Clinical and Epidemiological Differences Among Meningococcal C Conjugate Vaccine Failures and Non-Vaccinated Cases

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Abstract

Introduction
Although meningococcal C conjugate vaccines achieve high vaccine effectiveness, vaccine failures still occurs associated to a decline of bactericidal titres in time. Previous studies have found similar mortality between cases with meningococcal disease with prior vaccination compared to those non-vaccinated. However, nothing is known about if prior vaccination could protect against other outcomes or if the prognosis of the disease depends only on the severity of the clinical presentations.

Methods
We included 362 serogroup C laboratory confirmed cases (129 confirmed vaccine failures and 233 non-vaccinated cases) from the previous nationwide vaccine effectiveness study developed in Spain with data on 13 surveillance years after the conjugate vaccine introduction. Clinical diagnoses and procedures performed during the hospitalisation were obtained from the National Registry of Hospitalisations to compare epidemiological and clinical characteristics between cases presenting vaccine failure and non-vaccinated cases. Relationship among diagnoses and death event was also evaluated.

Results
Clinical information was found in 333 (92%) cases: 53.8% were men; 15.3% presented risk factors for the disease; 17.4% died (75.9% of them in ≤ 5 days); 28.8% developed meningitis, 51.7% septicemia and 16.8% both. Average age was lower in vaccine failure (mean: 6.2 years) vs. non-vaccinated cases (mean: 11.7 years). Average time to death was 3.4 vs. 5.6 days for vaccine failures vs. non-vaccinated cases and 5.3 vs. 2.8 days for meningitis vs. septicemia. Vaccine failures presented more septicemia (63.2% vs. 45.4%) but died less by it (12.2% vs. 23.5%) compared to non-vaccinated cases. Septicemia presented higher risk of heart disturbances, blood disorders, renal failure and shock/coma compared to meningitis (p < 0.05). Risk factors for the disease (aOR: 5.36; p = 0.046), as well as charlson comorbidity index (aOR: 8.24; p = 0.015) were independently associated to death event in the vaccine failure cases, in which respiratory failure was the main risk factor for death (aOR: 46.67; p < 0.001).

Conclusion
Vaccine failures were younger, presented less meningitis (with slower progression) and more septicemia but lower fatality-rates, and died less after 7 days than non-vaccinated cases. Severity of the disease seems to be related to clinical presentation. In vaccine failure cases risk factors for death were respiratory failure, risk factors for infection and charlson comorbidity index showing that this group might be more affected by respiratory concomitant diseases.

Keywords: Conjugate vaccine; Meningococcal disease; Serogroup C; Vaccine failures

Introduction
Meningococcal C conjugate vaccine effectiveness has been widely evaluated in different epidemiological studies [1-6]. In those studies vaccine effectiveness obtained was high and increased with the age of vaccination. Loss of vaccine effectiveness and the apparition of vaccine failures have been associated to an inadequate maintenance of circulating antibodies [7-9]. The effect of immaturity of the immune system in infants [10,11] to maintain the antibody levels in time has been widely studied in seroprevalence studies [9,12-17]. In line with this, in our previous nationwide study evaluating vaccine effectiveness after 13 years since the conjugate vaccine introduction, we found 63.9% of vaccine failures in those vaccinated before the year of age (2-3 doses), 32.08% in those vaccinated between 1 and 11 years (1 dose) and 3.88% in those vaccinated between 12-19 years (1 dose) [18].

Additionally, we should take into consideration that the meningococcus is a commensal of the human nasopharynx. The role of individual susceptibility and the presence of risk factors for the disease have been also widely studied. The presence of some immunodeficiencies [7,11,19-21], special determinants in the host [22], tobacco consumption [23,24] and coinfections with another respiratory diseases [25-28], among others factors, have been associated to the meningococcal disease.
Independently of those factors and although meningococcal conjugate vaccine primes for memory, the absence of circulating antibodies leave the individuals unprotected till a sufficient secondary immune response is achieved. Time to elicit an antibody response takes in reach its peak around 4 weeks in a primary response and around 6-7 days in a secondary response [29]. However, meningococcal disease presents a rapid progression, in most cases the disease progress before 7 days, and Auckland et al., found similar mortality by the disease in those vaccinated compared to those not vaccinated [30]. Similarly, in our previous study, using the data included in this one, we found that case-fatality rate was similar in vaccine failures and in non-vaccinated cases when adjusted by age [18].

