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Estimation of the incidence of invasive meningococcal disease using a capture-recapture model based on two independent surveillance systems

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ABSTRACT

Objectives: Invasive meningococcal disease (IMD) is an urgent notifiable disease and its early notification is essential to prevent cases. The objective of the study was to assess the sensitivity of two independent surveillance systems, the statutory disease reporting system (SDR) and the microbiological reporting system (MRS), and to estimate the incidence of IMD.

Settings: The study was performed in Catalonia, Spain, between 2011 and 2015. The variables collected were age, sex, year of report, size of municipality (< 10,000 and ≥ 10,000), clinical form, death, serogroup, country of birth and type of reporting centre (private and public). The capture-recapture analysis and 95% confidence intervals were calculated using the Chapman formula. Multinomial logistic regression was performed for adjusted estimation.

Results: The sensitivity of the two combined surveillance systems was 88.5% (85.0-92.0). SDR had greater sensitivity than the MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0). In 2014-2015, the sensitivity of both systems was higher (80.6%; 73.2–87.9 vs. 73.4%; 65.2–81.6) than in 2011-2013 (59.3%; 52.6–66.0 vs. 58.3%; 51.6–65.1). In private centres, the sensitivity was higher for SDR than for MRS (100%; 100–100 vs. 4.8%; -4.4–13.9). The adjusted estimate of cases was lower than that obtained using the Chapman formula (279; 266–296 vs. 313; 295–330). The estimated adjusted incidence of IMD was 0.7/100,000 persons-year.

Conclusions: The sensitivity of enhanced surveillance through the combination of two complementary sources was higher than for the sources individually. Factors associated with under-reporting in different systems should be analysed to improve IMD surveillance.

Keywords:

Meningococcal disease, Capture-recapture, estimated incidence, surveillance systems.

Strengths and limitations of this study

1. Early notification of Invasive meningococcal disease is essential to prevent cases.

2. Statutory disease reporting system had greater sensitivity than Microbiological reporting system.
3. Two surveillance sources was higher sensitivity than sources individually.
4. Factors associated with under-reporting should be analysed for invasive pneumococcal disease surveillance.

BACKGROUND

Invasive meningococcal disease (IMD) continues to be an important cause of morbidity and mortality, mainly in children aged < 4 years and adolescents. [1]

In the European regions, the incidence rate of confirmed IMD cases is around 0.6/100,000 persons, [2] similar to Spain (0.58/100,000 persons). [3] The highest incidence is for meningococcal serogroup B, accounting for 51.5% of confirmed IMD cases. The case fatality rate is around 10-15% [3, 4] and long-term sequelae occur in 10-20% of cases. [5]

IMD is an urgent notifiable disease and its early notification is essential to provide an adequate public health response in patients and their close contacts to prevent further cases. Epidemiological surveillance allows monitoring of the impact of public health interventions, including vaccination programmes. Therefore, a robust epidemiological and microbiological system with timely and accurate surveillance providing information on the frequency of cases and the distribution of circulating serogroups is crucial.

Evaluations of surveillance systems should be conducted regularly to increase their utility. [6-8] There are two reporting systems for the epidemiological surveillance of communicable disease in Catalonia: the statutory disease reporting system (SDR) and the microbiological reporting system (MRS). [9]

The capture-recapture method is a statistical method for estimating the real incidence of diseases in a population with two or more information sources. [10, 11] The method is valid if

four conditions are met: 1) the population under study has to be closed, i.e., there should be no changes during the study period; 2) there must be a method of determining whether an individual identified by one source is the same as an individual identified by the other; 3) each individual must have the same probability of being captured by either system; 4) the systems must be independent.

The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD.

METHODS

Information sources

Catalonia is a region in the northeast of Spain with a population of 7,508,106 in 2015. [12] The SDR is a passive surveillance system through which health professionals declare all infectious diseases subject to surveillance. The reporting of cases to the Public Health Agency of Catalonia (PHAC) is mandatory and includes confirmed cases of IMD and is regulated by a Decree. [9, 13]

The MRS is a surveillance system that consists of microbiologists notifying laboratory confirmed microorganisms that cause infectious diseases. The main objectives of the MRS are to confirm suspected cases of infectious diseases through the identification of the microorganisms and serogroups involved and to determine trends and changes in epidemiological patterns and microbiological resistance. [14]
The MRS was non-compulsory until 2015 and involved 50 health care centres representing over 83% of acute hospital beds. [15] Confirmed IMD cases were reported by microbiologists including sex, age, clinical presentation, serogroup and diagnostic method.

Both systems belong to the PHAC epidemiological surveillance network and, since 2014, transfer information automatically, but the independence of the sources is maintained.

Cases definition, inclusion, and exclusion criteria

A confirmed case of IMD was defined as laboratory confirmed if at least one of the following criteria was fulfilled: isolation in cultures or detection of *Neisseria meningitidis* DNA by PCR in a normally sterile site, detection of gram-negative diplococci or *N. meningitidis* antigen in cerebrospinal fluid.

Data collection

We made a retrospective study of confirmed IMD cases in Catalonia from January 2011 to December 2015. We extracted all IMD records from the MRS and SDR and linked the databases using the personal identification code (PIC). When the PIC was not available, data on notification, age and sex were used to identify duplicates between the two sources. In cases with inconclusive matching, the hospital was used as a fifth matching criterion.

Estimates were made for the entire 5-year period and by age , sex, year of report, size of municipality (<10,000 and ≥10,000), country of birth, number of hospital beds, clinical form (meningitis, with or without sepsis, sepsis, and others), serogroup, death and reporting centre (private or public).

Ethics statement

The study was not submitted for research ethics approval as the activities described were conducted as part of the legislated mandate of the Health Department of Catalonia, the competent authority for surveillance of communicable diseases according to Decree 203/2015 of the 15 September which created the epidemiological surveillance network of Catalonia. [9] All the study activities formed part of public health surveillance and did not require informed consent. Personal data were used only for the matching process and measures to protect the confidentiality of personal data were applied (access to the data restricted to the personnel involved in data analysis, and removal of personal data from the datasets after matching).

Patient and public involvement

No patient involved

Statistical methods

The total number of IMD cases was estimated using the two-source capture-recapture method, which uses Chapman's formula, [16] developed to reduce bias due to small samples:

$$N = \frac{(L1+1)(L2+1)}{a+1} - 1$$

$$95\%CI = N \pm 1.96\sqrt{\frac{(L1+1)(L2+1)(L1-a)(L2-a)}{(a+1)^2(a+2)}}$$

where L1 is the number of cases in the SDR dataset, L2 is the number of cases reported to MRS, and **a** is the number of cases captured by both systems. The sensitivity (Se) of case ascertainment by the two sources was also calculated as the proportion of true cases detected by each source, i.e. Se (1) =L1/N for source 1 and Se (2) =L2/N for source 2. The sensitivity of bothsources combined was calculated as the proportion of cases detected by one of the two sources or both, i.e., Se (1, 2) =(L1+L2-**a**)/N.

The independence of the sources was considered when applying the capture-recapture method. [17, 18] In the two-by-two table, where **a** represents cases reported by two sources or combinations of sources, **b** and **c** cases reported exclusively by either of the two sources and **x** the estimated non-reported cases by either of the sources, the odds ratio (OR = ax/bc) should not differ from one.

A multinomial logit model was used to evaluate patient characteristics and the probability of capture by different sources, which allows more precise estimates of the number of cases. [19, 20] We used a backwards stepwise procedure (using likelihood ratio tests, with a P-value >0.2

as the criterion for removing variables from the model), [21, 22] starting with a full model including all potential covariates, and we used the parameter estimates from the model to estimate the sizes of population subgroups and their 95% confidence intervals (CI). All analyses were made using R software version 3.0.1.

