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ORIGINAL ARTICLE

Implementation and impact of a meningococcal C conjugate vaccination program in 13- to 25-year-old individuals in Galicia, Spain

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Abstract
Background In response to increased case numbers of meningococcal group C disease, catch-up vaccination strategies have been shown to be successful. This paper describes the results of a repeat vaccination program in Galicia, Spain, and the strategy used for it.
Methods and results Three vaccination waves were performed: first, in 1996/1997 with a meningococcal group A and C polysaccharide vaccine in individuals aged 18 months to 19 years; second, in 2000 with a conjugate serogroup C polysaccharide vaccine in children born since 1993 and all children and adolescents up to 19 years not previously vaccinated; third, a campaign in 2006 that became necessary because of the development of a new Neisseria strain and an increase in both the incidence and lethality of meningococcal C disease. The conjugate vaccine de-O-acetylated group C meningococcal polysaccharide coupled to tetanus toxoid was used (GCMP-TT; brand name, NeisVac-C). Results: Applying a strategy based on model calculations derived from the UK setting and focusing on a population aged 13–25 years, including students, employees of companies, and underage individuals, a total of 286,000 subjects were vaccinated, resulting in global vaccination coverage of 82.2% (all age groups over 74%). Only 17 adverse events in 17 individuals were reported, which all were mild. Incidence of meningococcal disease serogroup C by season was reduced from 0.84 cases per 100,000 in 2004/05 to 0.76 cases per 100,000 in 2005/2006 to 0.18/100,000 in 2007/08. In parallel, mortality was also decreased from 8 cases during 2005/06 (0.29 per 100,000) to 1 case in 2007/2008 (0.03 per 100,000). No cases of breakthrough disease occurred in the vaccinated population.
Conclusion In Galicia, a series of vaccination campaigns, particularly focusing on high-risk groups, has shown high effectiveness, with a marked reduction in the disease incidence in the vaccination cohort accompanied by a relevant reduction in the overall population.

Keywords Vaccination · Meningococcal disease · Public health · Conjugated vaccines

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Introduction

Neisseria meningitidis is the leading cause of bacterial meningitis and septicemia in children and adolescents. It is associated with a high mortality rate of 10–15% and substantial morbidity rate; approximately 20% of survivors develop permanent sequelae (Rosenstein et al. 1999). The implementation of effective vaccination programs is key to controling meningococcal disease (Trotter and Ramsay 2007). While at least 13 serologically distinct groups are known, the great majority of invasive meningococcal disease is caused by the serotypes A, B, C, W_{135} and Y, with a preponderance of serotype B, although serotype C still has an important disease impact in European countries. Thus, meningococcal conjugate vaccines against only serogroup C are in widespread use.

Plain meningococcal group A and C polysaccharide vaccines are of limited value for routine immunization. They are poorly immunogenic in infants and children under 2 years of age, the age group at highest risk of contracting meningococcal disease. In addition, the immune response

induced by these vaccines is rather short lived, and re-vaccination is known to result in immunologic hyporesponsiveness (De Wals et al. 2001, Granoff et al. 1998, World Health Organization 2002). *Conjugated* polysaccharide vaccines, in which the capsular polysaccharide is covalently conjugated to a carrier protein, eliciting both B- and T-cell responses, are highly immunogenic in children younger than 2 years of age and have been shown to induce immunologic memory (Borrow and Findlow 2009). Therefore, meningococcal conjugate vaccines are suitable for use in routine childhood vaccination.

Also in Galicia—an autonomic administrative region in the northwest of Spain—meningococcal disease is endemic. Galicia has a meningitis surveillance system, and since 1995 it also has had an active surveillance system based on cases reported on a weekly basis by hospitals. Between 1990 and 1995 the incidence rate was about 3.5 cases per 100,000 individuals, and thus slightly higher than the average rate in Spain (3.1 cases/100,000). The majority of cases were caused by serogroup B. However, in 1995/96 the incidence of meningococcal disease rose sharply from 3.5 to 11.3 cases per 100,000, and 83% of cases were caused by serogroup C [most frequent strain *C:2b:P1.2,5, cluster A4, ST-8*; (BEG 1996)]. Fatal cases occurred in children and adolescents; there was heavy media coverage and considerable social alarm.

