.15
Serogroup C	404	1.01	179	0.44	233	0.57	175	0.43
Other serogroups	19	0.05	21	0.05	21	0.05	18	0.04
Non-groupable	37	0.09	46	0.11	53	0.13	60	0.15
Total definite cases	1067	2.67	713	1.77	858	2.12	721	1.77
Probable cases	530	1.33	285	0.71	294	0.73	227	0.56
All cases	1597	4.00	998	2.48	1152	2.84	948	2.32

The risk of suffering from serogroup C disease during the 2002/2003 season was 25% less than the previous season and 58% less compared with the season before vaccination. The risk of suffering from serogroup C disease was lower compared with that observed during each of the previous seasons except for 2000/2001. For the other serogroup categories, although the point estimates indicated a decrease in risk when comparing the last epidemiological season with each of the previous ones, the upper confidence interval is compatible with increasing risks. On the other hand, the incidence of non-groupable cases increased gradually throughout the study period and the risk was 59% higher in the season 2002/2003 if we compare it with the season 1999/2000. This increase is statistically significant [TABLES 1 and 2].

TABLE 2

Relative risk of suffering from meningococcal disease during 2002-2003 with respect to the previous three epidemiological years for the principal serogroups, Spain

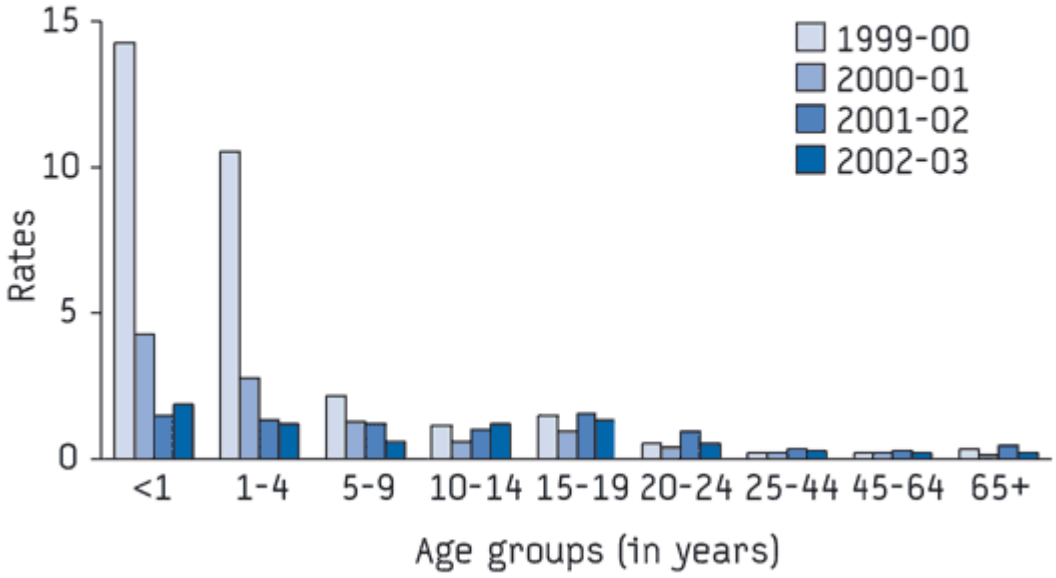
SEROGROUP	RELATIVE RISK		
	2002-2003/ 2001-2002 (CI 95%)	2002-2003/ 2000-2001 (CI 95%)	2002-2003/ 1999-2000 (CI 95%)
Serogroup B	**0.84** (0.74-0.96)	**0.99** (0.86-1.13)	**0.75** (0.66-0.85)
Serogroup C	**0.75** (0.61-0.91)	**0.96** (0.78-1.19)	**0.42** (0.35-0.51)
Other serogroups	**0.85** (0.42-1.68)	**0.84** (0.42-1.67)	**0.78** (0.33-1.79)
Non-groupable	**1.12** (0.76-1.66)	**1.27** (0.86-1.93)	**1.59** (1.03-2.46)
Total	**0.81** (0.75-0.89)	**0.93** (0.85-1.02)	**0.58** (0.53-0.63)