RESULTS

Patient characteristics

Patient characteristics by source are shown in Table 1. From 2011 to 2015, 212 IMD cases were reported to the SDR and 202 cases to the MRS, representing an incidence of 0.56 and 0.54 /100,000 persons-year, respectively. IMD due to serogroup B was the most-frequently reported serogroup (77.4% and 75.7% in the SDR and MRS, respectively). Around 63% of patients were aged < 15 years; the mean age was 21.4 for the SDR and 20.5 years for the MRS. Male sex was more frequent in the SDR (52.4%) than in the MRS (49%). The SDR presented the most cases in 2015 (48 cases; 22.6%) and the MRS (61 cases; 30.2%) in 2011. The SDR reported that 84% of patients lived in a municipality of ≥10,000 people compared with 73% in the MRS. In both sources, the number of cases declared in a hospital of ≥200 beds were around 70%. The main clinical form in both sources was meningitis (54.7% and 64.8%, respectively) and sepsis (38.7% and 32.7%, respectively). Reports from private centres represented 10% of cases in the SDR and 0.5% in the MRS. Twenty-two cases (10.4%) cases reported by the SDR died compared with 11 cases (5.4%) reported by the MRS .

Table 1. Sociodemographic, clinical and microbiological characteristics of invasive meningococcal disease cases reported to the SDR and MRS, Catalonia 2011-2015

	SDR (n=212)	MRS (n=202)
Age groups		
Mean (SD)	21.4 (27.9)	20.5 (26.7)
Median (IQR)	6 (36)	6 (32.3)
<2 years, n (%)	62 (29.8%)	61 (30.7%)
2 - 4 years, n (%)	35 (16.8%)	30 (15.1%)
5 - 14 years, n (%)	34 (16.3%)	35 (17.6%)
15 - 24 years, n (%)	12 (5.8%)	12 (6.0%)
25 - 34 years, n (%)	12 (5.8%)	9 (4.5%)
35 - 44 years, n (%)	10 (4.8%)	12 (6.0%)
45 - 54 years, n (%)	9 (4.3%)	7 (3.5%)
>55 years, n (%)	34 (16.3%)	33 (16.6%)
NAs	1 (0.5%)	2 (1.0%)
Sex, n (%)		
Male	111 (52.4%)	99 (49.0%)
Female	101 (47.6%)	103 (51.0%)
Year of report, n (%)		
2011	43 (20.3%)	61 (30.2%)
2012	41 (19.3%)	29 (14.4%)
2013	38 (17.9%)	30 (14.9%)
2014	42 (19.8%)	34 (16.8%)
2015	48 (22.6%)	48 (23.8%)
Size of municipality, n (%)		
<10,000 people	27 (12.7%)	28 (13.9%)
≥10,000 people	177 (83.5%)	148 (73.3%)
NAs	8 (3.8%)	26 (12.9%)
Country of birth, n (%)		
Spain	194 (91.5%)	188 (93.1%)
Other countries	18 (8.5%)	14 (6.9%)
Number of hospital beds, n (%)		
<200	60 (28.3%)	65 (32.2%)
≥200	149 (70.3%)	137 (67.8%)
NAs	3 (1.4%)	0 (0.0%)
Clinical form, n (%)		
Meningitis	116 (54.7%)	131 (64.8%)
Sepsis	82 (38.7%)	66 (32.7%)
Other forms	14 (6.6%)	4 (2.0%)
NAs	0 (0.0%)	1 (0.5%)
Serogroup, n (%)		
A	0 (0.0%)	2 (1.0%)
B	164 (77.4%)	153 (75.7%)
C	26 (12.3%)	21 (10.4%)
W135	4 (1.9%)	6 (3.0%)
Y	5 (2.4%)	2 (1.0%)
Y/ W135	1 (0.5%)	1 (0.5%)
Non-groupable	6 (2.8%)	4 (2.0%)
NAs	6 (2.8%)	13 (6.4%)
Type of reporting centre		
Private	21 (10.0%)	1 (0.5%)
Public	190 (90.0%)	201 (99.5%)

NAs: Not available; SDR: Statutory disease reporting; MDR: Microbiological reporting system

Capture-recapture analysis

The odds ratio (OR) was 1.01 (95%CI 0.62-1.66), reinforcing the independence of the two sources.

During the period studied, 212 and 202 IMD cases were reported by the SDR and MRS, respectively. One hundred thirty-seven cases (43.8%) coincided in both sources and 36 cases (11.5%) were not reported to either source. The estimated number of cases was 313 (95% CI 295–330) (Table 2) and the estimated incidence rate was 0.83/100,000 persons-year.

Table 2. Capture–recapture analysis of two datasets to estimate the total number of invasive meningococcal disease cases, Catalonia 2011-2015

		SDR		
		Identified	**Not identified**	**Total**
MRS	**Identified**	137	65	202
	Not identified	75	36	111
	Total	212	101	313

SDR: Statutory disease reporting
MRS: Microbiological reporting system

The sensitivity of the SDR was 67.9% (95%CI 62.7-73.1) and that of the MRS was 64.7% (95%CI 59.4-70.0) (P-<0.001) (Table 3). The sensitivity increased to 88.5% (95%CI 85.0-92.0) when the datasets were combined.

Table 3. Capture–recapture analysis of all invasive meningococcal disease cases reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	212	202	137	36	313 (295, 330)	67.9 (62.7, 73.1)	64.7 (59.4, 70.0)	3.2	***<0.001***
Age group									
<15 years	131	126	87	20	190 (177, 203)	69.1 (62.6, 75.7)	66.5 (59.8, 73.2)	2.6	*0.468*
≥15 years	80	74	49	16	121 (109, 133)	66.4 (58.0, 74.8)	61.4 (52.7, 70.1)	5.0	
Sex									
Male	111	99	71	16	155 (144, 166)	71.8 (64.7, 78.9)	64.0 (56.5, 71.6)	7.8	*0.588*
Female	101	103	66	20	158 (145, 171)	64.2 (56.7, 71.7)	65.5 (58.1, 72.9)	-1.3	
Year of report									
2011-2013	122	120	71	35	206 (187, 226)	59.3 (52.6, 66.0)	58.3 (51.6, 65.1)	1.0	***<0.001***
2014-2015	90	82	66	6	112 (106, 118)	80.6 (73.2, 87.9)	73.4 (65.2, 81.6)	7.2	
Size of municipality									
<10,000 people	27	28	22	2	35 (32, 37)	78.7 (65.0, 92.4)	81.6 (68.7, 94.6)	-2.9	*0.100*
≥10,000 people	177	148	110	23	238 (225, 252)	74.4 (68.9, 80.0)	62.2 (56.1, 68.4)	12.2	
Country of birth									
Spain	194	188	127	32	287 (271, 304)	67.6 (62.2, 73.0)	65.5 (60.0, 71.0)	2.1	*0.696*
Other countries	18	14	10	3	25 (20, 30)	72.3 (54.7, 89.9)	56.2 (36.7, 75.7)	16.1	
Number of hospital beds									
<200	60	65	40	13	97 (87, 108)	61.7 (52.1, 71.4)	66.9 (57.5, 76.2)	-5.1	*0.514*
≥200	149	137	97	22	210 (197, 224)	70.9 (64.7, 77.0)	65.2 (58.7, 71.6)	5.7	
Clinical form									
Meningitis	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	*0.936*
Sepsis	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	
Type of reporting centre									
Private	21	1	1	0	21 (21, 21)	100 (100, 100)	4.8 (-4.4, 13.9)	95.2	***0.002***
Public	190	201	136	26	281 (267, 295)	67.7 (62.2, 73.2)	71.6 (66.4, 76.9)	-3.9	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

There were no differences in sensitivity between in <15 years and ≥15 years age groups (P-value=0.468) in either source although it was higher in the <15 years (69.1%; 95%CI 62.6-75.7 in the SDR and 66.5%; 95%CI 59.8-73.2 in the MR) S. The age groups with the highest sensitivity were 2-4 years in the SDR, with 80.3% (95%CI 68.5-92.1), and 35-44 years in the MRS, with 80.5% (95%CI 60.4–100.0) (figure 1).