The case definition was considered to be *Neisseria meningitidis* when at least one of the following occurred:

- Isolation of *Neisseria meningitidis* in a totally sterile environment.
- Detection of the *Neisseria meningitidis* genome in a sterile environment.
- Detection of *Neisseria meningitidis* in CSF (cerebrospinal fluid)
- Diplococcus gram-negative display in CSF.

Confirmed cases came from microbiology laboratories of hospitals in the region. Some specimens were sent to the National Epidemiology Center for validation. Usually there was agreement between the National Epidemiology Center and the regionally confirmed cases, with only one case about which there was not agreement.

Vaccination campaign phase I in 1996/1997

In response to the situation, the Galician Regional Public Health Authorities assessed different control and contingency plans and decided to conduct a vaccination campaign between December 1996 and January 1997, using a meningococcal group A and C polysaccharide vaccine, the sole vaccine available at that time, that targeted all residents of Galicia aged 18 months to 19 years born after 1977 (Aboal Viñas et al. 1999). This resulted in a high coverage rate of more than 85% of the target population and served as a template that later was followed by the majority of other regions in Spain. As a consequence of this vaccination campaign, the incidence of meningococcal C disease was significantly reduced from 4.2 cases per 100,000 in the 1996/1997 season to 1.2 cases per 100,000 in the 1997/1998 season (the epidemiologic season goes from week 41 of 1 year to week 40 of the following year) and also a reduction in the number of suspected cases not confirmed microbiologically from 187 in 1996 to 148 in 1997. At the same time, serogroup C mortality decreased from 19 deaths in 1996 to 8 in 1997 (0.55 deaths per 100,000 in the 1996/1997 season to 0.22 in the 1997/1998 season). No changes were observed in the incidence of meningococcal B disease (BEG 1998) (Fig. 1).

Vaccination campaign phase II in 2000

In November 2000, once the MenC conjugate vaccine was available, it was included in the routine infant vaccination calendar at 2, 4 and 6 months of age. At the same time, the Galician Regional Public Health Authorities carried out a second phase of the meningococcal C vaccination campaign for children born after 1 January 1993 and vaccination of all children and adolescents up to 19 years of age who had not received any dose of the polysaccharide vaccine in the previous campaign. At the end of 2003, this schedule was shortened to two vaccinations at 2 and 4 months, as approved in the Summary of Product Characteristics of one of the meningococcal conjugate vaccines used. The catch-up vaccination combined with the amended routine infant vaccination calendar resulted in a significant decline in the number of laboratory-confirmed cases of group C meningitis in all age groups targeted for vaccination (Table 1).

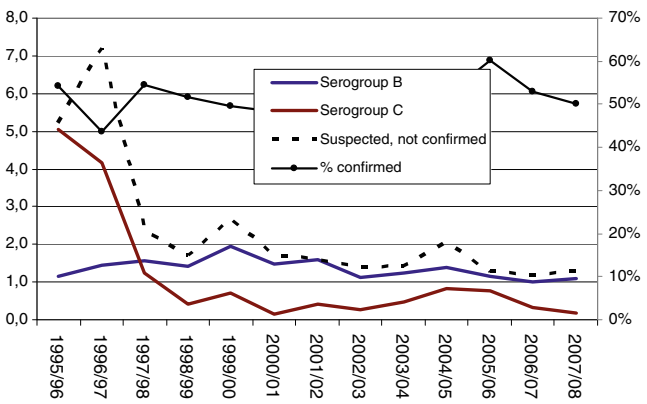

Fig. 1 Incidence (cases per 100,000 inhabitants in Galicia) of meningococcal disease between 1995 and 2008, of serogroups B, C and not confirmed cases. Solid lines are laboratory-confirmed cases; dotted lines denote suspected (unconfirmed) cases that occurred in addition to confirmed cases

Table 1 Laboratory-confirmed cases of serogroup C meningococcal disease in Galicia by age group and year

	Season												
	95/96	96/97	97/98	98/99	99/00	00/01	01/02	02/03	03/04	04/05	05/06	06/07	07/08
Age													
<2	33	37	21	4	5	0	1	0	0	0	0	0	1
2–4	37	19	4	2	3	0	0	0	2	2	2	0	1
5–9	22	13	2	1	7	2	0	1	0	1	1	3	1
10–14	16	5	0	1	1	0	0	2	1	3	0	0	1
15–19	18	16	1	1	0	2	2	2	2	8	3	0	0
20–24	2	3	0	1	1	0	1	0	2	1	3	0	1
>24	9	20	6	1	2	0	7	2	6	8	12	6	0
All	137	113	34	11	19	4	11	7	13	23	21	9	5

