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Research Article

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 63.97% 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.

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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-meningococcemia; 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.

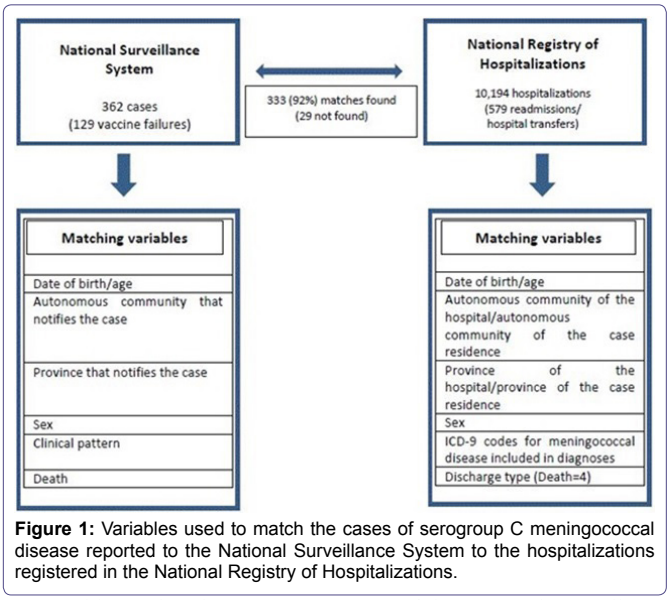

Figure 1: Variables used to match the cases of serogroup C meningococcal disease reported to the National Surveillance System to the hospitalizations registered in the National Registry of Hospitalizations.

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

	All (N = 333)		Vaccine failure cases (N = 117)		Non-vaccinated cases (N = 216)		p-value
Categorical variables	**N**	**%**	**N**	**%**	**N**	**%**	
Sex							
Men	179	53.8	63	53.8	116	53.7	0.98
Women	154	46.2	54	46.2	100	46.3	
Deaths	58	17.4	16	13.7	42	19.4	0.185
Clinical presentation							
Meningitis	96	28.8	25	21.4	71	32.9	0.027
Septicemia	172	51.7	74	63.2	98	45.4	0.002
Both (Meningitis+Septicemia)	54	16.8	16	13.7	38	17.6	0.355
Encephalitis	2	0.6	2	1.7	0	0	0.054
W-F syndrome	7	2.1	1	0.8	6	2.8	0.243
Carditis	1	0.3	0	0	1	0.5	0.461
Arthrophaty	1	0.3	0	0	1	0.5	0.461
Others	8	2.4	2	1.7	6	2.8	0.543
Quantitative variables	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**p-value**
Age	9.7 (7.90)	0-26	6.2 (4.21)	0-21	11.7 (8.73)	0-26	< 0.001
Days of stay	12.1 (14.57)	0-109	11.7 (14.43)	0-109	12.3 (14.68)	0-107	0.721
Days until death	5 (9.98)	0-46	3.4 (4.88)	0-16	5.6 (11.32)	0-46	0.634
Charlson Comorbidity Index	0.06 (0.25)	0-2	0.05 (0.26)	0-2	0.06 (0.25)	0-1	0.638

Table 1: General characteristics of all, vaccine failure and non-vaccinated meningococcal C disease cases.

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 χ^2 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 septicemia was the predominant clinical presentation, 51.7% of the cases presented it alone and 16.8% together with meningitis. Clinical presentations distribution was different among vaccine failure and non-vaccinated cases and vaccine failure cases presented a higher proportion of cases with septicemia (63.2% vs. 45.4%) than non-vaccinated cases (p = 0.002).

From 333 cases included, 21 (6.3%) presented a re-admission/hospital transfer during their hospitalisation. From them, 20 were re-admitted or transferred during the same day of discharge in the previous department/hospital and one of them was re-admitted 41 days after.