A decrease in the number of serogroup C cases [FIGURE 2] in children under ten years was observed during the last three seasons in this study. These children were either born after the conjugate vaccine was included in the routine vaccination schedule or were part of the target group for the catch-up campaign. In the epidemiological year 2002/2003, 38 cases due to serogroup C (1.0/100 000) were reported in children under -ten years, compared with 254

cases (6.6/100 000) during the season before Menc C conjugate vaccine was introduced, which represents an 85% reduction in the incidence at this age. On the other hand, although not statistically significant, there was an increase in the incidence in 10 to 14 -year olds.

FIGURE 2

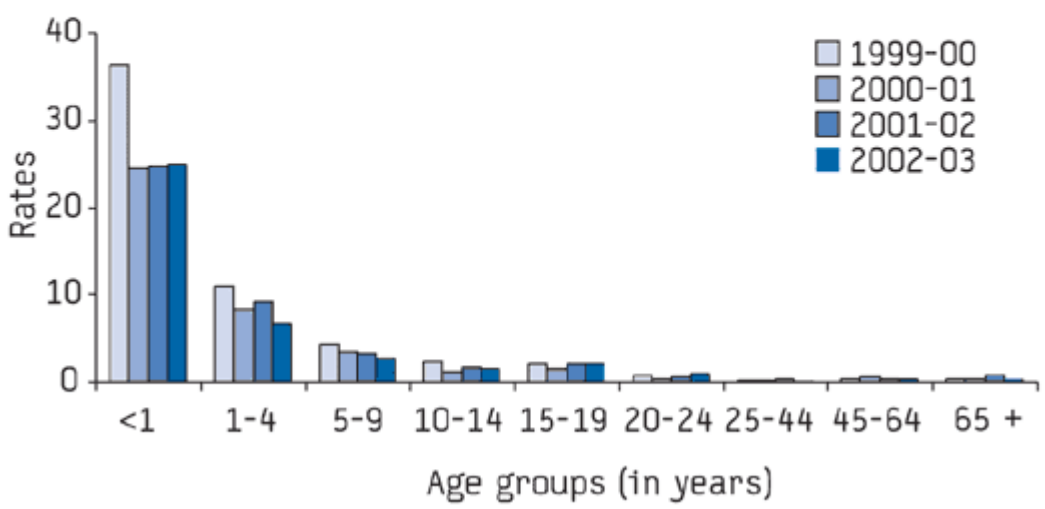
Meningococcal disease. Incidence of serogroup C during the study epidemiological years by age group. Spain, 1999–2003



The incidence of serogroup B disease in children under one year old in the 2000/2001 season decreased significantly in relation to the previous epidemiological year [FIGURE 3]. The distribution by age of serogroup B disease reflects the usual age distribution pattern with a large incidence for children under five years.

FIGURE 3

Meningococcal disease. Incidence of serogroup B during the study epidemiological years by age group. Spain, 1999–2003



Information on the clinical presentation of the disease (sepsis, meningitis, or both) was registered for 95% of cases during the season 2002/2003. Clinical sepsis was present in 46.9% of cases, and clinical meningitis in 38.4% (p = 0.01). Sepsis and meningitis together were present in 10% of the cases. The percentage of cases with sepsis was greater in serogroup C cases (52%) than in serogroup B cases (49%), but the difference is not statistically significant. Outcome is known for more than 95% of cases. In the epidemiological year 2002/2003, 88 deaths due to meningococcal disease were reported. During the same period, the number of deaths and the case fatality rate (CFR) for the most important serogroups were 33 and 7.5% for serogroup B, and 29 and 16.6% for serogroup C. Table 3 shows the number of deaths due to serogroup C disease by age before and after the introduction of the MenC conjugate vaccine. There was a continuous decrease in the mortality caused by serogroup C disease after vaccination, except in 2001/2002. Three deaths due to serogroup C occurred in the age groups targeted for vaccination in 2002/2003, compared with 30 deaths that occurred in the same age groups in the season prior to the 2000 vaccine campaign was launched. One of the three deaths was in a child who had received the complete course of three doses of conjugate vaccine in the routine vaccination programme. In the epidemiological year 2002/2003, there was a 36% reduction in CFR compared with that registered before vaccination.

