

## Research Article

# Updating Information About the Burden of Meningococcal Disease Hospitalisations in Spain

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## Abstract

### Introduction

Meningococcal disease remains an important public health problem worldwide due to its high lethality and high sequelae rates. Although meningococcal disease shows a decreasing incidence trend, vaccination against the current predominant serogroup (serogroup B) in Europe is not offered by routine in Spain and continuous surveillance is needed.

### Methods

Meningococcal disease (ICD-9: 036 codes in any diagnosis listed position) hospitalisations from 1997 to 2013 were obtained from the Spanish National Registry of Hospitalisations. Number of hospitalisations and deaths, hospitalisation and death rates, case fatality rates and average length of hospital stay were calculated for all meningococcal disease hospitalisations and for the main clinical presentations, meningitis and meningococemia. Data on number of hospitalisations were compared to cases reported to the National Surveillance System.

### Results

Between 1997 and 2013, there were 14,069 hospital discharges due to meningococcal disease. Of them, 13,267 (94.30%) were first hospitalisations and 802 (5.70%) readmissions/transfers. Most common clinical presentation were meningococemia alone

(41.04%; 5,774 hospitalisations), followed by meningitis alone (39.61%; 5,573 hospitalisations). Both clinical presentations appeared together in 1,885 (13.40%) hospitalisations. Hospitalisation rates decreased ( $p < 0.001$ ) from 1997 to 2013 from 3.98 to 0.65; from 1.65 to 0.25; and from 2.23 to 0.27 hospitalisations per 100,000 population for meningococcal disease, meningitis and meningococemia, respectively. Case fatality rate was 7.31% for all, 3.88% for meningitis and 9.56% for meningococemia. Meningococemia showed higher hospitalisation and death rates in 1-4 and 5-14 age-groups ( $p < 0.001$ ) and higher case fatality rate in all age-groups ( $p < 0.001$ ) than meningitis. Average length of stay was 11.46 days. High concordance (98%) among the National Surveillance System and the National Registry of Hospitalisation was found. Serogroup B cases notified decreased from 458 in 1997 to 193 cases in 2013.

### Discussion

Meningococemia is the most frequent clinical presentation in Spain with higher hospitalisation and death rates in the youngest groups and higher case fatality rates than the other predominant clinical presentation, meningitis. Meningococcal disease shows a decreasing trend and serogroup B cases decreased by 58% from 1997 to 2013 in absence of vaccination.

## Introduction

*Neisseria meningitidis* is an important cause of meningitis and septicaemia, with complications including deafness, disability or death [1]. Despite the success in reducing Invasive Meningococcal Disease (IMD) incidence and in developing vaccines against meningococcal serogroups A, C, W and Y [2], the development of a vaccine against meningococcus B has been a challenge [3,4]. In 2013 a new serogroup B vaccine has been approved for use in Europe, but only United Kingdom has recommended its introduction into the routine infant schedule [5]. In Spain it was introduced with hospital use only until the 1<sup>st</sup> of October, 2015 in which prescription was authorized but not funded [6]. Serogroup B is the predominant serogroup causing meningococcal disease at the moment in Europe. Nevertheless, serogroup B shows a decreasing trend in incidence parallel to serogroup C in most of the European countries [7] that it is attributed to a secular trend [8].

Similar situation was observed in Spain. Introduction of serogroup C conjugate vaccine in 2000 in the routine infant schedule and the development of different catch-up campaigns has resulted in an important decrease in incidence by this serogroup, with most of the remaining cases in older ages not targeted by any vaccination program [9]. Serogroup B incidence has decreased also, but it still accounted the 71% of the cases notified in 2012-2013 season to the Spanish National Surveillance System [10].

Nevertheless, other countries, as Canada, did not experience the same situation. A recent report from the Public Health Agency of Canada showed a decreasing trend of serogroup C after the introduction of serogroup C vaccination in the routine childhood immunization programs in 2007, however, serogroup B did not change across the 2006 and 2011 period [11].

Current information of the disease is necessary for the reassessment of the preventive measures. Hospitalisation burden of

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the disease was reviewed previously by Gil-Prieto et al. [12] including 1997-2008 period. The aim of this study is to update the information on hospitalisations associated to meningococcal disease. For that, we carried out a retrospective study of the hospitalisations for meningococcal disease in Spain between 1997 and 2013. Length of hospital stay, number of hospitalisations and death rates, as well as Case Fatality Rates (CFR), are useful parameters to evaluate the need and the cost-effectiveness of the preventive measures.