In 2011-2013, sensitivity for the SDR and the MRS were 59.3% (95%CI 52.6-66) and 58.3% (95%CI 51.6-65.1), respectively, lower than that in 2014-2015 (80.6%; 95%CI 73.2-87.9, for the SDR and 73.4%; 95%CI 65.2-81.6, for the MRS (P<0.001)) (Table 3). 2014 showed the highest sensitivity for both sources: 91.3% (95%CI 83.2-99.4) for the SDR and 73.9% (95%CI 61.2-86.6) for the MRS (Figure 2). 2011 was the only year in which the MRS had a higher sensitivity than the SDR (56.4%; 95%CI 47.1-65.8 and 39.8%; 95%CI 30.6-49.0, respectively). In private centres the sensitivity of the SDR was 100% (95%CI 100-100) and that of the MRS was 4.8% (95%CI -4.4-13.9). No differences were found in other characteristics analysed.

For l meningitis, 116 and 131 cases were reported by the SDR and the MRS, respectively. The estimated number of meningitis cases was 181, and 18 cases were not reported by either source. The highest sensitivity was detected in the MRS (72.5%; 95% CI 66-79) compared with the SDR (64.2%; 95%CI 57.2-71.2) (P<0.001) (Table 4). 2014-2015 showed a higher sensitivity in both sources compared with 2011-2013: 82.4% (95%CI 72.7-92) in the MRS and 75.6% (95%CI 64.7-86.5) in the SDR. Public centres had a higher sensitivity in the MRS (77.7%; 95%CI 71.4-84.0) and in the SDR (63.9%; 95%CI 56.6-71.2) (P<0.037).

Table 4. Capture–recapture analysis of meningococcal meningitis reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	***<0.001***
Age group									
<15 years	72	81	51	13	115 (104, 125)	63.1 (54.3, 72.0)	71.0 (62.7, 79.3)	-7.9	*0.682*
≥15 years	43	49	32	6	66 (60, 73)	65.5 (53.9, 77.0)	74.6 (64.1, 85.1)	-9.1	
Sex									
Male	62	69	47	7	91 (84, 98)	68.2 (58.6, 77.8)	75.9 (67.1, 84.7)	-7.7	*0.245*
Female	54	62	37	12	91 (81, 101)	59.9 (49.8, 70.0)	68.7 (59.2, 78.3)	-8.9	
Year of report									
2011-2013	71	82	47	18	124 (111, 137)	57.5 (48.8, 66.2)	66.4 (58.1, 74.7)	-8.9	***0.013***
2014-2015	45	49	37	3	60 (56, 64)	75.6 (64.7, 86.5)	82.4 (72.7, 92.0)	-6.7	
Size of municipality									
<10,000 people	19	20	16	1	24 (22, 26)	80.2 (64.1, 96.2)	84.4 (69.8, 99.0)	-4.2	*0.165*
≥10,000 people	93	93	65	12	133 (124, 143)	70.0 (62.2, 77.8)	70.0 (62.2, 77.8)	0.0	
Country of birth									
Spain	107	120	77	17	167 (155, 179)	64.3 (57.0, 71.5)	72.1 (65.3, 78.9)	-7.8	*0.862*
Other countries	9	11	7	1	14 (12, 17)	64.3 (39.2, 89.4)	78.6 (57.1, 100.0)	-14.3	
Number of hospital beds									
<200	31	40	23	6	54 (47, 61)	57.7 (44.5, 70.9)	74.5 (62.8, 86.2)	-16.8	*0.516*
≥200	84	91	61	11	126 (116, 135)	67.1 (58.9, 75.4)	72.7 (64.9, 80.5)	-5.6	
Type of reporting centre									
Private	9	1	1	0	9 (9, 9)	100.0 (100.0, 100.0)	11.1 (-9.4, 31.6)	88.9	***0.037***
Public	107	130	83	14	168 (158, 178)	63.9 (56.6, 71.2)	77.7 (71.4, 84.0)	-13.7	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

For sepsis, 82 cases and 66 cases were reported by the SDR and the MRS, respectively. The sensitivity was higher for the SDR (75.9%; 95%CI 67.9-84) than the MRS (61.1%; 95%CI 51.9-70.3) (Table 5). There were 108 estimated cases and 10 cases were not reported by either source. The sensitivity was higher in the <15 years than in the ≥15 years in both sources, but higher in the SDR (81.1%; 95%CI 71.1-91.1 versus 71%; 95%CI 59.4-82.5 for the MRS; P=0.0036), and higher in 2014-2015 than in 2011-2013 (87.6%; 95%CI 78-97.3 for the SDR and 71.9%; 95%CI 58.7-85.1 for the MRS) (P<0.015).

Serogroup B (Supplementary Table 1) showed the sensitivity of the SDR was higher than that of the MRS (74.6%; 95%CI 68.8-80.3 and 69.6%; 95%CI 63.5-75.6, respectively). There were differences according to the period and the type of centre. In 2014-2015, the sensitivity was 87.1% (95%CI 79.7-94.5) for the SDR and 78.3% (95%CI 69.2-87.4) for the MRS (P<0.002). In private centres, the sensitivity in SDR was 100% compared with 7.1% (95%CI -6.4-20.6) (P=0.004) in MRS. The sensitivity was higher for IMD serogroup C cases in SDR than in MRS (76.7%; 95%CI 62.5-90.9 and 62%; 95%CI 45.6-78.3, respectively) (Supplementary Table 2). All 22 deaths were reported in the SDR (CFR: 10.4%), and the sensitivity of the SDR was higher than that of the MRS (100%; 95CI% 100-100 vs 50%; 95%CI 29.1-70.9, P=0.104) (Supplementary Table 3).