Case-fatality rate (%) was 13.7% in vaccine failure cases and 19.4% in non-vaccinated cases (p = 0.185). Average time to death event was 3.4 days (75% of them died in ≤ 3.5 days) for vaccine failure cases and 5.6 days (75% of them died in ≤ 8 days) in non-vaccinated cases although non-statistically significant (p = 0.634).

Death outcome happened in most cases in the first days of hospitalisation (75.9% of the cases died in ≤ 5 days) and 21 (36.2%) of the deaths were reported the same day of hospitalisation. Only 3 (18.75%) cases of vaccine failure died after the 7th day of hospitalisation. All of them with an additional risk factor (concomitant infectious diseases). In non-vaccinated cases, 11 (26.19%) cases died after the 7th day of hospitalisation, 3 of them (42.86%) with an additional risk factor (2 of them with a concomitant infectious disease and 1 of them with immunodeficiency).

By clinical presentation, case-fatality rate (%) was 9.38% (N = 9) in meningitis cases, 18.60% (N = 32) in septicemia cases and 24.07% (N = 13) when both clinical presentations appear together (p = 0.015). Average time to death was 5.3 days (SD: 5.15) for meningitis (alone), 2.8 (SD: 4.85) for septicemia (alone) and 8.8 days (SD: 16.76) for those presenting both clinical presentations. Vaccine failures, although presenting more septicemia, died less frequently (12.2%) by septicemia (alone) than non-vaccinated cases (23.5%; p=0.049).

Although, we had higher proportion of men (53.8%) in overall cases, death event was more frequent in women (22.1%) compared to men (13.4%; p = 0.039).

	All (N=333)		Vaccination status				Clinical presentation					
			Vaccine failures cases (N=117)		Non-vaccinated cases (N=216)		Meningitis (N=96)		Septicemia (N=172)		Both (N=54)	
	N	%	N	%	N	%	N	%	N	%	N	%
Diagnoses described as risk factors for the disease*	51	15.3	17	14.5	34	15.7	17	17.7	26	15.1	6	11.1
-Concomitant infectious disease	33	9.9	13	11.1	20	9.3	12	12.5	16	9.3	4	7.4
-Neoplasms	2	0.6	1	0.9	1	0.5	1	1	1	0.6	0	0
-Immunodeficiencies	4	1.2	1	0.9	3	1.4	1	1	2	1.2	1	1.9
-Drugs/alcohol/tobacco abuse	14	4.2	1	0.9	13	6	5	5.2	7	4.1	2	3.7