## Methods

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 covered 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 (region, province and municipal code), outcome and cost per hospitalisation. All diagnoses performed during the hospitalisation were recorded as main diagnosis and up to thirteen secondary diagnoses.

All hospital discharges with 036 (meningococcal disease) ICD-9 codes in any diagnosis listed position were included in our study between 1997 and 2013:

- 036.0: Meningococcal meningitis
- 036.1: Meningococcal encephalitis
- 036.2: Meningococemia
- 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)
- 036.9: Meningococcal infection, unspecified

Yearly number of laboratory confirmed cases (overall and by serogroup) reported to the National Surveillance System for Infectious Diseases was provided from the National Centre for Epidemiology in order to compare both registries. In Spain, reporting of the weekly number of invasive meningococcal disease cases has been mandatory since 1964. In 1996 notification was enhanced to obtain further information including case-based epidemiological and microbiological data.

## Statistical methods

Data cleaning was done before the analysis. Hospitalisation cases with the same birth date and sex were checked in search of possible duplicates, readmissions and hospital transfers (in the same hospital, but different unit, or to another hospital) to avoid overestimation of the frequency of the disease when comparing to the National Surveillance System. A hospitalisation was considered to be a duplicated register when all values of the database were exactly the same, including all diagnoses and medical procedures, area and hospital. Readmissions were defined as any admission related to meningococcal disease after  $\leq 30$  days of the date of discharge. In the case of hospital transfers the subsequent admission were carried out

in the same or the day after the date of discharge in a different unit/hospital. Data of readmissions and hospital transfers were shown together in this study.

Number of hospitalisations and hospitalisation rates (per 100,000 population) for meningococcal disease were calculated by year, clinical presentation and age group. Additionally, deaths, mortality rates (per 100,000 population), CFR and average length of hospital stay were calculated by age-groups and clinical presentation.

The National Registry of Hospitalisations is a discharge database and the date used in this article is the date of discharge in order to evaluate the burden of the disease at hospital level. However, when we compared data from the National Registry of Hospitalisations with data from the National Surveillance System (incidence database) we used date (year) of hospitalisation instead of date of discharge to allow the comparisons with date of symptoms onset provided by the National Surveillance System.

Population used to calculate rates was obtained from the National Institute of Statistics.

Differences in proportions were assessed by the Chi-square test and the exact test of Fisher, if necessary. Differences in means were assessed by using the t test. To compare the changes in hospitalisation rates over time, we created two periods, pre-vaccination (1998-2000) and the latest period (2010-2013). We excluded year 1997 from the pre-vaccination period because there was an increased incidence due to a hyper-virulent strain of serogroup C that could help to overestimate the decrease of the disease [13,14]. Hospitalisation Rate Ratios (HRR) and their Confidence Intervals at 95% (CI95%) comparing the latest period with the pre-vaccination period (Reference) were calculated using Poisson regression. Statistical significance was considered when  $p$ -value was  $< 0.05$ . All analyses were performed using Stata v. 13 and Excel v. 7.0.

## Results

Between 1997 and 2013, a total of 14,102 hospital discharges related to meningococcal disease (ICD-9-CM: 036, in any diagnosis listed position) were registered in the National Registry of Hospitalisations. After data cleaning, we detected 33 (0.23%) duplicated records in all variables that were not included in the analysis. Only 3 duplicates were found after 2006.

Therefore, 14,069 hospitalisations discharges were included. Of them, 13,267 (94.30%) were first admissions and 802 (5.70%) were classified as readmissions or hospital transfers. In 13,032 (92.63%) hospitalisations the main diagnosis was meningococcal disease infection (036 codes) while in 1,037 (7.37%) meningococcal disease codes were included as secondary diagnoses.

Mean age (Standard Deviation: SD) of patients (excluding readmissions) was 17.83 (SD: 23.18) and median age was 6.25 (Interquartile range: 1.62-23.20) years old. Distribution of hospitalisations was similar by sex: 50.78% (6,737) were males, 49.18% (6,524) females and 0.03% (4) had missing information. Sex ratio (male/female) by age-group decreases with age ( $p < 0.001$ ): from 1.24 in the  $< 1$  year and 1.18 in the 1-4 years age-group to 0.74 in the 45-64 years and 0.47 in  $> 64$  years age-group. Men proportion was statistically higher in the  $< 1$  and 1-4 age-groups and lower in the 45-64 and  $> 64$  age groups, with similar distribution of men vs. women in the rest of the groups. The average length of stay was 11.46 days (SD: 12.95). Death outcome was registered in 1,028 patients (7.75%; 1,028/13,267 patients).