TABLE 3

TABLE 3

Number of deaths and case fatality rate (CFR) caused by serogroup C meningococcal disease by age group. Spain, epidemiological years 1999–2000 to 2002–2003

Age group	1999/2000		2000/2001		2001/2002		2002/2003	
	Deaths	CFR	Deaths	CFR	Deaths	CFR	Deaths	CFR
<1	10	18.2	3	17.7	3	50.0	1	12.5
1-4	17	10.9	3	7.3	3	14.3	2	10.5
5-9	3	7.0	4	16.0	3	13.0	0	0.0
10-14	1	3.4	1	8.3	1	5.0	3	12.0
15-19	7	17.5	3	13.0	8	21.6	4	12.9
20-24	2	11.8	1	8.3	11	39.3	3	20.0
25-44	4	15.4	2	9.1	7	16.7	8	25.0
45-64	3	17.7	6	37.5	5	20.8	2	11.1
65 +	4	16.7	2	18.2	11	34.4	6	37.5
Total	51	12.6	25	13.9	52	22.3	29	16.6

Coverage in the catch-up and routine immunisation programmes in 2001, 2002 and 2003 was estimated on the basis of coverage data from nine Spanish autonomous regions, which together account for 60% of the total Spanish population. The proportion of the vaccinated population in the catch-up displayed considerable homogeneity for children born between 1995 and 2000, with values above 92% for these birth cohorts. For the 2001, 2002 and 2003 routine childhood immunisation programmes, coverage values ranged from 90% to 95%.

During the epidemiological years after the introduction of the conjugate vaccine in the national schedule, 111 cases of serogroup C disease were reported throughout the country in patients in the vaccine target group (including those regions where the catch-up was extended to adolescents). Twenty three of them had received the vaccine, 78 had not, and the vaccination status was unknown in 10 cases. The number of cases for which the vaccination status was unknown fell during the last three seasons and status information is available for all cases during the 2002/2003 season. Of the 23 vaccinated cases, 15 were classified as confirmed vaccine failures (accomplished complete vaccination) and eight as probable failures (incomplete vaccination or fewer than 14 days between vaccination and first symptoms) [TABLE 4].

TABLE 4

Confirmed vaccine failures in cases of meningococcal disease vaccinated with conjugate vaccine by year of onset, age of patient at onset and year of vaccination. Spain, 2001–2003

Year of vaccination	Year of disease onset									
	2001			2002			2003			
	Age at onset									Total
	< 1	1-4	5-9	< 1	1-4	5-9	< 1	1-4	5-9	
2000		1	1		1			3	1	7
2001				1				6		7
2002								1		1
2003										
Total		1	1	1	1			10	1	15

Eleven of the 15 confirmed vaccination failures occurred during the season 2002/2003. Ten of these children were between one and four years of age, and only one of these cases had previously received the A+C polysaccharide vaccine during the 1997 vaccination campaign. Of the 15 vaccination failures, seven had received the vaccination during the catch-up campaign in 2000. The eight remaining cases had been vaccinated according to the routine vaccination schedule established, and all but one had received the vaccination in 2001. Failures were distributed throughout the country. According to figures provided by pharmaceutical companies on the number of doses of conjugate vaccine sold in Spain, we estimate that during the period 2000-2003, 2.6 vaccine confirmed failures per one million doses occurred.