Vaccination campaign phase III in 2006

From 2003/2004 a slight and continuous increase in both the incidence and the lethality of meningococcal C disease associated with the spread of the hyperinvasive, hypervirulent new strain [*C:2a:P1.5 (ET-37, ST-11*)] was observed (Cano et al. 2004). This increase affected in particular persons older than 13 years of age, as younger people were already vaccinated. This trend continued in the 2004/2005 season, and there was no reason to assume that it would not occur again in 2005/2006 because of the waning of protection with time and the increased exposure (BEG 2005).

Therefore, in response to the rising incidence of serogroup C disease, another meningococcal C vaccination catch-up campaign was planned for 13–25-year-old subjects who had not received the conjugated vaccine (born between 1 July 1980 and 31 December 1992) with the goal to reduce transmission and establish herd immunity.

The target population of this campaign was determined because the incidence increase was concentrated in people born before 1993, which meant 83% of the cases in the 2003/2004 and 2004/2005 campaigns. From these campaigns, 62% of the cases were people who had received the polysaccharide vaccine in the 1996/1997 vaccination campaign. At the end of the 2004/2005 campaign, adolescents and children between 14 and 23 years of age were the age group with a higher case incidence.

Materials and methods

Objectives

The objective of the catch-up vaccination program was to reduce the morbidity and mortality of meningococcal disease caused by serogroup C.

Design of vaccination program based on mathematical modeling

Different vaccination strategies were analyzed in the preparation phase by the government institution in charge of vaccination programs in Galicia, Dirección Xeral de Saúde Pública (DXSP). Trotter et al. in 2004 had investigated the direct and indirect (herd immunity) effects of a conjugate vaccine program in the UK and Wales [the UK was the first country to introduce meningococcal serogroup C conjugate vaccination in 2000 (Trotter and Edmunds 2002)] and developed a realistic, age-structured, dynamic mathematical model that was fitted to epidemiologic data (Trotter et al. 2005). The effects of a range of vaccine strategies, including hypothetical scenarios, were investigated using an estimated basic reproduction number of 1.36. Of six simulated introductory vaccination strategies, two were judged to be comparable to the situation in Galicia after this new catch-up campaign; one to be "strategy 3," routine vaccination plus a catch-up campaign up to 18 years of age; and another to be "strategy 4," routine vaccination plus a catch-up campaign up to 25 years of age. The DXSP considered that both strategies controlled the disease rapidly because of the catch-up vaccination, which had a great impact on MenC transmission. Long-term results obtained with both strategies were fully satisfactory and the main assumptions of the model appropriate.

However, there were two main differences between the model and the situation in Galicia, which were not considered to be an obstacle for the adoption of the models. First, the Galician population is older than the English and Welsh population, a difference that probably could lead to a lower prevalence of carriers among the total population; however, the difference was considered not to be relevant for the target populations of the program (adolescents). If the contact patterns between people were proportional to

age, a different age structure might result in a different pattern of effective contacts. However, there is evidence indicating that contact patterns are assortative, i.e., the frequency of contacts within a given age group is higher than in other age groups. Assuming an assortative contact pattern, the difference in the age structures between the populations in Galicia and those in England and Wales can be neglected. Second, the carrier prevalence of *Neisseria lactamica* and *Neisseria meningitidis* other than C serogroup could be assumed to be equivalent. This was because the investigation of carriers in Galicia during the vaccination campaign of 1996/97 gave similar results to the one used in the model (Fernandez et al. 1999). Up to 2005 the incidence of meningococcal disease caused by serogroups other than C was stable (Fig. 1). On the contrary, after the two vaccination campaigns there were no carrier prevalence data on meningococcus C in Galicia, although there are indications that allow assuming that the initial conditions were not very different. Initially, 1 year after the first vaccination campaign in 1996/97, the prevalence of adolescent carriers of meningococcus serogroup C was significantly lower compared to pre-campaign levels. Further, 1 year after the campaign the incidence of meningococcal C disease was drastically reduced (Table 1), also in age groups without vaccination, which can be explained by a decline in exposure to *N. meningitides* serogroup C—induced by vaccination or spontaneous.