Table 1 shows the distribution of hospitalisations in any diagnosis listed position due to MD infection by clinical presentation during the study period. From all hospitalisations, 2,085/14,069 (14.82%) presented more than one clinical presentation. Meningococcal Meningitis (MM) and Meningococemia (MC) clinical presentations appeared together in 1,885/14,069 (13.40%) hospitalisations. Only in 884/14,069 (6.28%) hospitalisations MM or MC did not appear as clinical presentation.

ICD-9: 036	N	Percentage (%)
Meningococcal meningitis (036.0)	7458	53.01
Meningococcal encephalitis (036.1)	169	1.20
Meningococemia (036.2)	7659	54.44
Waterhouse-Friderichsen syndrome (036.3)	133	0.95
Meningococcal carditis (036.4)	39	0.28
Other meningococcal infections (036.8)	346	2.46
-Neuritis (036.81)	7	0.05
-Arthropathy (036.82)	104	0.74
-Others (036.89)	235	1.67
Meningococcal infection, unspecified (036.9)	395	2.81

\*Total number of hospitalizations (N=14,069) are not the sum of clinical presentations. Some patient presented more than one clinical presentation

**Table 1:** Distribution of hospitalisations due to meningococcal disease (ICD-9: 036) by clinical presentation in any listed position. Spain, 1997-2013.

**Source:** National Registry of Hospitalisations. Ministry of Health, Social Services and Equality.

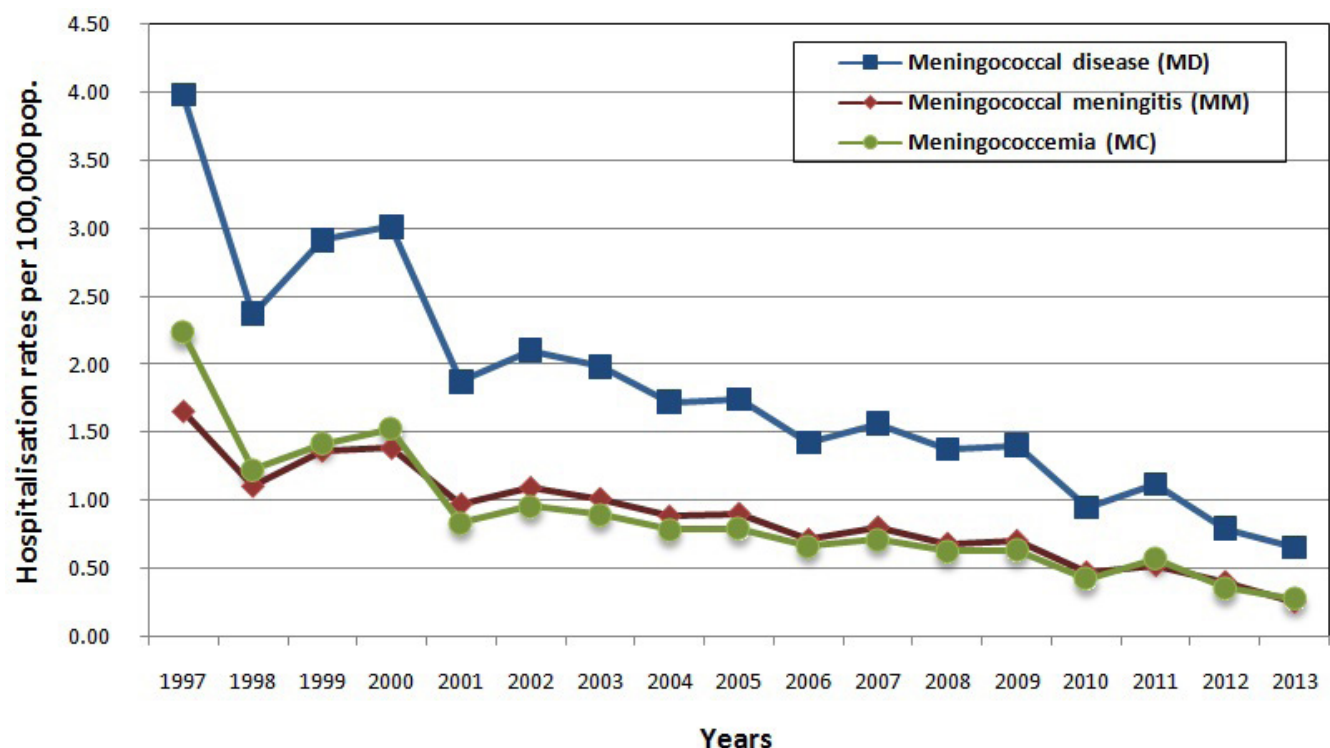
### Meningococcal disease hospitalisation rates

