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Changes in meningococcal C epidemiology and vaccine effectiveness after vaccine introduction and schedule modification

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ABSTRACT

Purpose: Meningococcal C conjugate vaccine was included in December 2000 in the Spanish childhood vaccination at 2, 4 and 6 months of age. In 2006, routine vaccination was modified to two doses at 2 and 4–6 months and a booster dose during the second year of age. Additionally, successive catch-up campaigns were launched to extend protection to older groups. This study provides long-term information about the vaccine effectiveness (VE) and the impact of vaccination in meningococcal C disease epidemiology in Spain.

Methods: We assessed surveillance data from season 1996/97 to season 2012/13 to describe changes in incidence and lethality of the disease. The vaccine-effectiveness study covered all cases notified from January 1st of 2001 onwards and evaluated vaccine effectiveness in both routines and in catch-up campaigns. To investigate the decline in protection over time, we compared the vaccine effectiveness within 1 year and more than one year since vaccination.

Results: The incidence of meningococcal serogroup C disease decreased first in those age-groups targeted for vaccination. But after 2006/07 season the decrease in incidence was generalised. Vaccine effectiveness was high in all vaccination programmes, although 2, 4–6 months (+ booster dose) routine showed higher overall vaccine effectiveness than 2, 4 and 6 months routine (99.3% vs. 90.2%). VE >1 year since vaccination was lower in 2, 4 and 6 months compared to 2 and 4–6 months (+ booster) routine (81.4% vs. 89.1%). For catch-up campaigns, VE increased and loss of VE decreased with the age of administration. Overall VE was 94.83 (CI95%: 93.37, 95.97), 98.82 (CI95%: 97.96, 99.31) and 90.89 (CI95%: 87.79, 93.21) for ≤1 and >1 year since vaccination, respectively.

Conclusions: The meningococcal C conjugate vaccination programme has been extremely successful in controlling the disease and continues to be evaluated and adapted to the changes in the epidemiology of the disease to ensure long-term vaccine protection.

1. Introduction

Meningococcal C conjugate vaccine was included in the Spanish vaccination schedule in December of 2000 at 2, 4 and 6 months of age. At the same time a catch-up campaign was undertaken in most Spanish regions targeted for children less than 6 years of age. Since 2000, additional successive catch-up campaigns were launched to extend vaccination up to adolescence (< 20 years) with differences in starting date, duration, targeted age-groups and coverage between regions.

In 2005, recommended routine vaccination schedule was modified based on the conclusions of the VE studies developed in Spain [1] and UK [2] that showed loss of VE after the elapse of more than 1 year since vaccination. The new schedule started in 2006 and it is currently in use with two priming doses of vaccine at 2 and 4–6 months and a booster during the second year of age. Vaccine coverage has been high since the introduction of the vaccine in the childhood vaccination calendar remaining over 95% since 2002, while booster coverage, slightly lower than priming coverage, remained over 94% since 2008. On the other hand, coverage in catch-up campaigns showed high heterogeneity among regions and targeted age-groups varying from an average coverage of 95% (range: 86.1%–98.9%) for two doses scheduled for infants between

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6–12 months; of 85% (range: 80%–97.5%) for one dose scheduled for children between >12 months to <6 years of age; and of 77% (range: 45.8%–96.1%) for one dose scheduled for children/adolescents ≥6 years.

Even though booster doses after the first year of age have proved to sustain population immunity against meningococcal serogroup C (MenC) disease and are recommended to achieve the control of the disease [3–5], vaccine failure related to loss of vaccine protection after 1 year of vaccination continued to be one of the main unresolved issues even after booster administration [6–8]. Seroprevalence studies in infants and adolescents showed a decline in effectiveness in infants parallel to a decline in serum bactericidal antibody (SBA) titres while adolescent effectiveness and SBA titres remained more stable in time [9–13]. Therefore, different studies support the idea that multiple doses in early infancy provide little if any additional benefit compared to a reduced primary vaccination schedule [14,15]. Furthermore, a recent study has concluded that a single priming dose of NeisVac-C® at 4 or 6 months of age followed by a booster dose at 12–13 months of age showed high seroprotection rates and SBA titres and can be an adequate alternative to the two-dose priming vaccination schedule [16]. However, it is known that MenC **conjugated to tetanus** toxoid produce higher levels of SBA [6,17] and those results could not be extrapolated to all MenC vaccine types. Additionally, some countries [9,18,19] are extending the recommendation of routine vaccination inclusion in adolescents to enhance long-term protection.

The aim of this study was both to assess the VE of the two different routine vaccination schedules applied in Spain and include the successive catch-up campaigns in children/adolescents up to 19 years of age to obtain a global estimation of the VE in the country. Loss of protection after 1 year of vaccination and VE related to age of administration of vaccine, as well as risk of MenC during the first year of life were assessed. This information may be useful in the current discussion about the need of a new vaccination schedule in Spain, and can be used, as well, to compare future vaccination scenarios.