-Congenital abnormalities	4	1.2	2	1.7	2	0.9	0	0	2	1.2	1	1.9
Sense organs disorders	**11**	**3.3**	**3**	**2.6**	**8**	**3.7**	**5**	**5.2**	**4**	**2.3**	**2**	**3.7**
-Hearing disorders	3	0.9	2	1.7	1	0.5	1	1	2	1.2	0	0
-Ocular disorders	8	2.4	1	0.9	7	3.2	4	4.2	2	1.2	2	3.7
Neurologic ocular disorders	3	0.9	0	0	3	1.4	2	2.1	0	0	1	1.9
Non-neurologic ocular disorders	5	1.5	1	0.9	4	1.9	2	2.1	2	1.2	1	1.9
Heart disturbances	**28**	**8.4**	**9**	**7.7**	**19**	**8.8**	**1**	**1**	**16**	**9.3**	**9**	**16.7**
-Heart failure	11	3.3	4	3.4	7	3.2	0	0	7	4.1	3	5.6
Circulatory system disorders	**30**	**9**	**12**	**10.3**	**18**	**8.3**	**4**	**4.2**	**16**	**9.3**	**8**	**14.8**
Blood disorders	**106**	**31.8**	**38**	**32.5**	**68**	**31.5**	**12**	**12.5**	**64**	**37.2**	**25**	**46.3**
-Abnormal platelet count	18	5.4	5	4.3	13	6	0	0	10	5.8	5	9.3
-Leucocitopenia/neutropenia	5	1.5	2	1.7	3	1.4	0	0	4	2.3	1	1.9
-Spleen disorders	2	0.6	0	0	2	0.9	0	0	2	1.2	0	0
Digestive disorders	**21**	**6.3**	**4**	**3.4**	**17**	**7.9**	**3**	**3.1**	**12**	**7**	**4**	**7.4**
Renal disorders	**43**	**12.9**	**9**	**7.7**	**34**	**15.7**	**4**	**4.2**	**24**	**14**	**12**	**22.2**
-Renal failure	35	10.5	8	6.8	27	12.5	1	1	21	12.2	11	20.4
Respiratory disorders	**55**	**16.5**	**17**	**14.5**	**38**	**17.6**	**11**	**11.5**	**35**	**20.3**	**7**	**13**
-Respiratory failure	21	6.3	7	6	14	6.5	2	2.1	13	7.6	4	7.4
Neurologic disorders**	**38**	**11.4**	**11**	**9.4**	**27**	**12.5**	**13**	**13.5**	**17**	**9.9**	**7**	**13**
Seizures/Collapse/Shock/Coma	**93**	**27.9**	**36**	**30.8**	**57**	**26.4**	**9**	**9.4**	**58**	**33.7**	**21**	**38.9**
-Shock/coma	89	26.7	34	29.1	55	25.5	7	7.3	56	32.6	21	38.9
Skin disorders	**26**	**7.8**	**11**	**9.4**	**15**	**6.9**	**4**	**4.2**	**13**	**7.6**	**8**	**14.8**
Joint disorders	**31**	**9.3**	**9**	**7.7**	**22**	**10.2**	**5**	**5.2**	**21**	**12.2**	**4**	**7.4**
Transplant/organ loss	**2**	**0.6**	**1**	**0.9**	**1**	**0.5**	**1**	**1**	**1**	**0.6**	**0**	**0**
Amputation	**5**	**1.5**	**1**	**0.9**	**4**	**1.9**	**1**	**1**	**0**	**0**	**4**	**7.4**