Figure 1 shows annual hospitalisation rates for all MD and for the two most common clinical presentations, MM and MC. An irregular decreasing trend was observed since 1997, although the decrease was more pronounced in years 2000 and 2001. Hospitalisation rates decreased ( $p < 0.001$ ) between 1997 and 2013 from 3.98 to 0.65 hospitalisations per 100,000 population for MD; from 1.65 to 0.25 hospitalisations per 100,000 population for MM; and from 2.23 to 0.27 hospitalisations per 100,000 population for MC.

From the 1,037 hospitalisations with meningococcal disease codes as secondary diagnoses, more frequent main diagnoses were: bacteremia (N=78; 7.52%); hypovolemic shock (N=58; 5.59%); HIV (N=52; 5.01%); pneumococcal meningitis (N=41; 3.95%); meningitis, unspecified bacterial agent (N=39; 3.76%); unspecified septicemia (N=29; 2.80%); pneumococcal pneumonia (N=14; 1.35%); pneumococcal sepsis (N=14; 1.35%); and multiple infections in the upper respiratory track (N=12; 1.16%).

### Hospitalisation rates by age-groups

Only in 6 hospitalisation records the age of the patient was not provided. Table 2 shows the number of hospitalisations and the hospitalisation rates for MD, MM and MC for the study period. Overall rates per clinical presentation (1.01 hospitalisations per 100,000 population for MM vs. 1.04 hospitalisations per 100,000 population for MC) weren't statistical different ( $p = 0.095$ ). MD, MM and MC presented the highest hospitalisation rate in the <1 year age-group (33.24, 17.62 and 18.60 hospitalisations per 100.000 pop.,



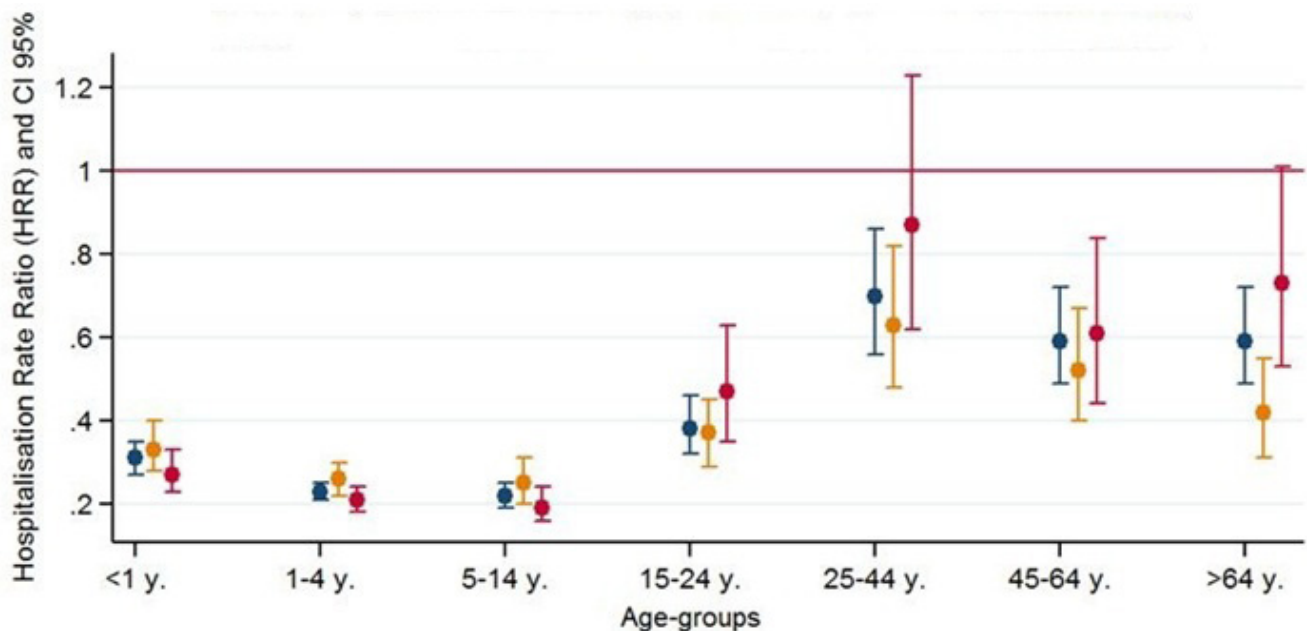
Source: National Registry of Hospitalisations. Ministry of Health, Social Services and Equality