The aim of this study was to describe and compare the epidemiological and clinical characteristics in cases presenting vaccine failure and in non-vaccinated cases. We evaluated if being previously vaccinated can be a protective factor for the different outcomes (for example: reduction in time of stay, less severe clinical patterns, etc.). Or if the patients that fail in maintaining the protection over time presented no differences with those not vaccinated, and differences are mainly due to clinical presentations severity. As secondary objective we assessed which diagnoses are related to death event in case of serogroup C meningococcal disease (for all, for vaccine failures and non-vaccinated cases, and by the main clinical presentations).

Methods

National surveillance system vaccine failures cases and non-vaccinated cases selection criteria

Active, prospective and population-based surveillance of Invasive Meningococcal Disease (IMD) is conducted in Spain since 1996 including case-based epidemiological information of the patients and microbiological information (including PorA variable regions information). Meningococcal C vaccine was included in the Spanish childhood vaccination schedule in December of 2000. Additionally, since 2000 successive catch-up campaigns were launched to extend vaccination up to adolescence (< 20 years).

Recently, we have published the results of a nationwide vaccine effectiveness study including all cases targeted for vaccination in Spain since the introduction of meningococcal C conjugate vaccine from January 1st of 2001 till the end of 2013 [4,18]. Methodology for the selection of cases targeted for vaccination from those notified to the National Surveillance System has been described in our previous studies [4,18]. The same cases included in the vaccine effectiveness studies were included in this study. In total, 362 cases targeted for vaccination between 0-19 years: 129 confirmed vaccine failures (laboratory confirmed MenC case with onset more than 14 days after the last dose of vaccine scheduled for each age-group) and 233 targeted for vaccination, but non-vaccinated cases (to be comparable to confirmed vaccine failures in the opportunity of being vaccinated).

National registry of hospitalisation database

Hospitalisations associated with meningococcal infection were obtained from the National Registry of Hospitalisations of the Ministry of Health, Social Services and Equality. This registry uses the ninth revision of the international classification of diseases, clinical modification (ICD-9-CM) to code the diagnoses and includes an estimated 98% of the public hospitals. Urgent hospitalisation in the public Health Care System (as is the case of meningococcal disease due to its severity) is cover for all population. The National Registry of Hospitalisations includes information of sex, age, date of birth, date of admission and date of discharge (length of hospitalisation), geographical location of cases/hospitals (autonomous community, province and municipal code) and discharge type. All diagnoses (main diagnose and up to thirteen secondary diagnoses) and procedures (up to 20 procedures) performed during the hospitalisation were recorded. All hospital discharges with 036 (meningococcal disease) ICD-9 codes in any listed position were included in our study between 2000 and 2013: 036.0-meningococcal meningitis; 036.1-meningococcal encephalitis; 036.2-meningococccemia; 036.3-Waterhouse-Friderichsen syndrome; 036.4-meningococcal carditis, unspecified, meningococcal pericarditis, meningococcal endocarditis, meningococcal myocarditis; 036.8-other meningococcal infections (optic neuritis and meningococcal arthropathy); and 036.9-meningococcal infection, unspecified. Data cleaning was performed before the analysis. Hospitalisation cases with the same birth date and sex were checked in search of readmissions and hospital transfers (in the same hospital, but different unit, or to another hospital) of the same patient.

From 2000 to 2013 a total 10,194 hospitalisations were recorded in the National Registry of Hospitalisations (579 readmissions/hospital transfers), in which cases of serogroup C notified to the National Surveillance System and included in this study were search.

Matching

Cases notified to the National Surveillance System were searched in the National Registry of Hospitalisations by means of the variables shown in figure 1.

As additional exclusion criteria, cases of the National Surveillance System included that were not found or with no match in some of the variables in the National Hospitalisation Registry were excluded from the analysis.

Statistical analysis

We described and compared clinical and epidemiological characteristics among cases with vaccine failure and cases with no prior vaccination. Clinical information was obtained from the diagnoses and procedures performed and recorded during the
hospitalisation. As we did not have cases identification or access to detailed clinical records, we cannot define which events persisted after the hospitalisation as sequels. Comparison of means was done by using T test or Wilcoxon test. Comparison of proportions was done by using chi test or logistic regression if the odds ratio was adjusted by other variables. We defined as a risk factor for the disease: the presence of a concomitant infectious disease, neoplasms, immunodeficiencies, drug/alcohol/tobacco abuse, and congenital abnormalities. Univariable analysis and forward stepwise logistic multivariable analysis was performed to assess the relationship between diagnoses and death event. Charlson comorbidity index was used to evaluate influence of comorbidity in clinical outcomes [31]: the Deyo adaptation for ICD-9 data was used [32].

Differences were considered statistically significant if p-value was < 0.05. All analyses have been performed using Stata v.13.