During the study period, 2113 strains of Neisseria meningitidis isolated from clinical cases with symptoms of meningitis and/or sepsis were received for characterisation by the national reference laboratory. The proportion of

characterisation by the national reference laboratory. The proportion of serogroup B cases increased gradually from 58.3% in 2000 to 68% in 2001 and 2002, reaching 72.9% during the first nine months of 2003. The frequency of serogroup C strains fell from 38.5% in 2000, to 27% in 2001, 22.6% in 2002, and finally to 20% in 2003. The percentage for 2003 corresponds to that observed in Spain during the 1980s, before the increase in serogroup C disease. Only slight increases were observed in the frequency of serogroups Y and W135, with the former rising from 1.2% in the year 2000 to 2.8% in 2003, and the latter from 1% to 1.9%. These increases are not statistically significant.
The serosubtypes which appear in the strains of serogroup C have undergone a considerable change. C:2a increased from around 20% in 2000 to 56% in 2003, a trend which began in 1999 before the new vaccine was introduced. The serosubtypes associated with serogroup B have not undergone modifications. 4:P1.15 strains have predominated (25%). Increases in non-typable strains (42%) were observed. This high percentage of non-typable strains is increasing, although non-serosubtypable strains only reach around 14%.
The isolation in the north of Spain of several B:2a:P1.5 strains (ST-11 lineage) is worthy to note. These may have their origin in C:2a:P1.5 strains which, after undergoing genetic recombination at the capsular operon level, express serogroup B capsule.

Discussion

The incidence of meningococcal disease, especially serogroup C, has fallen sharply during the last three epidemiological seasons in Spain covered by this study. It has been estimated that the risk of contracting the disease of this serogroup fell by 58% if we compare the incidence of the last epidemiological year in the study with that of the season before the conjugate vaccine was introduced. Nevertheless, we must bear in mind that the rates for the season 1999/2000, especially those of serogroup C, had already fallen considerably due to the vaccination campaign with polysaccharide vaccine in 1997. The increased incidence in the 10-14 year age group, although not statistically significant, deserves special mention, given that only about 35% of the population in this group has been vaccinated. No increase was observed among others adolescents or in young adults. Nevertheless, a continuous monitoring of the incidence in these age groups is needed in order to evaluate the current vaccination policy.
The proportion of vaccine failures detected is similar to that observed in other countries [8]. However, a large number of the confirmed vaccination failures occurred during the epidemiological year 2002/2003. Also, 8 out of 15 (53%) confirmed vaccine failures occurred in children who had been routinely immunised in infancy. These aspects could be related to a loss of protection with time since vaccination. The study currently being carried out on vaccine effectiveness may help clarify the issue. No relationship has been found between vaccination failures and a previous history of having received the polysaccharide vaccine.

The incidence of meningococcal disease caused by serogroup B and other serogroups has remained stable during the last three seasons. This circumstance is compatible with the cyclical evolution of the disease and suggests that we are in an interepidemic period. It can also be concluded that the analysis of the situation immediately after the introduction of this new conjugate vaccine, which could have led to the appearance of a new bacterial equilibrium, shows that there is no evidence of alterations in the populations of circulating meningococci. However, special mention must be made of the isolation of B:2a:P1.5 strains, previously mentioned in the results section. These strains could have relevant epidemic potential and, after two years of evolution, they are now being isolated in more areas of Spain, although only in small numbers. Future evolution of this strain will enable us to analyse the real importance of these processes of active immunisation in the selection of this type of antigenic recombinants.
We do not have any explanation for the increase in the number of non-groupable cases. The current use of microbiological techniques cannot be evaluated here, as we do not have information on the techniques used in the diagnosis of each case.
Finally, we must stress the importance of maintaining epidemiological surveillance of this disease, as well as on improving the quality of the information collected from each case. This will enable us to observe changes in the presentation pattern of the disease, and in the identification of vaccination failures with a view to reviewing the functioning of current prevention programmes.

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Back to Table of Contents
Previous
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To top | Recommend this page