**Figure 1:** Meningococcal Disease (MD), Meningococcal Meningitis (MM) and Meningococemia (MC) hospitalisation rates (per 100,000 pop.) in Spain (1997-2013).

Age-groups	MD		MM		MC	
	N	Rates (CI95%)	N	Rates (CI95%)	N	Rates (CI95%)
<1 y.	2486	33.24 (31.94; 34.57)	1318	17.62 (16.68; 18.60)	1391	18.60 (17.63; 19.60)
1-4 y.	4127	14.04 (13.62; 14.48)	1880	6.40 (6.11; 6.69)	2734	9.30 (8.96; 9.66)
5-14 y.	2497	3.45 (3.31; 3.59)	1196	1.65 (1.56; 1.75)	1591	2.20 (2.09; 2.31)
15-24 y.	1755	1.94 (1.85; 2.03)	1201	1.33 (1.25; 1.41)	703	0.78 (0.72; 0.84)
25-44 y.	1076	0.45 (0.43; 0.48)	692	0.29 (0.27; 0.31)	398	0.17 (0.15; 0.19)
45-64 y.	1037	0.59 (0.56; 0.63)	603	0.35 (0.32; 0.37)	411	0.24 (0.21; 0.26)
>64 y.	1085	0.88 (0.82; 0.93)	563	0.45 (0.42; 0.49)	430	0.35 (0.31; 0.38)
Total	14069	1.91 (1.88; 1.95)	7453	1.01 (0.99; 1.04)	7658	1.04 (1.02; 1.07)

**Table 2:** Hospitalisations number and rates (per 100,000 population), in any listed position, due to Meningococcal Disease (MD), Meningococcal Meningitis (MM) and Meningococemia (MC) by age-group. Spain, 1997-2013.

**Source:** National Registry of Hospitalisations. Ministry of Health, Social Services and Equality.



Reference period: 1998-2000 (pre-vaccination period). CI 95% were calculated using Poisson distribution

Source: National Registry of Hospitalisations. Ministry of Health, Social Services and Equality.

**Figure 2:** Hospitalisation Rate Ratios (HRR, CI95%) for Meningococcal Disease (MD), Meningococcal Meningitis (MM) and Meningococemia (MC) in any diagnosis listed position comparing the last period (2010-2013) with the pre-vaccination period (1998-2000).

respectively). Hospitalisations rates decreased with age. However, MC clinical presentation showed higher rates than MM ( $p < 0.001$ ) in the 1-4 years age-group (9.30 vs. 6.40 hospitalisations per 100,000 pop.), and in the 5-14 years age-group (2.20 vs. 1.65 hospitalisations per 100,000 pop.).

Comparing the pre-vaccination period (1998-2000) with the latest information of the disease (period 2010-2013) an important decrease in the rates was observed ( $p < 0.001$ ), except for MC in 25-44 and >64 years age-groups, in which the decrease was not statistically

significant ( $p = 0.866$  and  $p = 0.191$ , respectively). Overall, hospitalisation rates decreased 67% (HRR: 0.33; CI95%: 0.31-0.35), 66% (HRR: 0.34; CI95%: 0.31-0.37) and 70% (HRR: 0.30; CI95%: 0.27-0.32) for MD, MM and MC, respectively. Groups with the highest reduction in the disease incidence were those directly affected by the routine vaccination programs against meningococcal disease by serogroup C, mainly those groups  $\leq 14$  years old (Figure 2).