Results

From the 362 cases notified to the National Surveillance System 333 (92%) were found in the National Registry of Hospitalisation. Cases were no match was found were distributed uniformly among vaccine failure (N = 12; 9.3%) and non-vaccinated cases (N = 17; 7.3%). For those vaccinated, average age of vaccination was 1.3 years (Standard Deviation-SD: 3.05; range: 0-17 years) and average time since vaccination was 3.9 years (SD: 2.66; range: 0-12 years).

In table 1, we describe general characteristics of the cases included in the study. From 333 cases included, 179 (53.8%) were men and 154 (46.2%) women. Average age was 9.7 years (SD: 7.90) for all cases. Average age was lower in vaccine failures (mean: 6.2 years; SD: 4.21) than in non-vaccinated cases (mean: 11.7 years; SD: 8.73; p < 0.001).

Meningitis alone appears in 28.8% of all cases included and 16.8% together with meningitis. Meningitis alone appears in 28.8% of all cases included and 16.8% together with meningitis.

In table 1, we describe general characteristics of all, vaccine failure and non-vaccinated meningococcal C disease cases.

| Categorical variables | All (N = 333) | Vaccine failure cases (N = 117) | Non-vaccinated cases (N = 216) | p-value |
|-----------------------|--------------|-------------------------------|-------------------------------|---------|
| Sex                   |              |                               |                               |         |
| Men                   | 179          | 63                            | 116                           | 53.8\%  | 53.8\%  | 53.7\%  | 0.98    |
| Women                 | 154          | 54                            | 100                           | 46.2\%  | 46.2\%  | 46.3\%  |
| Deaths                | 58           | 16                            | 42                            | 17.4\%  | 13.7\%  | 19.4\%  | 0.185   |
| Clinical presentation |              |                               |                               |         |
| Meningitis            | 96           | 25                            | 71                            | 28.8\%  | 21.4\%  | 32.9\%  | 0.027   |
| Septicemia            | 172          | 74                            | 98                            | 51.7\%  | 63.2\%  | 45.4\%  | 0.002   |
| Both (Meningitis+Septicemia) | 54 | 16 | 38 | 16.8\%  | 13.7\%  | 17.6\%  | 0.355   |
| Encephalitis          | 2            | 0                             | 2                             | 0.6\%   | 1.7\%   | 0\%     | 0.054   |
| W-F syndrome          | 7            | 1                             | 6                             | 2.1\%   | 0.8\%   | 2.8\%   | 0.243   |
| Carditis              | 1            | 0                             | 1                             | 0.3\%   | 0\%     | 0.5\%   | 0.461   |
| Arthrophy             | 1            | 0                             | 1                             | 0.3\%   | 0\%     | 0.5\%   | 0.461   |
| Others                | 8            | 2                             | 6                             | 2.4\%   | 1.7\%   | 2.8\%   | 0.543   |
| Quantitative variables|              |                               |                               |         |
| Age                   | 9.7 (7.90)   | 6.2 (4.21)                    | 11.7 (8.73)                   | 0.001   |
| Days of stay          | 12.1 (14.57) | 11.7 (14.43)                  | 12.3 (14.68)                  | 0.721   |
| Days until death      | 5 (9.98)     | 3.4 (4.88)                    | 5.6 (11.32)                   | 0.634   |
| Charlson Comorbidity Index | 0.06 (0.25) | 0.05 (0.26) | 0.06 (0.25) | 0.638 |

Table 1: General characteristics of all, vaccine failure and non-vaccinated meningococcal C disease cases.
Average time of hospital stay was similar in vaccine failures vs. non-vaccinated cases (p = 0.638), ranging from 0-2 in vaccine failures and from 0-1 in non-vaccinated cases.

In table 2, we show the most relevant diagnoses and procedures found in the patients included in the study. In total there were 51 (15.3%) cases that between the diagnoses performed during the hospitalisation presented at least one described as risk factor for the disease: 17 (14.5%) within the vaccine failures and 34 (15.7%) within the non-vaccinated cases. From them, 9.9% (N = 33) of the cases presented a concomitant infectious disease, 4.2% (N = 14) drug/alcohol/tobacco abuse, 1.2% (N = 4) immunodeficiencies, 1.2% (N = 4) congenital abnormalities, and 0.6% (N = 2) neoplasms. From 14 cases with drug/alcohol/tobacco abuse 10 (71.43%) of them smoke tobacco: alone (8) or in combination with alcohol or other drugs (2). The other 4 (28.57%) cases with drug/alcohol/tobacco abuse presented abuse of cocaine, cannabis or alcohol.