Table 5. Capture–recapture analysis of meningococcal septicaemia reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	***<0.001***
Age at notification, years									
<15 years	48	42	34	4	60 (55, 64)	81.1 (71.1, 91.1)	71.0 (59.4, 82.5)	10.1	***0.036***
≥15 years	34	23	16	8	49 (40, 58)	70.3 (57.4, 83.1)	47.5 (33.4, 61.6)	22.7	
Sex									
Male	43	27	22	5	53 (47, 59)	81.8 (71.3, 92.2)	51.3 (37.8, 64.8)	30.4	*0.315*
Female	39	39	28	5	55 (49, 60)	72.0 (60.0, 83.9)	72.0 (60.0, 83.9)	0.0	
Year of report									
2011-2013	43	34	22	11	66 (56, 77)	65.2 (53.6, 76.7)	51.5 (39.5, 63.6)	13.6	***0.015***
2014-2015	39	32	28	2	45 (42, 48)	87.6 (78.0, 97.3)	71.9 (58.7, 85.1)	15.7	
Size of municipality									
<10,000 people	7	7	5	1	10 (8, 12)	72.2 (44.0, 100.0)	72.2 (44.0, 100.0)	0.0	*0.918*
≥10,000 people	71	52	43	6	86 (80, 93)	82.9 (74.9, 90.8)	60.7 (50.3, 71.0)	22.2	
Country of birth									
Spain	73	63	47	9	98 (90, 106)	74.7 (66.1, 83.3)	64.5 (55.0, 74.0)	10.2	*0.275*
Other countries	9	3	3	0	9 (9, 9)	100.0 (100.0, 100.0)	33.3 (2.5, 64.1)	66.7	
Number of hospital beds									
<200	25	23	16	4	36 (31, 42)	70.0 (55.0, 85.1)	64.4 (48.7, 80.1)	5.6	*0.831*
≥200	56	43	34	6	71 (65, 78)	79.2 (69.7, 88.7)	60.8 (49.4, 72.2)	18.4	
Type of reporting centre									
Private	9	0	0	0	9 (9, 9)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.988*
Public	73	66	50	8	97 (89, 104)	75.9 (67.3, 84.4)	68.6 (59.3, 77.9)	7.3	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

The results of the multinomial logit model for all cases are shown in Table 6. The variables considered significant in defining the sensitivity of the two sources were year of report (2011-2013 versus 2014-2015) and size of municipality. With these variables in the model, the adjusted estimate of the total number of cases was 279 cases (95%CI 266-296) and the estimated incidence rate was 0.7/100,000 persons-year.

Table 6. Variables defining the sensitivity of the SDR and MRS in detecting invasive meningococcal diseases cases. Multinomial logit model

	OR (95%CI)	*p-value*
Year of report (2014-2015)	2.29 (1.35, 3.89)	***0.002***
Size of municipality (≥10,000 people)	0.51 (0.23, 1.12)	*0.093*

OR: odds ratio; n estimate: 279 (266, 296)

DISCUSSION

The sensitivity obtained by combining the two surveillance system for IMD cases was 88.5%, greater than for each source s (67.9% and 64.7%, respectively). Globally, the SDR showed higher sensitivity than the MDR, mainly for cases of sepsis, l serogroup B and serogroup C, although for meningitis the sensitivity of the MDR was higher than that of the SDR.

Similar studies found greater sensitivities by combining data systems than we did. Baldovin et al. [23] in Italy, reported an overall sensitivity of 94.7% by combining four data sources (mandatory notification system, laboratory surveillance, invasive bacterial surveillance and hospital discharge). Jansson et al. [24], in Sweden, found a global sensitivity of 98.7%, 91.1% for clinical notification and 85.4% for laboratory reporting. In Austria a good agreement between the National Reference Center for meningococci and the hospital discharge was found, although a clinical review of hospital discharge data was necessary to detect false positive cases recorded. [25]

The sensitivity was similar in children aged <15 years than in persons aged ≥15 years in both sources (69.1% for the SDR and 66.5% for the MRS; P=0.468). Gibson et al., [26] in Australia,

analysed IMD sensitivity in children aged < 15 years in three sources: notifiable system, hospitalized patients and mortality data. They found a greater sensitivity (99.5%) than we did, although 15% of hospitalized children were false-positive cases.

We found a greater sensitivity for meningitis in the MRS than in the SDR (72.5% vs 64.2%). A possible explanation is that meningitis is considered a more serious disease and, therefore, microbiologists are more sensitive to its reporting. It is difficult to compare our results with those of other studies, since other sources of information were used or the independence of data sources was presumed but not demonstrated, [25] which is essential when using the capture-recapture method.

Notification of confirmed cases of IMD by laboratories is essential in epidemiological surveillance. [27] Molecular information on circulating serogroups that is required to implement public health measures such as vaccination is essential to control the disease [28] and evaluate the impact of available vaccines.

In the absence of automated electronic reporting, monitoring and increasing the speed of laboratory reports may allow the public health department to administer chemoprophylaxis and vaccination to contacts. [28] Although a higher sensitivity has been reported for electronic reporting than for paper-based reports by some authors, [29] during the study period, electronic surveillance was used in the SDR but not in the MDR, which may explain, at least in part, why the MDR had a lower sensitivity than the SDR. [30]

In the multinomial model, the 2014-2015 period and the size of the municipality show a higher sensitivity in the SDR, suggesting that IMD was well recorded in the two surveillance systems, although 36 cases (11.5%) were not captured by either source. This suggests there was underreporting, despite the clinical severity of the disease. It is very important to improve

reporting by all physicians and microbiologists to the SDR and MDR to assess the impact of interventions such as immunization.

The estimated IMD incidence rate of 0.7/100, 000 persons-year found in the multinomial model is less than that found using capture-recapture (0.83/100,000 persons-year) but higher than that calculated using the SDR (0.56/100,000 persons-year) or MDR data (0.54/100,000 persons-year). Other European studies showed incidence rates of between 0.39 [23] and 1.18/100,000 persons-year. [25]

The sensitivity of the two sources were intermediate (67.9% for the SDR and 64.7% for the MRS). The lower sensitivity of the MRS may be due to the fact that the MRS is a sentinel system with a coverage of 82% of acute hospital beds and without private centres. In our series, 21 cases (10%) included in the SDR were reported by private centres, while only one case (0.5%) was reported to the MSR; this patient was finally transferred to a public hospital. The inclusion of cases that have an equal probability of selection in one source might lead to an overestimation. Other authors have reported this limitation when the hospital discharge data set includes probable cases which are not included in the reference centre. [25]

Death was registered in 22 cases (10.5%), similar to that reported in other European countries (ECDC) but slightly lower than that observed in Italy (14%) using the capture-recapture method. [23] All cases were reported to the SDR but only 50% were reported to the MRS, indicating that clinical data are better in the SDR than in the MRS. Other authors have used mortality data for capture-recapture analysis and concluded that all deaths were reported in notifiable systems. [26]

The sensitivity of the sources studied for the surveillance of IMD cannot be generalized to other diseases because physicians' or microbiologists' perception of the importance of IMD differs from that of other diseases. [29]

The main strength of this study is that the two sources had wide coverage. The SDR is a universal epidemiological surveillance source and, unlike the MDR, is a sentinel source, with a high coverage of 83%. Cases with PIC accounted for 85.5% of all cases reported to detect whether cases were coincident or not. In addition, the independence of the two sources was demonstrated, complying with the premise of the capture-recapture method.

A limitation of the study was that not all cases had the same probability of being selected from a given source. Cases diagnosed in private centres or public centres that did not participate in the MRS could not be reported by this system and this may explain, at least in part, the lower sensitivity than the SDR. This highlights the importance of including public and private centres to increase the robustness of the MRS. Another limitation was that we did not analyse the role of the electronic surveillance system, although a previous study detected greater sensitivity of the SDR when electronic surveillance was introduced. [30]

CONCLUSIONS

The sensitivity of enhanced surveillance through the combination of two complementary sources (statutory reporting by physicians and microbiological reporting by microbiologists) was higher than that of the individual sources. These systems are complementary and constitute the basic sources of information necessary for adequate epidemiological surveillance of IMD. Specific studies to estimate the factors associated with under-reporting are needed to reinforce epidemiological surveillance of this disease.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent of publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

PC analyzed and interpreted data, studied conception and design of the study and writes the manuscript; MV and NS did statistical analysis; GC revised and collected data; TG,SH,LR collected data; MJ revised the study and AD did critical revision and got funding.