#### Mortality rates and Case Fatality Rates (CFR)

From the 14,069 hospitalisation discharges registered between 1997 and 2013, there were 1,028 deaths registered: 289 (28.11%)



Age groups	Deaths			Mortality Rate (per 100,000 pop) (CI 95%)			Case fatality Rate % (CFR) (CI 95%)		
	MD	MM	MC	MD	MM	MC	MD	MM	MC
<1 y.	123	20	97	1.64 (1.37; 1.96)	0.27 (0.16; 0.41)	1.30 (1.05; 1.58)	4.95 (4.11; 5.90)	1.52 (0.93; 2.34)	6.97 (5.65; 8.51)
1-4 y.	199	25	178	0.68 (0.59; 0.78)	0.09 (0.06; 0.13)	0.61 (0.52; 0.70)	4.82 (4.18; 5.54)	1.33 (0.86; 1.96)	6.51 (5.59; 7.54)
5-14 y.	100	29	77	0.14 (0.11; 0.17)	0.04 (0.03; 0.06)	0.11 (0.08; 0.13)	4.00 (3.26; 4.87)	2.42 (1.62; 3.48)	4.84 (3.82; 6.05)
15-24 y.	160	54	110	0.18 (0.15; 0.20)	0.06 (0.04; 0.08)	0.12 (0.10; 0.15)	9.12 (7.76; 10.64)	4.50 (3.38; 5.87)	15.65 (12.86; 18.86)
25-44 y.	105	31	70	0.04 (0.04; 0.05)	0.013 (0.089; 0.019)	0.03 (0.02; 0.04)	9.76 (7.98; 11.81)	4.48 (3.04; 6.36)	17.59 (13.71; 22.22)
45-64 y.	131	41	91	0.07 (0.06; 0.09)	0.023 (0.017; 0.032)	0.052 (0.042; 0.064)	12.63 (10.56; 14.99)	6.80 (4.88; 9.22)	22.14 (17.83; 27.18)
>64 y.	210	89	109	0.17 (0.15; 0.19)	0.07 (0.06; 0.09)	0.09 (0.07; 0.11)	19.35 (16.83; 22.16)	15.81 (12.70; 19.45)	25.35 (20.81; 30.58)
Total	1028	289	732	0.14 (0.13; 0.15)	0.039 (0.035; 0.044)	0.10 (0.09; 0.11)	7.31 (6.87; 7.77)	3.88 (3.44; 4.35)	9.56 (8.88; 10.28)

**Table 3:** Number of deaths, mortality rate (per 100,000 pop.) and fatality rate related to Meningococcal Disease (MD), Meningococcal Meningitis (MM) and Meningococemia (MC), by age-groups. Meningococcal disease codes in any listed position. Spain, 1997-2013.

**Source:** National Registry of Hospitalisations. Ministry of Health, Social Services and Equality.

Age-group	MD (SD)	MM (SD)	MC (SD)
<1 y.	10.52 (9.57)	11.44 (9.33)	10.15 (9.94)
1-4 y.	9.50 (10.42)	9.11 (6.67)	9.84 (11.92)
5-14 y.	9.60 (9.21)	9.28 (7.02)	9.90 (9.92)
15-24 y.	12.02 (12.30)	11.29 (8.00)	13.23 (16.03)
25-44 y.	14.88 (19.78)	14.27 (13.31)	16.17 (23.41)
45-64 y.	17.03 (20.44)	16.40 (17.05)	17.96 (24.38)
>64 y.	15.76 (15.55)	17.13 (15.34)	14.40 (16.14)
Total	11.46 (12.95)	11.58 (10.47)	11.24 (13.91)

**Table 4:** Average length of stay (days) for Meningococcal Disease (MD), Meningococcal Meningitis (MM) and Meningococemia (MC) by age-group in Spain (1997-2013). Meningococcal codes in any listed position.

**Source:** National Registry of Hospitalisations. Ministry of Health, Social Services and Equality.

of them related to MM and 732 (71.21%) to MC in any diagnosis listed position (Table 3). As described above (Table 2) highest hospitalisation rates were found in <1 and 1-4 age-groups. Similarly, highest mortality rates were found in the same age-groups. CFR in contrast to mortality rates increased with age ( $p < 0.001$ ). Lowest mortality rates and CFR were found in 5-14 years age-group for MD and MC and in 1-4 years age-group for MM. Overall, CFR was 7.31% for MD, 3.88% for MM and 9.56% for MC (Table 3).