Most frequent diagnose during the hospitalisation was blood disorder (N=106; 31.8%), followed by seizures/collapse/shock/coma (N=93; 27.9%) and respiratory disorders (N=55; 16.5%). Comparing between vaccine failures and non-vaccinated cases, drug/alcohol/tobacco abuse was higher in non-vaccinated cases (p = 0.025), but it is important to mention that non-vaccinated cases were older than vaccine failures. Apart from the increase in drug/alcohol/tobacco abuse was higher in non-vaccinated cases (p = 0.036). However, after adjusting by age, age was the only

### Table 2: Distribution of diagnoses and procedures registered during the hospitalisation for all cases, by vaccination status and by clinical presentation.

| Diagnoses described as risk factors for the disease* | Vaccine failures (N=117) | Non-vaccinated cases (N=216) | Meningitis (N=96) | Septicemia (N=172) | Both (N=54) |
|------------------------------------------------------|--------------------------|-------------------------------|-------------------|-------------------|-------------|
| N %                                                  | N %                      | N %                           | N %               | N %               | N %         |
| **Neurologic ocular disorders**                      | 3 0.9                    | 0 0                           | 1 1.0             | 2 1.2             | 0 0          |
| **Sense organs disorders**                           | 11 3.3                   | 2 0.9                         | 5 5.2             | 4 2.3             | 3 3.7       |
| **Respiratory disorders**                            | 55 16.5                  | 17 8.4                        | 38 17.6           | 11 11.5           | 35 20.3     |
| **Digestive disorders**                              | 34 15.7                  | 17 7.9                        | 17 7.9            | 3 3.1             | 12 7.7      |
| **Vascular system disorders**                        | 30 12.9                  | 9 2.1                         | 18 8.3            | 4 4.2             | 16 9.3      |
| **Blood disorders**                                  | 106 31.8                 | 38 32.5                       | 68 31.5           | 12 12.5           | 64 37.2     |
| **Seizures/Collapse/Coma**                           | 93 27.9                  | 36 30.8                       | 57 26.4           | 9 9.4             | 58 33.7     |
| **Other**                                            | 89 26.7                  | 34 29.1                       | 55 25.5           | 7 7.3             | 56 32.6     |
| **Skin disorders**                                   | 26 7.8                   | 11 9.4                        | 15 6.9            | 4 4.2             | 13 7.6      |
| **Joint disorders**                                  | 31 9.3                   | 9 3.2                         | 22 10.2           | 5 5.2             | 21 12.2     |
| **Amputation**                                       | 2 0.6                    | 1 0.9                         | 1 0.5             | 1 1.2             | 0 0         |
| **Respiratory failure**                              | 21 6.3                   | 4 3.4                         | 17 7.9            | 3 3.1             | 12 7.7      |
| **Non-neurologic ocular disorders**                  | 5 1.5                    | 1 0.9                         | 4 1.9             | 1 1.2             | 0 0         |
| **Heart disturbances**                               | 28 8.4                   | 9 7.7                         | 19 8.8            | 1 1               | 16 9.3      |
| **Heart failure**                                    | 11 3.3                   | 4 3.4                         | 7 3.2             | 0 0               | 7 4.1       |
| **Neurologic**                                       | 4 1.2                    | 2 1.7                         | 3 1.4             | 2 2.1             | 2 1.2       |
| **Drug/alcohol/tobacco abuse**                       | 14 4.2                   | 1 0.9                         | 13 6              | 5 5.2             | 7 4.1       |
| **Neoplasms**                                        | 2 0.6                    | 1 0.9                         | 1 0.5             | 1 1.2             | 0 0         |
| **Immunodeficiencies**                               | 4 1.2                    | 1 0.9                         | 3 1.4             | 1 1               | 2 1.2       |
| **Congenital abnormalities**                         | 4 1.2                    | 2 1.7                         | 2 0.9             | 0 0               | 2 1.2       |
| **Drug/alcohol/tobacco abuse**                       | 14 4.2                   | 1 0.9                         | 13 6              | 5 5.2             | 7 4.1       |
| **Neoplasms**                                        | 2 0.6                    | 1 0.9                         | 1 0.5             | 1 1.2             | 0 0         |
| **Immunodeficiencies**                               | 4 1.2                    | 1 0.9                         | 3 1.4             | 1 1               | 2 1.2       |
| **Congenital abnormalities**                         | 4 1.2                    | 2 1.7                         | 2 0.9             | 0 0               | 2 1.2       |
| **Drug/alcohol/tobacco abuse**                       | 14 4.2                   | 1 0.9                         | 13 6              | 5 5.2             | 7 4.1       |
| **Neoplasms**                                        | 2 0.6                    | 1 0.9                         | 1 0.5             | 1 1.2             | 0 0         |
| **Immunodeficiencies**                               | 4 1.2                    | 1 0.9                         | 3 1.4             | 1 1               | 2 1.2       |
| **Congenital abnormalities**                         | 4 1.2                    | 2 1.7                         | 2 0.9             | 0 0               | 2 1.2       |

- Risk factors for the disease: concomitant infectious disease, neoplasms, immunodeficiencies, drug/alcohol abuse, and congenital abnormalities.
- Neurologic disorders excluding sense organs neurologic disorders.