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931 Figure 1. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

932 Figure 2. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

933

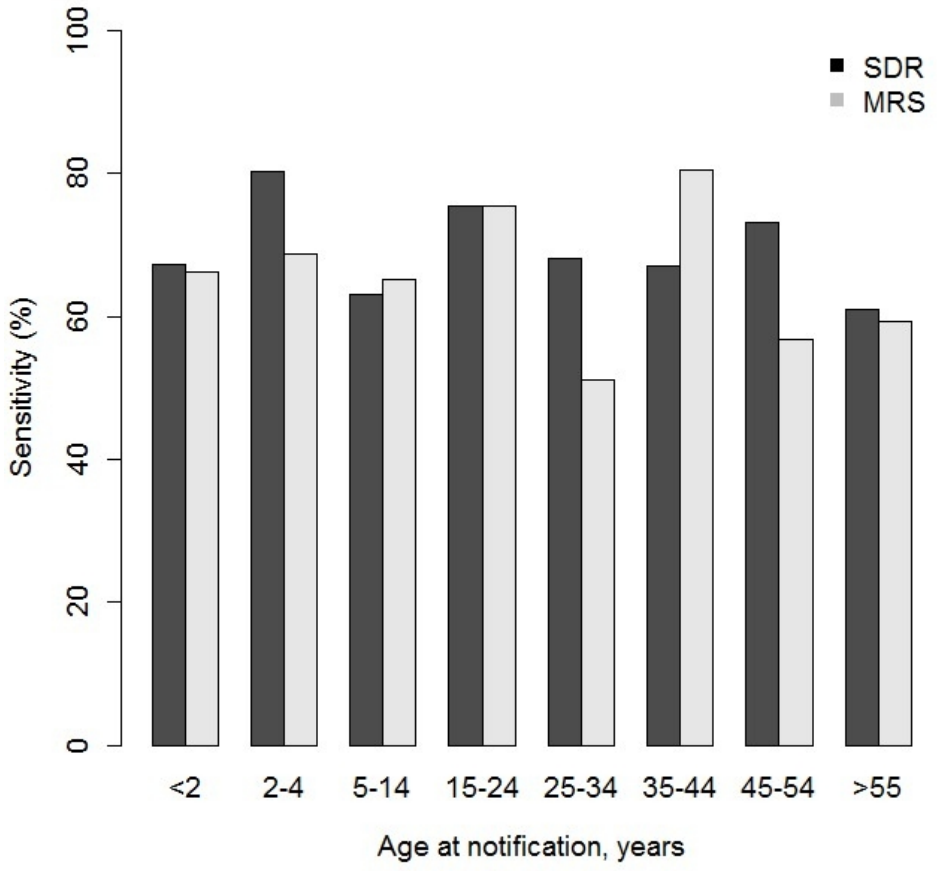

Figure 1. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

176x172mm (96 x 96 DPI)

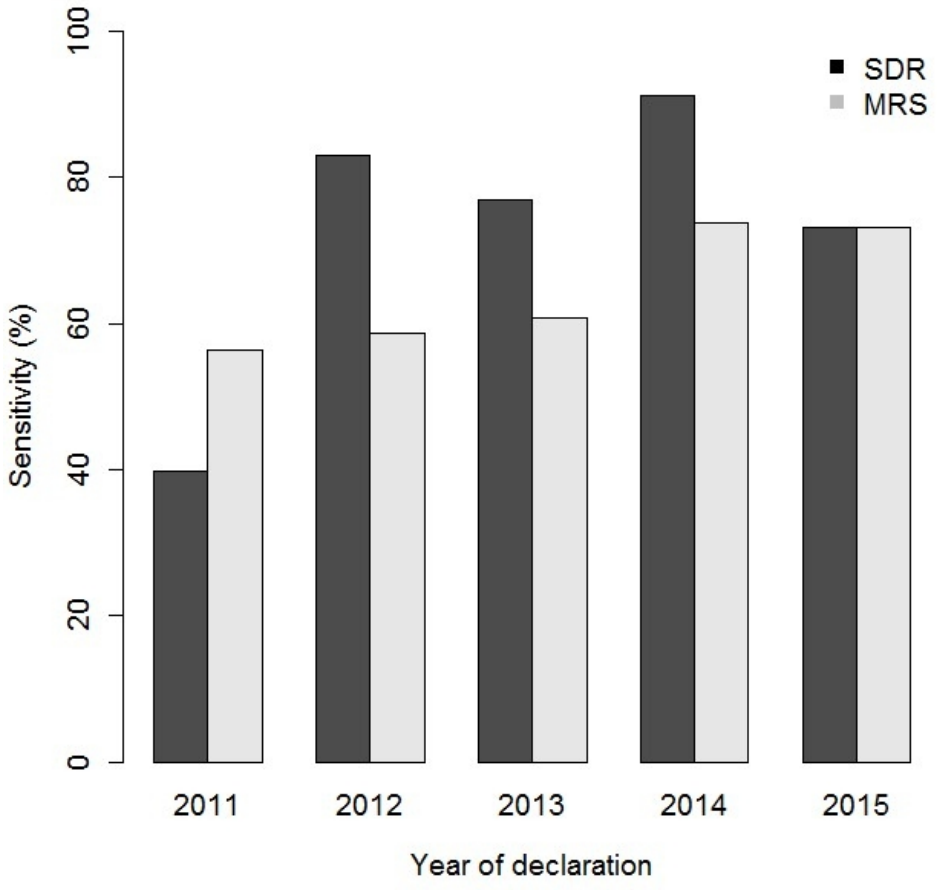

Figure 2. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

172x172mm (96 x 96 DPI)

Supplementary table 1. Capture–recapture analysis of serogroup B meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	164	153	114	17	220 (209, 232)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	***<0.001***
Age group									
<15 years	110	110	78	13	155 (146, 165)	71.0 (63.8, 78.1)	71.0 (63.8, 78.1)	0.0	*0.656*
≥15 years	53	42	35	4	64 (59, 69)	83.5 (74.3, 92.6)	66.1 (54.5, 77.8)	17.3	
Sex									
Male	86	76	62	6	106 (100, 112)	81.7 (74.3, 89.1)	72.2 (63.6, 80.7)	9.5	*0.099*
Female	78	77	52	13	116 (106, 126)	67.7 (59.1, 76.2)	66.8 (58.2, 75.4)	0.9	
Year of report									
2011-2013	95	91	60	18	144 (132, 157)	66.1 (58.3, 73.8)	63.3 (55.4, 71.2)	2.8	***0.002***
2014-2015	69	62	54	3	80 (76, 83)	87.1 (79.7, 94.5)	78.3 (69.2, 87.4)	8.8	
Size of municipality									
<10,000 people	22	24	20	1	27 (26, 28)	83.3 (69.1, 97.6)	90.9 (79.9, 100.0)	-7.6	*0.059*
≥10,000 people	137	114	91	12	172 (163, 181)	79.9 (73.9, 85.9)	66.5 (59.4, 73.5)	13.4	
Country of birth									
Spain	152	144	107	16	205 (194, 215)	74.4 (68.4, 80.4)	70.4 (64.2, 76.7)	3.9	*0.631*
Other countries	12	9	7	2	16 (13, 19)	78.9 (58.4, 99.5)	59.2 (34.5, 83.9)	19.7	
Number of hospital beds									
<200	49	52	33	9	77 (69, 86)	63.7 (53.0, 74.5)	67.6 (57.2, 78.1)	-3.9	*0.095*
>=200	113	101	81	8	141 (134, 148)	80.3 (73.7, 86.8)	71.7 (64.3, 79.2)	8.5	
Clinical form									
Meningitis	91	100	70	9	130 (122, 138)	70.1 (62.2, 77.9)	77.0 (69.7, 84.2)	-6.9	*0.972*
Sepsis	66	51	43	5	79 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	
Type of reporting centre									
Private	14	1	1	0	14 (14, 14)	100 (100, 100)	7.1 (-6.4, 20.6)	92.9	***0.004***
Public	149	152	113	13	201 (192, 210)	74.4 (68.4, 80.4)	75.9 (70, 81.8)	-1.5	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