### Length of stay

During the seventeen years included in the study, a total number of 161,350 days of stay were reported in the National Registry of Hospitalisations related to meningococcal disease. Average days of stay increased from 11.08 (SD: 8.62) to 14.04 (SD: 14.00) for MM ( $p < 0.001$ ). No changes in MC hospitalisations length of stay were observed ( $p = 0.549$ ). The average length of stay (days) for the whole period was shown in table 4. Length of stay increased with age in adults in MD, MM and MC ( $p < 0.001$ ), although it was higher in <1 year than in 1-4 ( $p < 0.001$ ) and 5-14 ( $p < 0.001$ ) years age-groups.

### Comparison among the National Surveillance System and the National Registry of Hospitalisations

Table 5 shows the number of confirmed cases notified to the National Surveillance System and the numbers of hospitalisations registered in the National Registry of Hospitalisations with MD codes as main diagnose and excluding readmissions and hospital transfers. Overall ratio among both was of 0.98 (Range: 0.91; 1.09).

In 1997 serogroup C was more frequent than serogroup B (57.51% vs. 31.14%). However, after 1997 that was still influenced by the presence of a hyper-virulent strain of serogroup C, serogroup C proportion decreased up to 9.20% in 2013. For the whole study period, serogroup B was the predominant serogroup (62.61% of the cases), followed by serogroup C (26.55%). Serogroup A (0.31%), serogroup W (1.67%) and serogroup Y (0.64%) were rare.

### Discussion

This study describes the burden of hospitalisations related to meningococcal disease and the changes occurred in the disease due to the different public health control and preventive measures. It actualizes also the previous study developed by Gil-Prieto et al. [12] that covered 1997-2008 period. Although, Gil-Prieto et al., included the first years of this study it is important to take into account that we carried out a previous data cleaning to identify possible duplicates and readmission/hospital transfers. This is important because due to the severity of meningococcal disease and, sometimes, the long periods for recovering, we expected hospital transfers to different units or hospitals and readmissions to continue sequelae treatments. Moreover, readmissions/hospital transfers identification was essential to allow comparisons between the hospitalisations and the cases notified (incidence) of the disease. After data cleaning, we detected only 0.23% of duplicates (most of them concentrated in the first years) showing the high reliability of the registry. Additionally, we identified 5.70% readmissions/hospital transfers.

Regarding to meningococcal disease hospitalisations, we observed an irregular decreasing trend in the hospitalisation rates since 1997. That decrease was more accentuated after 2000, mostly due to the

Year	National Surveillance System (Confirmed cases)	SG B (%)		SG C (%)		SG A (%)		SG W (%)		SG Y (%)		NT/Others (%)		National Registry of Hospitalisations (Main diagnose/First admission)	Ratio (Confirmed cases/Hospitalisations) (%)
1997	1471	458	31.14	846	57.51	2	0.14	15	1.02	1	0.07	120	8.16	1488	0.99
1998	853	492	57.68	284	33.29	1	0.12	14	1.64	2	0.23	55	6.45	888	0.96
1999	1043	591	56.66	365	35.00	3	0.29	9	0.86	1	0.10	65	6.23	1099	0.95
2000	1.052	595	56.56	373	35.46	2	0.19	18	1.71	1	0.10	53	5.04	1152	0.91
2001	713	467	65.50	163	22.86	9	1.26	11	1.54	3	0.42	47	6.59	731	0.98
2002	874	535	61.21	221	25.29	1	0.11	15	1.72	5	0.57	71	8.12	830	1.05
2003	791	531	67.13	174	22.00	3	0.38	18	2.28	6	0.76	49	6.19	794	1.00
2004	708	481	67.94	145	20.48	2	0.28	20	2.82	3	0.42	46	6.50	701	1.01
2005	687	496	72.20	123	17.90	1	0.15	8	1.16	16	2.33	37	5.39	712	0.96
2006	606	482	79.54	74	12.21	0	0.00	10	1.65	6	0.99	14	2.31	590	1.03
2007	633	510	80.57	74	11.69	0	0.00	5	0.79	7	1.11	22	3.48	661	0.96
2008	570	440	77.19	76	13.33	3	0.53	8	1.40	3	0.53	27	4.74	585	0.97
2009	556	422	75.90	69	12.41	4	0.72	13	2.34	7	1.26	31	5.58	596	0.93
2010	406	295	72.66	52	12.81	3	0.74	8	1.97	2	0.49	34	8.37	408	1.00
2011	440	314	71.36	69	15.68	1	0.23	9	2.05	4	0.91	23	5.23	472	0.93
2012	336	211	62.80	54	16.07	2	0.60	13	3.87	5	1.49	35	10.42	341	0.99
2013	261	193	73.95	24	9.20	0	0.00	6	2.30	5	1.92	22	8.43	240	1.09
All	12000	7513	62.61	3186	26.55	37	0.31	200	1.67	77	0.64	751	6.26	12288	0.98