2. Methods

Data on cases of meningococcal disease reported in Spain were obtained from the National Notifiable Disease Surveillance System. Reporting of the weekly number of invasive meningococcal disease (IMD) has been mandatory since 1964, but in 1996 notification was enhanced to obtain further information including case-based epidemiological and microbiological data.

Epidemiological seasons for IMD were defined as yearly periods between week 41 of one year and week 40 of the following year. Cases of confirmed MenC from epidemiological season 1996/97 to 2012/13 were included in the analysis. Three periods of interest were defined: *pre-vaccine period* (season 1997/98 to season 1999/00), *routine-1 vaccination period* (season 2000/01 to 2005/06) and *routine-2 vaccination period* (season 2006/07 to season 2012/13). Increased incidence due to hyper-virulent strain of serogroup C in season 1996/97 [20,21] was described but excluded from *pre-vaccine period* to avoid overestimating the impact of vaccine.

Age-specific incidence and case fatality rates were calculated for the three periods. Incidence risk ratios (IRR) were calculated for all and by age-group taking the *pre-vaccine period* as reference to have an idea of possible herd immunity effect of the vaccine in non-vaccine targeted age-groups. Period midpoint population data for the rates were obtained from the National Institute of Statistics.

The VE study covered the period from January 1st of 2001 to December 1st of 2013. MenC confirmed cases were included in the analysis if they were target for any of the vaccination campaigns developed (routine or catch-up). Vaccination status was notified by means of four variables: vaccinated (yes/no), vaccine number of doses, type of vaccine and date of last dose of vaccine. Vaccinated cases information was completed with data from a relational vaccine failure database which collects more information about suspected and confirmed cases of meningococcal vaccine failure provided by the Spanish Regions, including dates and trade name of each vaccine dose administered not included in the surveillance database to confirm the routine assignment and correct scheduled vaccination. A confirmed vaccine failure was defined as a laboratory-confirmed case of MenC disease with onset more than 14 days after the last dose of vaccine scheduled for each age-group. Suspected vaccine failures were excluded from the VE analysis.

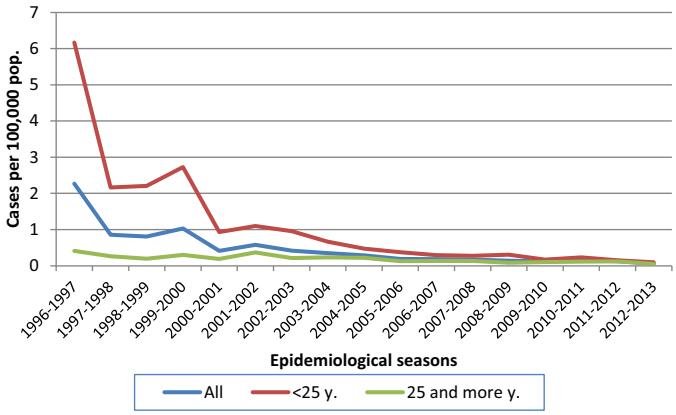

Fig. 1. Trends of MenC disease incidence by epidemiological season for all laboratory confirmed cases, for those under 24 years and those aged 24 years and older in Spain.

Vaccine coverage information was provided by the Ministry of Health, Social Services and Equality [22]. Information of coverage was obtained by region for both vaccine routines and for each catch-up campaign. Two Spanish regions, Ceuta and Melilla, were excluded from the analysis due to low number of cases and difficulties in estimating vaccine coverage.

VE based in the reduction of attack rate in those vaccinated compared to unvaccinated population in the same cohort, was estimated using the screening method [23]. Data were grouped by region, year and vaccination programme (routine/catch-up campaign). Cases (Ni), vaccinated cases (Vi) and coverage (PPVi) were calculated for each category. A logistic regression model was applied taken as dependent variable the percentage of cases vaccinated (as binomial data 1 values for cases vaccinated, 0 values for non-vaccinated cases) and the PPVi logit as the offset variable. To investigate the decline in protection over time, we compared VE within 1 year of scheduled vaccination with more than one year after vaccination VE.

3. Results

3.1. Trends in MenC disease incidence

From 1996/97 till the end of 2012/13 season a total number of 3,331 cases of laboratory confirmed MenC disease were reported. Trends of incidence by epidemiological season are shown in Fig. 1 for all, < 25 years cases and ≥ 25 years. In 1996/97 season MenC in Spain showed still higher incidence due to hyper-virulent strain of serogroup C (2.27 cases per 100,000 pop.) similar to other European countries during the mid-1990s [24,25]. Between 1997/98 and 1999/00 seasons the MenC incidence rates remained around 0.9 cases per 100,000 pop. After the introduction of the MenC conjugate vaccine in 2000/01 season, the rates decreased notably, mainly due to a decrease in incidence in the < 25 years targeted