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

*Risk factors for the disease: concomitant infectious disease, neoplasms, immunodeficiencies, drug/alcohol abuse, and congenital abnormalities.

**Neurologic disorders excluding sense organs neurologic disorders.

Average time of hospital stay was similar in vaccine failures vs. non-vaccinated cases (p = 0.721) and by clinical presentation (p = 0.204). Average charlson comorbidity index was similar among vaccine failures and 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 in non-vaccinated cases, we only found significant higher proportion of renal disorders in non-vaccinated cases (p = 0.036). However, after adjusting by age, age was the only

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 septicaemia 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%)	Septicemia (n = 32; 18.60%)	Both (n = 13; 24.07%)
		OR (CI95%)	OR (CI95%)	OR (CI95%)	OR (CI95%)	OR (CI95%)	OR (CI95%)
Sex	**Ref. Men**	**1.83 (1.03;3.25)***	1.6 (0.55;4.63)	1.94 (0.98;3.95)	2.38 (0.59;9.51)	1.95 (0.89;4.25)	0.92 (0.26;3.34)
Age group	**Ref. ≤ 13 years**	**2.52 (1.42;4.49)***	3.1 (0.71;13.50)	**2.38* (1.18;4.78)**	**10.32 (1.24;86.08)***	**3.24 (1.45;7.22)***	2.34 (0.64;8.50)
Risk factors for the disease	**Yes**	1.19 (0.56;2.54)	2.26 (0.63;8.06)	0.87 (0.33;2.26)	1.37 (0.26;7.26)	1.05 (0.36;3.03)	3.8 (0.66;21.77)
Heart disturbances	**Yes**	**5.01 (2.23;11.23)****	3.65 (0.81;16.41)	**5.73 (2.16;15.22)****	-	**4.08 (1.39;11.96)***	**5.78 (1.26;26.45)***
Heart failure	**Yes**	**14.51 (3.72;56.56)****	7.07 (0.92;54.29)	**28.83 (3.37;246.85)***	-	**12.78 (2.36;69.31)***	7.27 (0.60;87.85)
Renal failure	**Yes**	**7.89 (3.74;16.62)****	**8.08 (1.79;36.60)***	**7.5 (3.17;17.75)****	-	**8.73 (3.26;23.36)****	**10.79 (2.41;48.42)***
Respiratory failure	**Yes**	**5.0 (2.01;12.42)***	**22.5 (3.89;130.02)****	2.48 (0.78;7.82)	-	**4.38 (1.36;14.11)***	**12.00 (1.13;127.98)***
Circulatory disorders	**Yes**	**2.65 (1.17;6.03)***	**3.87 (1.01;14.83)***	2.25 (0.79;6.39)	-	2.17 (0.70;6.76)	4.11 (0.86;19.68)
Blood disorders	**Yes**	**3.06 (1.71;5.47)****	2.37 (0.81;6.89)	**3.47 (1.73;6.96)****	0.86 (0.10;7.59)	**2.63 (1.20;5.75)***	**5.78 (1.37;24.34)***
Abnormal platelet count/Leucocitopenia/Neutropenia/ Spleen disorders	**Yes**	**8.54 (3.45;21.14)****	4.67 (0.72;30.42)	**9.94 (3.42;28.85)****	-	**9.0 (2.71;29.74)****	3.8 (0.66;21.77)
Digestive disorders	**Yes**	**3.23 (1.27;8.18)***	2.18 (0.21;22.33)	**3.28 (1.17;9.21)***	-	**3.52 (1.04;11.92)***	**12.00 (1.13;127.97)***
Neurologic disorders	**Yes**	2.15 (1.00;4.63)	**4.48 (1.14;17.57)***	1.54 (0.60;3.93)	3.85 (0.83;17.86)	0.93 (0.25;3.45)	**5.63 (1.07;29.73)***
Seizures/Collapse/ Shock/Coma	**Yes**	**9.31 (4.95;17.51)****	**9.63 (2.84;32.63)****	**10.00 (4.70;21.28)****	**13.12 (2.66;64.66)***	**5.31 (2.34;12.07)****	**17.05 (3.22;90.28)***

Table 3: Univariable analysis for the relationship 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).

* <0.05

** <0.001

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; $p = 0.005$) and shock/coma (aOR: 6.83; CI95%: 2.92 to 15.95; $p < 0.001$).

Table 3 shows the results of the univariable analysis for the association between distribution of demographic characteristics and diagnoses in cases with death outcome for all and by prior vaccination (vaccine failure or no vaccination) and clinical presentation (meningitis, septicemia or both). Sense organs disorders, skin disorders, joint disorders and transplants or organ loss or amputation were not related to death event 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: 4.81; CI95%: 0.30 to 77.99; $p = 0.269$) (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 septicaemia 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). In those with known information more frequent PorA Variable regions were VR1, VR2: 5, - in 48.19% of the isolates (58.54% in vaccine failures and 38.10% in non-vaccinated cases); 5-1, 10-8