Supplementary table 2. Capture–recapture analysis of serogroup C meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*p-value*
All cases	26	21	16	3	34 (30, 39)	76.7 (62.5, 90.9)	62.0 (45.6, 78.3)	14.8	***0.035***
Age group									
<15 years	4	4	4	0	4 (4, 4)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0	*0.992*
≥15 years	22	17	12	4	31 (25, 37)	71.4 (55.5, 87.4)	55.2 (37.6, 72.8)	16.2	
Sex									
Male	13	11	7	3	20 (15, 26)	65.0 (44.1, 85.9)	55.0 (33.2, 76.8)	10.0	*0.368*
Female	13	10	9	1	15 (13, 16)	90.3 (75.0, 100.0)	69.4 (45.7, 93.2)	20.8	
Year of report									
2011-2013	12	10	6	4	20 (14, 26)	61.9 (40.2, 83.5)	51.6 (29.3, 73.8)	10.3	*0.110*
2014-2015	14	11	10	1	16 (14, 17)	90.9 (76.6, 100.0)	71.4 (48.9, 94.0)	19.5	
Size of municipality									
<10,000 people	3	2	2	0	3 (3, 3)	100.0 (100.0, 100.0)	66.7 (13.3, 100.0)	33.3	*0.591*
≥10,000 people	21	15	12	3	27 (23, 30)	80.5 (65.3, 95.7)	57.5 (38.5, 76.4)	23.0	
Country of birth									
Spain	22	19	14	3	30 (26, 35)	74.1 (58.3, 89.8)	64.0 (46.7, 81.2)	10.1	*0.945*
Other countries	4	2	2	0	4 (4, 4)	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	50.0	
Number of hospital beds									
<200	7	5	5	0	7 (7, 7)	100.0 (100.0, 100.0)	71.4 (38.0, 104.9)	28.6	*0.283*
≥200	18	16	11	3	26 (22, 31)	69.5 (51.8, 87.2)	61.8 (43.1, 80.5)	7.7	
Clinical form									
Meningitis	16	16	11	3	24 (20, 27)	69.3 (50.4, 88.1)	69.3 (50.4, 88.1)	0.0	*0.908*
Sepsis	8	4	4	0	8 (8, 8)	100.0 (100.0, 100.0)	50.0 (15.4, 84.7)	50.0	
Type of reporting centre									
Private	4	0	0	0	4 (4, 4)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.992*
Public	22	21	16	2	29 (26, 33)	76.4 (60.9, 91.9)	72.9 (56.7, 89.2)	3.5	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

Supplementary table 3. Capture–recapture analysis of all deaths due to meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	22	11	11	0	22 (22, 22)	100.0 (100.0, 100.0)	50.0 (29.1, 70.9)	50.0	*0.104*
Age group									
<15 years	6	4	4	0	6 (6, 6)	100.0 (100.0, 100.0)	66.7 (28.9, 100.0)	33.3	*0.346*
≥15 years	16	7	7	0	16 (16, 16)	100.0 (100.0, 100.0)	43.8 (19.4, 68.1)	56.3	
Sex									
Male	16	7	7	0	16 (16, 16)	100.0 (100.0, 100.0)	43.8 (19.4, 68.1)	56.2	*0.346*
Female	6	4	4	0	6 (6, 6)	100.0 (100.0, 100.0)	66.7 (29.0, 100.0)	33.3	
Year of report									
2011-2013	16	6	6	0	16 (16, 16)	100.0 (100.0, 100.0)	31.3 (8.5, 54.0)	68.8	*0.080*
2014-2015	6	5	5	0	6 (6, 6)	100.0 (100.0, 100.0)	83.3 (53.5, 100.0)	16.7	
Size of municipality									
<10,000 people	3	3	3	0	3 (3, 3)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0	*0.991*
≥10,000 people	19	8	8	0	19 (19, 19)	100.0 (100.0, 100.0)	42.1 (19.9, 64.3)	57.9	
Country of birth									
Spain	20	10	10	0	20 (20, 20)	100.0 (100.0, 100.0)	50.0 (28.1, 71.9)	50.0	*1.000*
Other countries	2	1	1	0	2 (2, 2)	100.0 (100.0, 100.0)	50.0 (0.0, 100.0)	50.0	
Number of hospital beds									
<200	4	2	2	0	4 (4, 4)	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	50.0	*0.822*
≥200	16	9	9	0	16 (16, 16)	100.0 (100.0, 100.0)	56.3 (31.9, 80.6)	43.7	
Clinical form									
Meningitis	7	4	4	0	7 (7, 7)	100.0 (100.0, 100.0)	57.1 (20.5, 93.8)	42.9	*0.648*
Sepsis	15	7	7	0	15 (15, 15)	100.0 (100.0, 100.0)	46.7 (21.4, 71.9)	53.3	
Type of reporting centre									
Private	2	0	0	0	2 (2, 2)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.992*
Public	20	11	11	0	20 (20, 20)	100.0 (100.0, 100.0)	55 (33.2, 76.8)	45	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,11,12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	5,14,15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Estimation of the incidence of invasive meningococcal disease using a capture-recapture model based on two independent surveillance systems, in Catalonia, Spain

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ABSTRACT

Objectives: Invasive meningococcal disease (IMD) is an urgent notifiable disease and its early notification is essential to prevent cases. The objective of the study was to assess the sensitivity of two independent surveillance systems, and to estimate the incidence of IMD.

Design: We used **c**apture-recapture model based on two independent surveillance systems**,** the statutory disease reporting system (SDR) and the microbiological reporting system (MRS) of the Public Health Agency of Catalonia, between 2011 and 2015. The capture-recapture analysis and 95% confidence intervals were calculated using the Chapman formula. Multivariate vector generalized linear model was performed for adjusted estimation.

Measures: The variables collected were age, sex, year of report, size of municipality (< 10,000 and ≥ 10,000), clinical form, death, serogroup, country of birth and type of reporting centre (private and public).

Results: The sensitivity of the two combined surveillance systems was 88.5% (85.0-92.0). SDR had greater sensitivity than the MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0). In 2014-2015, the sensitivity of both systems was higher (80.6%; 73.2–87.9 vs. 73.4%; 65.2–81.6) than in 2011-2013 (59.3%; 52.6–66.0 vs. 58.3%; 51.6–65.1). In private centres, the sensitivity was higher for SDR than for MRS (100%; 100–100 vs. 4.8%; -4.4–13.9). The adjusted estimate of IMD cases was lower than that obtained using the Chapman formula (279; 266–296 vs. 313; 295–330). The estimated adjusted incidence of IMD was 0.7/100,000 persons-year.

Conclusions: The sensitivity of enhanced surveillance through the combination of two complementary sources was higher than for the sources individually. Factors associated with under-reporting in different systems should be analysed to improve IMD surveillance.

Keywords:

Meningococcal disease, Capture-recapture, estimated incidence, surveillance systems.