SG: Serogroup

**Table 5:** Number of confirmed cases (overall and by serogroup) notified to the National Surveillance System, number of hospitalisations related to Meningococcal Disease (MD) as main diagnose and first admission registered in the National Registry of Hospitalisations and the ratio between confirmed cases and hospitalisations. Spain, 1997-2013.

implementation of the conjugated vaccine for meningococcal C serogroup in the National Vaccination Programs. The decrease in meningococcal disease has been described in most European countries [7] and although it has been more marked in the serogroup C due to vaccination programs, it has been also reported in serogroup B. Independently, of the reduction in serogroup B incidence, this serogroup is still the main cause of meningococcal disease, up to 71% of the cases in Spain in 2012-2013 season [10]. In Spain vaccination against serogroup B has been approved only for hospital use [15,16] until the 1<sup>st</sup> of October of 2015 in which prescription was approved (but not funded) [6]. A study, carried out with samples from different European countries gave estimated strain coverage of 69% (CI95% 48-85) for Spanish isolates [17] and cost-effectiveness of the vaccine has been controversial due to high cost of the vaccine and low incidence [18-20].

We found that sex ratio of hospitalisation was over 1 ( $p < 0.001$ ) in <1 and 1-4 years age-groups and decreases with age. In older groups were women who were mostly affected (Sex ratio > 64 years = 0.47). However those results are related with higher number of men births and higher women survival, so therefore should be taken cautiously.

From all hospitalisations, 93.72% were due to MM and/or MC and only 6.28% hospitalisations were related to other clinical presentations. Higher meningeal tropism has been reported in other studies resulting in higher proportion of MM compared to MC [21], however in Spain we have higher proportion of MC. That is important if we considered differences in outcomes. MM and MC showed a similar decreasing trends, and both presented the highest hospitalisation and mortality rates in <1 year age-group, but we found that MC showed higher hospitalisation rates in 1-4 and 5-14 age-groups than MM. Additionally, MC due to its seriousness also

presented higher mortality rates and CFR than MM, not exclusively in the youngest age-groups (<1, 1-4 and 5-14 years age-groups), but in all age-groups.

In spite of improvement in diagnose and treatments, overall CFR has remained around 7-8% in Europe in the last years [22], similarly to our results in which overall CFR was 7.31%. Although mortality rates are higher at younger ages because hospitalisation rate is also high in infants, CFR increased with age for all, MM and MC. Similarly, length of stay increased with age, although it was higher in <1 year than in 1-4 and 5-14 years age-group.

Hospital discharges with meningococcal codes as secondary diagnoses were associated with shock, unspecified agents or other specified agents (including HIV). Due to the severity of the disease we expected main diagnoses related to acute symptoms while meningococcal disease is confirmed. Additionally, relationship of meningococcal disease with concomitant infections [23-25] and immunodeficiency [26,27] has been described previously.

When we compared confirmed cases reported to the National Surveillance System and hospitalisations (first admission and main diagnoses) included in the National Registry of Hospitalisations overall ratio found was 0.98. That implies a very good coherence in between both, the National Surveillance System and the National Registry of Hospitalisations. We have to consider that the National Registry of Hospitalisations is a discharge database and year 2013 admissions could be slightly higher when 2014 database will be available. Although, the National Registry of Hospitalisations does not provide information of serogroup, in the hospital practice *Neisseria meningitidis* infection is confirmed through blood culture or lumbar puncture and samples are sent to the Reference Laboratories to more

specific strain determination. Therefore we expected good coherence among both databases.

Some limitations derived from the use of the National Registry of Hospitalisations were presented in previous studies [12,28]. However, introduction of new technologies and computerization in data management has improved notably the quality of this registry in the last years. Additionally, one of the strength of our study is the evaluation of the quality of the data previous to our analyses which showed a low number of duplicates and a high concordance with the National Surveillance System when transfers/readmissions were identified. Valuable information can be obtained combining epidemiological information with information collected during the hospitalisation to improve the knowledge of the disease.

## Conflicts of Interest

The authors declare no conflicts of interest.

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