All	Adj. Odds Ratio	Std. Err.	z	P > z	[95% Conf.	Interval]
Heart failure	9.43	7.564	2.8	0.005	1.96	45.43
Age group	2.86	0.986	3.04	0.002	1.45	5.62
Seizures/Collapse/Shock/Coma	7.43	2.567	5.81	0	3.78	14.62
Abnormal platelet count/ Leucocitopenia/Neutropenia/Spleen disorders	3.12	1.652	2.15	0.031	1.11	8.81
Vaccine failures	**Adj. Odds Ratio**	**Std. Err.**	**z**	**P > z**	**[95% Conf.**	**Interval]**
Charlson comorbidity index	8.24	7.231	2.4	0.015	1.48	46.01
Heart failure	27.1	31.215	2.86	0.004	2.83	259.13
Respiratory failure	46.67	47.626	3.77	0	6.32	344.85
Risk factors for the disease	5.36	4.503	2	0.046	1.03	27.8
Abnormal platelet count/ Leucocitopenia/Neutropenia/Spleen disorders	11.85	13.438	2.18	0.029	1.28	109.37
Non-vaccinated	**Adj. Odds Ratio**	**Std. Err.**	**z**	**P > z**	**[95% Conf.**	**Interval]**
Heart failure	17.3	21.913	2.25	0.024	1.45	207.05
Age group	2.42	1.045	2.04	0.041	1.04	5.64
Seizures/Collapse/Shock/Coma	7.76	3.208	4.96	0	3.45	17.45
Abnormal platelet count/ Leucocitopenia/Neutropenia/Spleen disorders	3.63	2.376	1.97	0.049	1.01	13.1
Meningitis	**Adj. Odds Ratio**	**Std. Err.**	**z**	**P > z**	**[95% Conf.**	**Interval]**
Seizures/Collapse/Shock/Coma	9.9	9.056	2.51	0.012	1.65	59.47
Agegroup	10.52	11.75	2.11	0.035	1.18	93.99
Septicemia	**Adj. Odds Ratio**	**Std. Err.**	**z**	**P > z**	**[95% Conf.**	**Interval]**
Heart failure	10.95	10.246	2.56	0.011	1.75	68.54
Age group	2.72	1.274	2.14	0.033	1.09	6.81
Seizures/Collapse/Shock/Coma	3.01	1.459	2.27	0.023	1.16	7.78
Renal failure	4.07	2.363	2.41	0.016	1.3	12.7
Both (Meningitis+Septicemia)	**Adj. Odds Ratio**	**Std. Err.**	**z**	**P > z**	**[95% Conf.**	**Interval]**
Seizures/Collapse/Shock/Coma	17.05	14.499	3.34	0.001	3.22	90.28

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).

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

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).

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 2-12 months and at 12 years in 2014 in order to ensure long-term protection [18].

However, in spite of the reduction of vaccine failures with the age, we still found vaccine failures (3.88%) in those vaccinated at 12-19 years [18]. Previous studies of antibody persistence in adults vaccinated with NeisVac-C between 18 and 39 years old showed that although 28 days after vaccination all of them presented rSBA titres ≥ 8, after 12 months 12.3% and 20.2% had unprotective (rSBA < 8) or low (rSBA < 128) levels, respectively [33]. Moreover, the ones that lost the protection after one year did not reach protective SBA titres until 7 days post-rechallenge. This seems to be in accordance with the fact that a secondary response to an antigen reactivates immune memory and reach its peak in 6-7 days [29]. Therefore, independently from the vaccination age, due to the rapid progression of meningococcal disease those vaccinated who lose the protective antibody titres might present a similar progression of the disease than those not vaccinated.

Most studies have focused in which mechanisms are involved in loss of protection. Nevertheless, there is not so much information about if vaccine failures presented different clinic than non-vaccinated cases, mostly because countries that included vaccination have experienced a huge decrease in the incidence and low number of vaccine failures. In the case of Spain there were 6,017,266 births between 2001 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 do 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

a worse progression in vaccine failures, might be associated with a higher proportion of septicemia, 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 septicemia among serogroup C cases which present higher mortality. Septicemia 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 septicemia (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 stablish 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 septicemia cases. Therefore, differences among diagnoses were mainly found when comparing meningitis and septicemia 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 septicemia 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 septicaemia 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 sequels; 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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References

1. Campbell H, Borrow R, Salisbury D, Miller E (2009) Meningococcal C conjugate vaccine: the experience in England and Wales. Vaccine 2: 20-29.