Notably, with the introduction of conjugated vaccine and its high acceptance in Galicia (as evidenced by high vaccination coverage), the most informative group for the estimate of exposition was lost. In 2004/2005 in Galicia similar rates were observed as in the UK in 1998/1999 (Trotter et al. 2002): 5.8 versus 7.9 cases/100,000 inhabitants (age 15–19 years) and 2.3 versus 1.9 (age 20–24 years). Further, as in the UK at the end of the 1990s, in Galicia the increased case number was associated with strain *ST-11 complex ET-37, C: 2a:P1.5*.

On the basis of these data, the DXSP decided to implement a strategy ("number 4") with routine vaccination plus the vaccination of individuals<26 years, aiming at vaccination coverage as established in the model calculation (Table 2). The higher age range was chosen in order to offset the shortfall in recruitment as during the first vaccination campaign only 50% of the subjects aged 18–19 years had been vaccinated.

The program had to generate two effects, a direct effect through individual immunity and an indirect effect by generation of herd immunity. According to the model, herd immunity could be generated only if the vaccination coverage in the different age groups was achieved. For this reason, minimum vaccination coverage was predefined by different groups of age (Table 2). These coverage rates had to be high enough to stop transmission.

Target population

All individuals born within 1 July 1980 to 31 December 1992 (aged 13–25 years) were included. The only applicable criterion for non-eligibility for this vaccination was the presence of a contraindication for meningococcal C vaccination such as pregnancy or allergy to any of the components of the vaccine. Immunosuppressant subjects could be vaccinated; HIV infection was no contraindication.

The definition of the target group was designated taking into account the epidemiology of the disease in Galicia and the population suffering from the illness during the 2004/05 season and considering that the previous vaccination campaign against meningococcus C had been directed at children born after 1 January 1993. In 2004/05 in Galicia more than 55% of meningococcal disease attributable to serogroup C occurred in the age range of 13–25 years old, but only 10% in younger individuals. The main risk of considering this target is not achieving the intended coverage. Because of the model used, the coverage is a fixed value; therefore, if this coverage is not reached, the results will not be valid. For this reason, different strategies to reach a high number of individuals had to be implemented.

Vaccine

In the campaign conjugate vaccine de-O-acetylated group C meningococcal polysaccharide coupled to tetanus toxoid was used (GCMP-TT; brand name: NeisVac-C, manufacturer: Baxter BioSience, Vienna, Austria) (Pollabauer et al. 2005). Extensive evidence has been accumulated on the immunogenicity, safety and posology of GCMP-TT as well as its epidemiological impact. The pooled protection rate, defined as the proportion of subjects with serum bactericidal antibody (SBA) levels≥1:8, was 99.4% (CI: 98.2–99.9%) in seven clinical trials covering all age groups. After a catch-up vaccination campaign in the UK (where 5–8-year-old children were primarily given GCMP-TT), vaccine effectiveness in the target population (i.e., 2-month-old infants to 18-year-old adolescents) was 95% (CI: was 92–97%) within 1 year and 90% (CI: 83–94%) more than 1 year after vaccination. Furthermore, a routine immunization program using a one-dose GCMP-TT vaccination at the age of 14 months was introduced in 2002 in The Netherlands. In parallel a catch-up campaign targeting all children from 1–18 years was conducted.

In addition to this data, no vaccination failure occurred in people vaccinated with NeisVac-C by the time of making the decision for the vaccine to be used during the campaign.

Another factor that contributes to the high immunogenicity is the choice of the carrier protein that may derive from enhanced T-cell priming by the TT carrier; the TT

Table 2 The 2006 vaccination coverage as planned and achieved by group of age and number of people vaccinated during the campaign

n.a., not applicable

Age group	13–14	15	16	17	18–21	22–25	All
Coverage planned (%)	85	80	70	60	45	45	n.a.
Coverage Achieved (%)	91.0	97.3	97.6	94.7	78.6	74.1	82.2
Number vaccinees (n)	39,617	21,895	23,026	23,256	87,259	90,469	285,522

carrier is very stable, so the vaccine remains stable at high temperatures. This vaccine can be stored for 9 months out the refrigerator, which contributes to the logistics and the cost reduction of a catch-up vaccination campaign.

Logistics of the campaign

This catch-up vaccination campaign lasted 21 weeks from 6 February 2006 to 30 June 2006. During the entire period, the catch-up campaign was performed in parallel with the primary immunization of infants at 2 and 4 months of age.