Average of diagnoses and procedures registered during the hospitalisation for all cases, by vaccination status and by clinical presentation.
significant parameter that explained the differences among groups (p < 0.001).

Comparing clinical presentations (meningitis vs. septicemia) septicemia cases had higher adjusted by age (years) risk of presenting heart disturbances (aOR: 11.19; CI95%: 1.44 to 87.08; p = 0.021), blood disorders (aOR: 4.61; CI95%: 2.30 to 9.27; p < 0.001), renal disorders (aOR: 5.28; CI95%: 1.71 to 16.26; p = 0.004) or renal failure (aOR: 18.41; CI95%: 2.39 to 142.09; p = 0.005) in those that were not related to death event in any of the groups (overall, by vaccine failures cases, non-vaccinated cases, meningitis, septicemia and both). Sensitivity analysis (Table 3) showed results similar to those obtained in the main analysis, with similar adjusted odds ratios and significance levels. These results suggest that the differences observed in clinical presentations were not related to death outcome in any of the groups (overall, by vaccination status or by clinical presentation).

Risk of death was higher in women (OR: 1.83; p = 0.039), in > 13 years (OR: 2.52; p = 0.002) and it was especially high in those that suffered heart failure (OR: 14.51; p < 0.001), seizures/collapse/shock/coma (OR: 9.31; p < 0.001), abnormal platelet count/leucocitopenia/neutropenia/spleen disorders (OR: 8.54; p < 0.001) or renal failure (OR: 7.89; p < 0.001). Inside the group of those with abnormal platelet count/leucocitopenia/neutropenia/spleen disorders: highest risk of death outcome was found in those with leucocitopenia/neutropenia (OR: 20.30; CI95%: 2.23 to 185.14; p = 0.008) compared to abnormal platelet count (OR: 8.96; CI95%: 3.31 to 24.28; p = 0.001) and spleen disorders (OR: 5.78; CI95%: 0.30 to 228.25; p = 0.005) (Table 3).

Heart failure seemed to be more involved in death outcome in non-vaccinated cases (OR: 28.83; p = 0.002) than in vaccine failures (OR: 7.07; p = 0.060) which seemed to be more affected by respiratory failure (OR: 22.5; p < 0.001).

Multivariable analysis was shown in table 4. Heart failure was the main risk factor for death in all (aOR: 9.43; p = 0.005), non-vaccinated cases (aOR: 17.30; p=0.024) and septicemia cases (aOR: 10.95; p = 0.011). Respiratory failure was the main risk factor for death (aOR: 46.67; p < 0.001) in vaccine failures and seizures/collapse/shock/coma was the main risk factor in those with meningitis alone (aOR: 9.90; p = 0.012) or in combination with sepsis (aOR: 17.05; p = 0.001). Risk factors for the disease (aOR: 5.36; p = 0.046), as well as charlson comorbidity index (aOR: 8.24; p = 0.015) were independently associated to death event in the vaccine failure cases.

PorA variable regions information was provided in 24.92% of cases (in 19.44% of non-vaccinated cases and in 35.04% of vaccine failures cases). In those with known information more frequent PorA variable regions were VR1, VR2: 5-7 in 48.19% of the isolates (58.54% in vaccine failures and 38.10% in non-vaccinated cases); 5-1, 10-8

**Table 3:** Univariable analysis for the relationships among demographic and clinical characteristics and death outcome in meningococcal C cases (overall and for vaccine failures cases, non-vaccinated cases, meningitis, septicemia and both).