2. Campbell H, Andrews N, Borrow R, Trotter C, Miller E (2010) Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. Clin Vaccine Immunol 17: 840-847.

3. De Wals P, Deceuninck G, Lefebvre B, Boulianne N, De Serres G (2011) Effectiveness of serogroup C meningococcal conjugate vaccine: a 7-year follow-up in Quebec, Canada. Pediatr Infect Dis J 30: 566-569.

4. Garrido-Estepa M, León-Gómez I, Herruzo R, Cano R (2014) Changes in meningococcal C epidemiology and vaccine effectiveness after vaccine introduction and schedule modification. Vaccine 32: 2604-2609.

5. Larrauri A, Cano R, García M, Mateo Sd (2005) Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain. Vaccine 23: 4097-4100.

6. Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME (2004) Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 364: 365-367.

7. Foster RA, Carlring J, Lees A, Borrow R, Ramsay M, et al. (2010) Functional T-cell deficiency in adolescents who experience serogroup C meningococcal disease despite receiving the meningococcal serogroup C conjugate vaccine. Clin Vaccine Immunol 17: 1104-1110.

8. Rezaei N, Siadat SD, Aghamohammadi A, Moin M, Pourpak Z, et al. (2010) Serum bactericidal antibody response 1 year after meningococcal polysaccharide vaccination of patients with common variable immunodeficiency. Clin Vaccine Immunol 17: 524-528.

9. Snape MD, Kelly DF, Lewis S, Banner C, Kibwana L, et al. (2008) Seroprotection against serogroup C meningococcal disease in adolescents in the United Kingdom: observational study. BMJ 336: 1487-1491.

10. Kruschinski C, Zidan M, Debertin AS, von Hörsten S, Pabst R (2004) Age-dependent development of the splenic marginal zone in human infants is associated with different causes of death. Hum Pathol 35: 113-121.

11. Siegrist CA (2001) Neonatal and early life vaccinology. Vaccine 19: 3331-3346.

12. de Voer RM, Mollema L, Schepp RM, de Greeff SC, van Gageldonk PG, et al. (2010) Immunity against Neisseria meningitidis serogroup C in the Dutch population before and after introduction of the meningococcal c conjugate vaccine. PLoS One 5: 12144.

13. de Whalley PC, Snape MD, Plested E, Thompson B, Nuthall E, et al. (2013) Long-term seroprotection after an adolescent booster meningococcal serogroup C vaccination. Arch Dis Child 98: 686-691.

14. Richmond P, Borrow R, Goldblatt D, Findlow J, Martin S, et al. (2001) Ability of 3 different meningococcal C conjugate vaccines to induce immunologic memory after a single dose in UK toddlers. J Infect Dis 183: 160-163.

15. Sakou II, Tzanakaki G, Tsolia MN, Sioumala M, Barbouni A, et al. (2009) Investigation of serum bactericidal activity in childhood and adolescence 3-6 years after vaccination with a single dose of serogroup C meningococcal conjugate vaccine. Vaccine 27: 4408-4411.

16. Snape MD, Kelly DF, Salt P, Green S, Snowden C, et al. (2006) Serogroup C meningococcal glycoconjugate vaccine in adolescents: persistence of bactericidal antibodies and kinetics of the immune response to a booster vaccine more than 3 years after immunization. Clin Infect Dis 43: 1387-1394.

17. Trotter CL, Borrow R, Findlow J, Holland A, Frankland S, et al. (2008) Seroprevalence of antibodies against serogroup C meningococci in England in the postvaccination era. Clin Vaccine Immunol 15: 1694-1698.

18. Garrido-Estepa M, Nuñez OG, León-Gómez I, Cano R, Herruzo R (2015) Meningococcal C conjugate age-dependant long-term loss of effectiveness. Vaccine 33: 2221-2227.

19. Figueroa J, Andreoni J, Densen P (1993) Complement deficiency states and meningococcal disease. Immunol Res 12: 295-311.