Vaccines were automatically supplied to public primary care centers in adequate quantities to cover the first needs of the campaign, and further supplies were delivered according to the needs communicated to the DXSP. In private vaccination points, vaccines were supplied after a previous request for doses given to the DXSP. A mailing was sent to all general doctors, pediatricians, nurseries and primary care pharmacists explaining the justification, vaccine to use, schedule, precautions and possible adverse events, target population, dates and logistics of the campaign. Such information was also distributed to public and private vaccination centers, including hand-out materials to facilitate the access to the vaccination (letter of presentation of the campaign, instructions, numeric registers of the administered vaccine, brochures including information about the campaign, posters, vaccination cards for adults and adolescents, pre-paid postage envelopes). All materials were prepared by the DXSP staff, and material distribution was completed by the end of January.

The aim was to inform as many possible vaccination points as possible as well as individuals in the target population about the campaign and to offer the vaccination. Focu was placed on certain risk groups who were specifically targeted: the population aged 13–25 years including students, employees of companies and underage individuals. To facilitate the access to vaccination for students, an agreement between the Education and Health Departments was signed with the intention to administer the vaccine in the education centers (schools, colleges, professional colleges and universities) using special vaccination equipment. Furthermore, exclusive information materials for professors, students and their parents were distributed. Children and adolescents under 18 years were only vaccinated if informed consent of parents was available (but received information material in any case). Social care centers for children under the age of 18 years (*Centros de menores*) were also a special objective of this campaign, as the majority of the people who live there are a risk population. Special vaccination staff was sent to these centers and followed the same instructions as for colleges.

Disabled people aged 13 to 25 years were considered a target group in which a special strategy could increase vaccination coverage. For that reason, before the vaccination date, information materials were distributed to these centers where vaccination was administered by medical personnel of the center or by special vaccination staff.

Companies with adequate medical or paramedical staff could perform vaccination themselves for the target population, and vaccines were supplied directly to the companies together with the information and documentation materials.

Apart from these specific measures intended to increase coverage, a numeric registration system of the administered vaccines was set up to guarantee the records of coverage achieved and to have robust records to evaluate catch-up vaccination measures if needed. In order to obtain consistency of this vaccination in the future, vaccinations were recorded (together with the age group of the vaccinee) on a vaccination card and in the clinical charts of the individual. This documentation was to be sent to the DXSP.

Results

Coverage

In total, the following centers participated in the campaign: 733 health care centers, 710 schools/colleges/professional colleges, 3 universities, 72 social care centers, 61 centers for disabled and 32 companies. The response rate from these centers was 100%.

The total number of individuals vaccinated during the campaign was 285,522. Table 2 shows the number of individuals vaccinated during the campaign by age group. Global vaccination coverage achieved in the campaign was 82.21%. Rates in the individual age groups are shown in the table.

Figure 2 displays the cumulative coverage during the vaccination weeks by age group. Already by week 5, the coverage had reached 50% in the oldest age group and up to 80% in the younger age groups. There were no

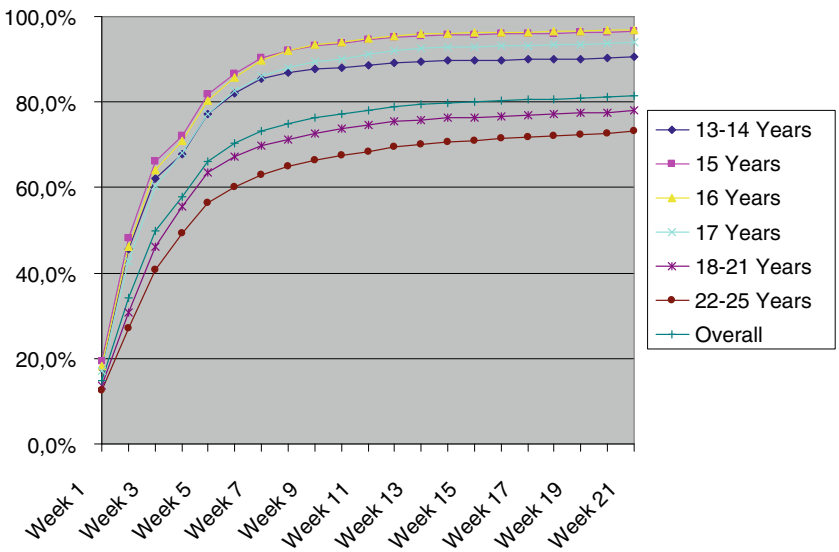

Fig. 2 Vaccination coverage of the 2006 campaign in the various age groups over time. Description provided in the text

significant differences in coverage among the four provinces in Galicia.