Strengths and limitations of this study

- Early notification of Invasive meningococcal disease is essential to prevent cases.
- This study was strengthened by a wide coverage by means of two epidemiological surveillance sources: The Statutory Disease Reporting System (SDR), based on passive reporting of health professionals, and the Microbiological Reporting System (MRS), based on confirmed-laboratory cases.
- SDR had greater sensitivity than MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0) but the sensitivity of both surveillance sources together was higher than each source individually.
- Factors associated with under-reporting should be analysed for invasive meningococcal disease (IMD) surveillance.

BACKGROUND

Invasive meningococcal disease (IMD) continues to be an important cause of morbidity and mortality, mainly in children aged < 4 years and adolescents. [1]

In the European regions, the incidence rate of confirmed IMD cases was 0.62/100,000 persons-year in 2018 [2], and in Spain it was 0.86/100,000 persons. [3] Six serogroups (A, B, C, W, X, Y) currently cause almost all cases of this life-threatening disease worldwide. Case fatality rate is about 10% in developed countries [4-6], and 40-65% present with meningitis, but meningococcemia and pneumonia are also frequent [4], being the serogroup involved related both with the case fatality rate [7] and the predominant clinical form. [8] Serogroup B causes more than a third part of IMD [4,9] but in some countries or population groups the proportion is even higher. [10,11] In Spain, from 2009 to 2018, serogroup B accounted for 64% of IMD cases. [12] A high proportion, up to 60% [13] of IMD cases, are affected by a range of sequelae and health related impairement in the quality of life of survivors and their families. [14]

IMD is an urgent notifiable disease and its early notification is essential to provide an adequate public health response in patients and their close contacts to prevent further cases. Epidemiological surveillance allows monitoring of the impact of public health interventions, including vaccination programmes. Therefore, a robust epidemiological and microbiological

system with timely and accurate surveillance providing information on the frequency of cases and the distribution of circulating serogroups is crucial.

Evaluations of surveillance systems should be conducted regularly to increase their utility. [15-17] There are two reporting systems for the epidemiological surveillance of communicable disease in Catalonia: the statutory disease reporting system (SDR) and the microbiological reporting system (MRS). [18]

The capture-recapture method is a statistical method for estimating the real incidence of diseases in a population with two or more information sources. [19, 20] The method is valid if four conditions are met: 1) the population under study has to be closed, i.e., there should be no changes during the study period; 2) there must be a method of determining whether an individual identified by one source is the same as an individual identified by the other; 3) each individual must have the same probability of being captured by either system; 4) the systems must be independent.

The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD.

METHODS

Information sources

Catalonia is a region in the northeast of Spain with a population of 7,508,106 in 2015. [21]

The SDR is a passive surveillance system through which health professionals report all infectious diseases subject to surveillance. The reporting of cases to the Public Health Agency of Catalonia (PHAC) is mandatory and includes confirmed cases of IMD and is regulated by a Decree. [18, 22]

The MRS is a surveillance system that consists of microbiologists notifying laboratory confirmed microorganisms that cause infectious diseases. The main objectives of the MRS are to confirm

suspected cases of infectious diseases through the identification of the microorganisms and serogroups involved and to determine trends and changes in epidemiological patterns and microbiological resistance. [23]

The MRS was non-compulsory until 2015 and involved 50 health care centres representing over 83% of acute hospital beds. [24] Confirmed IMD cases were reported by microbiologists including sex, age, clinical presentation (meningitis, bacteraemia of unknown focus and other clinical presentations), serogroup and diagnostic method.

Both systems belong to the PHAC epidemiological surveillance network and, since 2014, transfer information automatically, but the independence of the sources is maintained.

Cases definition, inclusion, and exclusion criteria

A confirmed case of IMD was defined as laboratory confirmed if at least one of the following criteria was fulfilled: isolation in cultures or detection of *Neisseria meningitidis* DNA by PCR in a normally sterile site, detection of gram-negative diplococci or *N. meningitidis* antigen in cerebrospinal fluid.

Data collection

We made a retrospective study of confirmed IMD cases in Catalonia from January 2011 to December 2015. We extracted all IMD records from the MRS and SDR and linked the databases using the personal identification code (PIC). When the PIC was not available, data on notification, age and sex were used to identify duplicates between the two sources. In cases with inconclusive matching, the hospital was used as a fifth matching criterion.

Estimates were made for the entire 5-year period and by age, sex, year of report, size of municipality (<10,000 and ≥10,000), country of birth, number of hospital beds, clinical form (meningitis, with or without sepsis, sepsis, and others), serogroup, death and reporting centre (private or public).

Ethics statement

The study was not submitted for research ethics approval as the activities described were conducted as part of the legislated mandate of the Health Department of Catalonia, the competent authority for surveillance of communicable diseases according to Decree 203/2015 of the 15 September which created the epidemiological surveillance network of Catalonia. [18] All the study activities formed part of public health surveillance and did not require informed consent. Personal data were used only for the matching process and measures to protect the confidentiality of personal data were applied (access to the data restricted to the personnel involved in data analysis, and removal of personal data from the datasets after matching).

Patient and public involvement

No patient involved

Statistical methods

The total number of IMD cases was estimated using the two-source capture-recapture method, which uses Chapman's formula, [25] developed to reduce bias due to small samples:

$$N = \frac{(L1+1)(L2+1)}{a+1} - 1$$

$$95\%CI = N \pm 1.96\sqrt{\frac{(L1+1)(L2+1)(L1-a)(L2-a)}{(a+1)^2(a+2)}}$$

where L1 is the number of cases in the SDR dataset, L2 is the number of cases reported to MRS, and **a** is the number of cases captured by both systems. The sensitivity (Se) of case ascertainment by the two sources was also calculated as the proportion of true cases detected by each source, i.e. Se (1) =L1/N for source 1 and Se (2) =L2/N for source 2. The sensitivity of both sources combined was calculated as the proportion of cases detected by one of the two sources or both, i.e., Se (1, 2) =(L1+L2-**a**)/N.

The independence of the sources was considered when applying the capture-recapture method. [26, 27] In the two-by-two table, where **a** represents cases reported by two sources or combinations of sources, **b** and **c** cases reported exclusively by either of the two sources and **x** the estimated non-reported cases by either of the sources, the odds ratio (OR = ax/bc) should not differ from one.

As a multivariate model, a vector generalized linear model (VGLM) from the generalized additive model (GAM) framework [28] was used to evaluate patient characteristics and the probability of capture by the different sources taking into account the covariates: age (<15 vs >=15), gender, year of notification (2011-2013 vs 2014-2015), size of the municipality (<10,000 vs >=10.000), country of birth (Spain vs other), number of hospital beds (<200 vs >=200) and diagnosis (meningitis vs septicaemia). The outcome for the model is a two column matrix with 0 and 1 indicating if the record is identified by SDR or MRS. We used a backwards stepwise procedure (using likelihood ratio tests, with a p-value >0.2 as the criterion for removing variables from the model) [29, 30] to eliminate covariates, starting with a full model including all described covariates, and we used the parameter estimates from the model to estimate the sizes of population subgroups and calculate incidence rates. The 95% confidence intervals (CI) were calculated, allowing for uncertainty in the total number of cases estimated. For each of the described covariates, VLGM with source notification as outcome was used to test differences in sensitivities. All analyses were made using R software version 3.0.1.