20. Haralambous E, Dolly SO, Hibberd ML, Litt DJ, Udalova IA, et al. (2006) Factor H, a regulator of complement activity, is a major determinant of meningococcal disease susceptibility in UK Caucasian patients. Scand J Infect Dis 38: 764-771.

21. Holdsworth RJ, Irving AD, Cuschieri A (1991) Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. Br J Surg 78: 1031-1038.

22. Emonts M, Hazelzet JA, de Groot R, Hermans PW (2003) Host genetic determinants of Neisseria meningitidis infections. Lancet Infect Dis 3: 565-577.

23. Bagaitkar J, Demuth DR, Scott DA (2008) Tobacco use increases susceptibility to bacterial infection. Tob Induc Dis 4: 12.

24. Fischer M, Hedberg K, Cardosi P, Plikaytis BD, Hoesly FC, et al. (1997) Tobacco smoke as a risk factor for meningococcal disease. Pediatr Infect Dis J 16: 979-983.

25. Cartwright KA, Jones DM, Smith AJ, Stuart JM, Kaczmarski EB, et al. (1991) Influenza A and meningococcal disease. Lancet 338: 554-557.

26. Hubert B, Watier L, Garnerin P, Richardson S (1992) Meningococcal disease and influenza-like syndrome: a new approach to an old question. J Infect Dis 166: 542-545.

27. Travaglini M, Gubler J, Bühlmann U, Goetschel P (2001) Varicella zoster virus infection complicated by Neisseria meningitidis bacteraemia in two children. Eur J Pediatr 160: 399.

28. Tuite AR, Kinlin LM, Kuster SP, Jamieson F, Kwong JC, et al. (2010) Respiratory virus infection and risk of invasive meningococcal disease in central Ontario, Canada. PLoS One 5: 15493.

29. Siegrist CA. Vaccine immunology: Section 1: General aspects of vaccination. Edited by WHO. Pg no: 1-20.

30. Auckland C, Gray S, Borrow R, Andrews N, Goldblatt D, et al. (2006) Clinical and immunologic risk factors for meningococcal C conjugate vaccine failure in the United Kingdom. J Infect Dis 194: 1745-1752.

31. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40: 373-383.

32. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45: 613-619.

33. Wing JB, Smart L, Borrow R, Findlow J, Findlow H, et al. (2011) Kinetics of immune responses to nasal challenge with meningococcal polysaccharide one year after serogroup-C glycoconjugate vaccination. Clin Infect Dis 52: 1317-1323.

34. National Institute of Statistics (2015) Demography and population/Demographic phenomena Vital Statistics, Birth Statistics, Spain.

35. Ministry of Health, Social Services and Equality. Vaccination coverage: STATISTICAL DATA. Ministry of Health, Social Services and Equality PUBLICATIONS CENTRE, Madrid, Spain.

36. Pace D, Pollard AJ (2012) Meningococcal disease: clinical presentation and sequelae. Vaccine 2: 3-9.

37. Hubacek JA, Stüber F, Fröhlich D, Book M, Wetegrove S, et al. (2001) Gene variants of the bactericidal/permeability increasing protein and lipopolysaccharide binding protein in sepsis patients: gender-specific genetic predisposition to sepsis. Crit Care Med 29: 557-561.

38. Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, et al. (2015) Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 60: 27-35.

39. Diez-Domingo J, Planelles-Cantarino MV, Baldo-Torrenti JM, Ubeda-Sansano I, Jubert-Rosich A, et al. (2010) Antibody persistence 12 months after a booster dose of meningococcal-C conjugated vaccine in the second year of life. Pediatr Infect Dis J 29: 768-770.

40. Pollard AJ, Perrett KP, Beverley PC (2009) Maintaining protection against invasive bacteria with protein-polysaccharide conjugate vaccines. Nat Rev Immunol 9: 213-220.