Adverse events

Notification of adverse events was performed through the surveillance system of adverse events after vaccination (RASV) of the DXSP. A total of 17 adverse notification events, from 17 different individuals, were reported, which all were mild. Most adverse events occurred immediately after vaccination and manifested as local reactions such as redness, pain, edema, mild fever, headache and arthralgia. Dizziness related to orthostatic hypotension was observed in some school and colleges when the vaccine was administered in the presence of other students.

Preventive effect

Incidence of meningococcal disease serogroup C of 0.84 cases per 100,000 in 2004–2005 was reduced to a rate of 0.18 per 100,000 in 2007–2008. None of the meningococcal disease cases occurred in the population vaccinated during the campaign. Figure 1 and Table 1 show the reduction of incidence in the period after the vaccination campaign. In parallel, mortality was also reduced from eight cases in 2005–2006 to one case in 2007–2008.

Discussion

Galicia has a well-established epidemiological surveillance system that provides, among others, reliable incidence rates of meningococcal C disease. Based on these observations, a series of successful vaccination campaigns was launched in 1996.

The DXSP considered the incidence increase of meningococcal C cases and related mortality in 2003–2004 to be likely due to the waning of protection over time and also to the increase in exposure. Analyses by age group provided evidence that the population at particular risk was those aged 13–25 years (individuals born before 1993).

The latest catch-up vaccination campaign was launched with the expectation that the high-risk population would obtain a double benefit by a direct effect in the vaccinated population and by an indirect effect creating herd immunity in the non-vaccinated population.

As reported by Trotter et al., catch-up vaccination targeting teenagers generated substantial herd immunity and was important in controlling disease rapidly (Trotter et al. 2005). Our outcomes confirm that models based on experience in comparable epidemiological settings can be used to plan vaccination campaigns. The critical success factor according to the model was to achieve vaccination coverage across all age groups, which could only be achieved by the unanimous support of the many parties involved in this campaign. The overall coverage (and the rates achieved in each age group) exceeds by far the coverage that according to the model of Trotter et al. is necessary for a marked decline of meningococcal disease by both direct and indirect effects. (Trotter et al. 2005) It is worth pointing out that the population aged 18–25 years is recognized to be a group in which it is rather difficult to achieve high coverage rates.

In November 2006, the routine vaccination schedule was modified to include a booster dose in the second year of age. This schedule was implemented as a consequence of new findings on vaccine effectiveness in routine immunization programs in infants. The data, published in late 2004, showed that vaccine effectiveness within 1 year of the completion of a primary vaccination course was high

(93%); however, the immunity waned 1 year after completion of the primary series (Trotter et al. 2004). A booster dose in the second year of age was recommended in order to generate long-term protection, and the schedule was modified to follow this recommendation to 2, 4 and 18 months of age.

Results obtained in the campaign were highly satisfactory. Targeted vaccination coverage was clearly overachieved, and disease incidence and mortality was reduced substantially. A decisive factor for these results was the cooperation of all parties involved in the campaign: health authorities, health care personnel, vaccination centers, hospitals, responsible persons in the education system, universities, colleges, vaccination centers and most importantly the general public. The vaccination campaign was very well accepted by the public, which is reflected both in the high coverage rates and in the development of the campaign.

Conclusion

In Galicia, the excellent results obtained in the catch-up vaccination campaign with particular focus on groups difficult to reach for preventive measures together with the maintenance of routine immunization in infants has led to a substantial reduction in the incidence of meningococcal disease. This is attributable to the direct effect of the vaccination on individual immunity but also to an indirect effect, herd immunity, as a vaccination coverage necessary to stop transmission was achieved.

Continuous epidemiological surveillance of meningococcal disease presently confirms the expected benefits. The Galician Health Authorities will continuously survey the meningococcal C disease epidemiology to assess the effectiveness of this vaccination campaign in the long term.

Another aspect to point out is the importance of implementing specific actions for population groups whose vaccine uptake is expected to be low. It was demonstrated in our program that distinctively designed activities for such groups can be successful and result in high vaccination coverage.

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