| Factors related to death outcome in MenC cases | Factors related to death outcome in vaccine failures and non-vaccinated cases | Factors related to death outcome in meningitis and septicemia cases |
|-----------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------|
| **Variables**                                 | All (N = 58; 17.24%)                                                         | Vaccine failures (n = 16; 19.44%)                                  |
|                                               | Non-vaccinated cases (n = 42; 13.68%)                                         | Meningitis (n = 9; 9.38%)                                         |
|                                               | Sepsicemia (n = 32; 18.60%)                                                  | Both (n = 13; 24.07%)                                            |
|                                               | OR (CI95%)                                                                   | OR (CI95%)                                                      | OR (CI95%) |
| Sex                                           | Ref.                                                                          | Men                                                                  |
| Age group                                     | Ref. ≤ 13 years                                                             | 1.83 (1.03,3.25)*                                               |
|                                               | OR (CI95%)                                                                   | 1.6 (0.55,4.63)                                                | 2.83 (0.98,9.35) |
|                                               | 3.1 (0.71,13.50)                                                            | 2.38 (0.59,9.51)                                               | 1.95 (0.89,4.25) |
|                                               | 2.25 (1.14,4.49)*                                                           | 10.32 (1.24,86.08)*                                            | 3.24 (1.45,7.22)* |
|                                               | 3.46 (0.80,16.14)                                                           | 0.92 (0.26,3.34)                                               |
|                                               | 2.25 (0.79,6.39)                                                            | 1.05 (0.36,3.03)                                               | 3.6 (0.66,21.77) |
| Risk factors for the disease                  | Yes                                                                         | Yes 8.54 (3.45,21.14)**                                         | 9.0 (2.71,29.74)** |
|                                               | 3.67 (0.81,3.69)                                                            | 3.8 (1.37,24.34)**                                             | 3.8 (0.66,21.77) |
|                                               | 3.47 (1.73,6.96)                                                            | -                                                                     | - | 12.00 (1.13,127.98)* |
|                                               | 3.28 (1.73,9.21)                                                            | 9.0 (2.71,29.74)**                                             | 3.8 (0.66,21.77) |
|                                               | 2.37 (0.61,14.23)*                                                           | 2.63 (1.20,5.75)*                                              | 5.78 (1.37,24.34)** |
| Circulatory disorder                          | 2.58 (1.05,6.39)                                                            | 2.17 (0.70,6.76)                                               | 4.11 (0.86,19.68) |
|                                               | 3.87 (1.01,14.83)                                                            | -                                                                     | 12.00 (1.13,127.97)* |
| Blood disorders                               | 3.06 (1.71,5.47)**                                                           | 9.48 (0.86,10.79)                                              | 9.1 (0.20,6.75)* |
|                                               | 2.37 (0.61,8.69)                                                             | 2.63 (1.20,5.75)*                                              | 5.78 (1.37,24.34)** |
| Abnormal platelet count/leucocitopenia/Neutropenia/spleen disorders | Yes                                                                      | 9.0 (2.71,29.74)**                                             | 3.8 (0.66,21.77) |
|                                               | 4.67 (0.72,30.42)                                                            | -                                                                     | 9.0 (2.71,29.74)** |
|                                               | 9.94 (3.42,28.85)**                                                           | -                                                                     | 3.8 (0.66,21.77) |
| Digestive disorders                           | 3.32 (1.27,8.18)                                                            | 3.52 (1.04,11.92)                                              | 12.00 (1.13,127.97)* |
|                                               | 2.18 (0.21,22.33)                                                            | -                                                                     | 12.00 (1.13,127.97)* |
| Neurologic disorders                          | 2.15 (1.00,4.63)                                                             | 1.54 (0.60,3.93)                                               | 5.63 (1.97,28.73)* |
|                                               | 4.48 (1.14,17.57)**                                                          | 3.85 (0.83,17.86)                                              | 5.63 (1.97,28.73)* |
| Seizures/Collapse/Shock/Coma                   | Yes                                                                         | 10.00 (4.70,21.28)**                                           | 7.51 (3.24,12.07)** |
|                                               | 9.31 (4.95,17.51)**                                                          | 13.12 (2.66,64.66)*                                            | 17.05 (3.22,90.28)* |
|                                               | 9.63 (2.84,32.63)**                                                           | -                                                                     | 12.00 (1.13,127.97)* |

* p < 0.05
** p < 0.001
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Discussion

Previous studies developed by our group were focused on assess vaccine effectiveness of meningococcal C disease [4,18]. It is known that vaccine failures are more frequent at younger ages. Therefore, based on previous studies and the epidemiological situation in Spain the infant vaccination schedule has been changed and adapted from the initial schedule that started in December of 2000 with 3 doses at 2-4-6 months, to 3 doses at 2-4-12/15 months in 2006 and to 3 doses at 2-4-12 months in 2010. The infant vaccination schedule has been adapted from the initial schedule that started in December of 2000 with 3 doses at 2-4-6 months, to 3 doses at 2-4-12/15 months in 2006 and to 3 doses at 2-4-12 months in 2010. Between 2010 and 2013 [34]. In our previous studies we reported 84 vaccine failures in 13 years and an average coverage of 96% [35] for those infants vaccinated by routine [4,18]. This represents around 0.001% of vaccine failures among those vaccinated by routine, which is the age-group with higher proportion of vaccine failures, in our country. Thus, we only found information about vaccine failures vs. non-vaccinated cases from Auckland et al., study in which they found similar mortality in those vaccinated compared to those not vaccinated [30].

With this study we wanted to provide further information regarding the epidemiological and clinical characteristics of patients with vaccine failure and to compare them with those not vaccinated. We found that even mortality was not statistically significant different in vaccine failures and non-vaccinated cases [18], time to death was 3.38 (Range: 0-16 days) for vaccine failures and 5.62 (Range: 0-46 days) for non-vaccinated cases. This result that might suggest

Table 4: Multivariable analysis for the relationship among death outcome in meningococcal C cases and demographic and clinical characteristics (including charlson comorbidity index) adjusted by age of vaccination and time since vaccination (overall; in vaccine failures and non-vaccinated cases; and by the main clinical presentations).

| Vaccine failures | Adj. Odds Ratio | Std. Err. | z  | P > z | [95% Conf. Interval] |
|------------------|----------------|-----------|----|-------|---------------------|
| Heart failure    | 9.43           | 7.564     | 2.8| 0.005 | 1.96                |
| Age group        | 2.86           | 0.986     | 3.04| 0.002 | 1.45                |
| Seizures/Collapse/Shock/Coma | 7.43   | 2.567     | 5.81| 0     | 3.78                |
| Abnormal platelet count/Leucocitopenia/Neutroopenia/Spleen disorders | 3.12 | 1.652 | 2.15| 0.031 | 1.11                |

| Vaccine failures | Adj. Odds Ratio | Std. Err. | z  | P > z | [95% Conf. Interval] |
|------------------|----------------|-----------|----|-------|---------------------|
| Heart failure    | 17.3           | 21.913    | 2.25| 0.024 | 1.45                |
| Age group        | 2.42           | 1.045     | 2.04| 0.041 | 1.04                |
| Seizures/Collapse/Shock/Coma | 7.76   | 3.208     | 4.96| 0     | 3.45                |
| Abnormal platelet count/Leucocitopenia/Neutroopenia/Spleen disorders | 3.63       | 2.376     | 1.97| 0.049 | 1.01                |

| Meningitis       | Adj. Odds Ratio | Std. Err. | z  | P > z | [95% Conf. Interval] |
|------------------|----------------|-----------|----|-------|---------------------|
| Seizures/Collapse/Shock/Coma | 9.9    | 9.056     | 2.51| 0.012 | 1.85                |
| Agegroup         | 10.52         | 11.75     | 2.11| 0.035 | 1.18                |

| Septicemia       | Adj. Odds Ratio | Std. Err. | z  | P > z | [95% Conf. Interval] |
|------------------|----------------|-----------|----|-------|---------------------|
| Heart failure    | 10.95          | 10.246    | 2.56| 0.011 | 1.75                |
| Age group        | 2.72           | 1.274     | 2.14| 0.033 | 1.09                |
| Seizures/Collapse/Shock/Coma | 3.01  | 1.459     | 2.27| 0.023 | 1.16                |
| Renal failure    | 4.07           | 2.363     | 2.41| 0.016 | 1.3                 |
| Both (Meningitis+Septicemia) |17.05 | 14.499 | 3.34| 0.001 | 3.22                |

All models were adjusted by age of vaccination (years) and time since vaccination (years).

Table 4: Multivariable analysis for the relationship among death outcome in meningococcal C cases and demographic and clinical characteristics (including charlson comorbidity index) adjusted by age of vaccination and time since vaccination (overall; in vaccine failures and non-vaccinated cases; and by the main clinical presentations).

in 24.10% of the isolates (21.95% in vaccine failures and 26.19% in non-vaccinated cases); and 5, 2 in 12.05% of the isolates (9.76% in vaccine failures and 14.29% in non-vaccinated cases).
a worse progression in vaccine failures, might be associated with a higher proportion of septicaemia, which presents faster disease progression than meningitis, among vaccine failures compared to non-vaccinated cases.

We described in one of our previous studies that case-fatality rate increased notably after the introduction of conjugate vaccine against serogroup C in December of 2000 in Spain [4]. That increase was not only related to the age of the cases and it was also observed by age-group. A possible explanation about this could be the increase in septicaemia among serogroup C cases which present higher mortality. Septicaemia was more frequent in those with vaccine failure than in those without prior vaccination. Regarding this, we found that average time to death was shorter in septicaemia (alone) cases than in meningitis (alone) cases. The slower progression of meningitis may be involved in the reduction of cases of this clinical presentation in vaccinees and in the reduction of average time to death event if they can achieve a secondary response on time in at least 7 days. In line with this, we only found 3 (18.75%) vaccine failures that died after the 7th day of hospitalisations and all of them had concomitant infectious diseases.

We found 15.3% of cases with risk factors for the disease. Risk factors for the disease might be related to susceptibility to get the disease early after losing the protection if they are exposed to meningococcus. However, it is important to consider that we are using a database with clinical diagnoses performed during the hospital stay and we cannot know in depth the information about the risk factors in patients before being hospitalised. We found 4.2% of cases with drug/alcohol/tobacco abuse diagnoses, most of them (10/14) smokers with nicotine withdrawal symptoms. Relationship among tobacco and risk of developing meningococcal disease has been widely studied [23,24]. However, we could not stabilish if smoking could influence prognosis of the disease. None of the smokers in our study developed respiratory failure and we could not relate smoking with this outcome or other with our data and the low number of patients included in the study.

Distribution of diagnoses and procedures was similar among vaccine failures and non-vaccinated cases, however, frequency of complications and the severity of them (26.73% of shock/coma; 3.3% of heart failure; 2.1% of amputation or organ loss; etc.) show the importance of protecting the population against the disease. Our results regarding diagnoses are similar to previous studies [36] and we found a high proportion of neurologic and sense organs disorders in meningitis cases and a high proportion of shock/coma, blood and renal disorders in septicaemia cases. Therefore, differences among diagnoses were mainly found when comparing meningitis and septicaemia in which heart failure, renal failure and shock/coma were more frequent.

In contrast to our results, Hubacek et al., [37] found worse prognosis in men than in women in septicaemia cases, while we found that death event was more frequent in women compared to men. In addition, risk of death event was higher for women (OR: 1.83, p = 0.039) compared to men and the OR in women compared to men was also > 1 for septicemia also, although it was not statistically significant. Age was also independently associated to death, especially relevant in those with meningitis (aOR: 9.95, p = 0.040, in multivariable analysis).

Sadarangani et al., studied the risk factors for death and complications, and found that age, shock, seizures, bruising, abnormal platelet count, symptoms onset within 24 hours of admission or admission to the intensive care unit were independently associated with death [38]. Similarly, we found that age, seizures/collapse/shock/coma and abnormal platelet count were independently associated to death and heart failure was the main risk factor for death in all, non-vaccinated cases and septicemia cases. Additionally, we found that respiratory failure was the main risk factor for death in vaccine failures and seizures/collapse/shock/coma for those with meningitis alone or in combination with sepsis. Death event risk in vaccine failures increased also with charlson comorbidity index and the presence of risk factors of the disease that did not appear as risk factors for the rest of categories.

Although microbiological information is provided more frequently in the last years, we only have information about PorA variable regions of a quarter of the cases with no remarkable differences among vaccine failures and non-vaccinated cases.

Limitations of this study are: first, we did not use identifying information of patients and we did not access to their clinical records. Cases match between databases was achieved in 92% of cases; however, we do not expect biased results because the remaining 8% were distributed similarly among groups; second, clinical information of patients before and after the hospitalisation was not available in the National Registry of Hospitalisations. This would have been very useful to improve information about risk factors diagnosed before the hospitalisation and to know which diagnoses continued after the discharge as complications or permanent sequel; third, National Registry of Hospitalisations does not provide dates for each diagnose, therefore we could not follow the appearance of symptoms in time; fourth, the number of cases included in vaccine effectiveness study was low and there could be limited statistical power to detect certain differences among groups or evaluate the disease in more detail. Nevertheless, this is derived from the low proportion of vaccine failures among those vaccinated and we still consider relevant this study to identify information gaps for future in deep research; fifth, we do not have information about the type of vaccine failure. However, waning of the protective antibodies have been sufficiently described [9,12-16,39,40] and most of the cases of meningococcal disease are related to secondary vaccine failures. Moreover, in our previous study we observed an accumulation of vaccine failures ≥ 2 years since vaccination while vaccine effectiveness at 0-1 years since vaccination was near to 100% [18]. That correlates with seroprevalence studies reported waning of circulating antibodies and the presence of secondary vaccine failures in our study population. Mainly because vaccine failures apparition is related to vaccination age, vaccine failure cases included in our study were younger than non-vaccinated cases.

Conclusion

Vaccine failures were younger and presented more septicemia but lower fatality-rates than non-vaccinated cases. Severity of the disease was not related to prior vaccination and seems related to clinical presentation and age-group, showing an increasing trend of death rate from meningitis to septicemia and to both clinical presentations together. Risk factors for infection and charlson comorbidity index were independently associated to death event in vaccine failure cases, in which the main risk factor for death was respiratory failure, showing this group is maybe more affected by respiratory concomitant diseases. Shorter average time to death and lower rates of meningitis (with slower progression) in vaccine failures might be related to a secondary response after 7 days.
Conflict of Interest Statement
The authors declare that they have no competing interests.

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