RESULTS

Patient characteristics

Patient characteristics by source are shown in Table 1. From 2011 to 2015, 212 IMD cases were reported to the SDR and 202 cases to the MRS, representing an incidence of 0.56 and 0.54 /100,000 persons-year, respectively. IMD due to serogroup B was the most-frequently reported serogroup (77.4% and 75.7% in the SDR and MRS, respectively). Around 63% of patients were

aged < 15 years; the mean age was 21.4 for the SDR and 20.5 years for the MRS. Male sex was more frequent in the SDR (52.4%) than in the MRS (49%). The SDR presented the most cases in 2015 (48 cases; 22.6%) and the MRS (61 cases; 30.2%) in 2011. The SDR reported that 84% of patients lived in a municipality of ≥10,000 people compared with 73% in the MRS. In both sources, the number of cases declared in a hospital of ≥200 beds were around 70%. The main clinical form in both sources was meningitis (54.7% and 64.8%, respectively) and sepsis (38.7% and 32.7%, respectively). Reports from private centres represented 10% of cases in the SDR and 0.5% in the MRS. Twenty-two cases (10.4%) cases reported by the SDR died compared with 11 cases (5.4%) reported by the MRS.

Table 1. Sociodemographic, clinical and microbiological characteristics of invasive meningococcal disease cases reported to the SDR and MRS, Catalonia 2011-2015

	SDR (n=212)	MRS (n=202)
Age groups		
Mean (SD)	21.4 (27.9)	20.5 (26.7)
Median (IQR)	6 (36)	6 (32.3)
<2 years, n (%)	62 (29.8%)	61 (30.7%)
2 - 4 years, n (%)	35 (16.8%)	30 (15.1%)
5 - 14 years, n (%)	34 (16.3%)	35 (17.6%)
15 - 24 years, n (%)	12 (5.8%)	12 (6.0%)
25 - 34 years, n (%)	12 (5.8%)	9 (4.5%)
35 - 44 years, n (%)	10 (4.8%)	12 (6.0%)
45 - 54 years, n (%)	9 (4.3%)	7 (3.5%)
>55 years, n (%)	34 (16.3%)	33 (16.6%)
NAs	1 (0.5%)	2 (1.0%)
Sex, n (%)		
Male	111 (52.4%)	99 (49.0%)
Female	101 (47.6%)	103 (51.0%)
Year of report, n (%)		
2011	43 (20.3%)	61 (30.2%)
2012	41 (19.3%)	29 (14.4%)
2013	38 (17.9%)	30 (14.9%)
2014	42 (19.8%)	34 (16.8%)
2015	48 (22.6%)	48 (23.8%)
Size of municipality, n (%)		
<10,000 people	27 (12.7%)	28 (13.9%)
≥10,000 people	177 (83.5%)	148 (73.3%)
NAs	8 (3.8%)	26 (12.9%)
Country of birth, n (%)		
Spain	194 (91.5%)	188 (93.1%)
Other countries	18 (8.5%)	14 (6.9%)
Number of hospital beds, n (%)		
<200	60 (28.3%)	65 (32.2%)
≥200	149 (70.3%)	137 (67.8%)

NAs	3 (1.4%)	0 (0.0%)
Clinical form, n (%)		
Meningitis	116 (54.7%)	131 (64.8%)
Septicaemia	82 (38.7%)	66 (32.7%)
Other forms	14 (6.6%)	4 (2.0%)
NAs	0 (0.0%)	1 (0.5%)
Serogroup, n (%)		
A	0 (0.0%)	2 (1.0%)
B	164 (77.4%)	153 (75.7%)
C	26 (12.3%)	21 (10.4%)
W135	4 (1.9%)	6 (3.0%)
Y	5 (2.4%)	2 (1.0%)
Y/ W135	1 (0.5%)	1 (0.5%)
Non-groupable	6 (2.8%)	4 (2.0%)
NAs	6 (2.8%)	13 (6.4%)
Type of reporting centre		
Private	21 (10.0%)	1 (0.5%)
Public	190 (90.0%)	201 (99.5%)

NAs: Not available; SDR: Statutory disease reporting; MDR: Microbiological reporting system

Capture-recapture analysis

The odds ratio (OR) was 1.01 (95%CI 0.62-1.66), reinforcing the independence of the two sources.

During the period studied, 212 and 202 IMD cases were reported by the SDR and MRS, respectively. One hundred thirty-seven cases (43.8%) coincided in both sources and 36 cases (11.5%) were not reported to either source. The estimated number of cases was 313 (95% CI 295–330) (Figure 1) and the estimated incidence rate was 0.83/100,000 persons-year.

The sensitivity of the SDR was 67.9% (95%CI 62.7-73.1) and that of the MRS was 64.7% (95%CI 59.4-70.0) (P-<0.001) (Table 2). The sensitivity increased to 88.5% (95%CI 85.0-92.0) when the datasets were combined.

Table 2. Capture–recapture analysis of all invasive meningococcal disease cases reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	212	202	137	36	313 (295, 330)	67.9 (62.7, 73.1)	64.7 (59.4, 70.0)	3.2	***<0.001***
Age group									
<15 years	131	126	87	20	190 (177, 203)	69.1 (62.6, 75.7)	66.5 (59.8, 73.2)	2.6	*0.468*
≥15 years	80	74	49	16	121 (109, 133)	66.4 (58.0, 74.8)	61.4 (52.7, 70.1)	5.0	
Sex									
Male	111	99	71	16	155 (144, 166)	71.8 (64.7, 78.9)	64.0 (56.5, 71.6)	7.8	*0.588*
Female	101	103	66	20	158 (145, 171)	64.2 (56.7, 71.7)	65.5 (58.1, 72.9)	-1.3	
Year of report									
2011-2013	122	120	71	35	206 (187, 226)	59.3 (52.6, 66.0)	58.3 (51.6, 65.1)	1.0	***<0.001***
2014-2015	90	82	66	6	112 (106, 118)	80.6 (73.2, 87.9)	73.4 (65.2, 81.6)	7.2	
Size of municipality									
<10,000 people	27	28	22	2	35 (32, 37)	78.7 (65.0, 92.4)	81.6 (68.7, 94.6)	-2.9	*0.100*
≥10,000 people	177	148	110	23	238 (225, 252)	74.4 (68.9, 80.0)	62.2 (56.1, 68.4)	12.2	
Country of birth									
Spain	194	188	127	32	287 (271, 304)	67.6 (62.2, 73.0)	65.5 (60.0, 71.0)	2.1	*0.696*
Other countries	18	14	10	3	25 (20, 30)	72.3 (54.7, 89.9)	56.2 (36.7, 75.7)	16.1	
Number of hospital beds									
<200	60	65	40	13	97 (87, 108)	61.7 (52.1, 71.4)	66.9 (57.5, 76.2)	-5.1	*0.514*
≥200	149	137	97	22	210 (197, 224)	70.9 (64.7, 77.0)	65.2 (58.7, 71.6)	5.7	
Clinical form									
Meningitis	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	*0.936*
Sepsis	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	
Type of reporting centre									
Private	21	1	1	0	21 (21, 21)	100 (100, 100)	4.8 (-4.4, 13.9)	95.2	***0.002***
Public	190	201	136	26	281 (267, 295)	67.7 (62.2, 73.2)	71.6 (66.4, 76.9)	-3.9	
Serogrup									
B	164	153	114	17	220 (209, 231)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	*0.636*

C	26	21	16	3	34 (29, 39)	76.7 (62.5, 90.9)	61.9 (45.6, 78.3)	14.8	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

There were no differences in sensitivity between in <15 years and ≥15 years age group (P-value=0.468) in either source although it was higher in the <15 years (69.1%; 95%CI 62.6-75.7 in the SDR and 66.5%; 95%CI 59.8-73.2 in the MRS). The age groups with the highest sensitivity were 2-4 years in the SDR, with 80.3% (95%CI 68.5-92.1), and 35-44 years in the MRS, with 80.5% (95%CI 60.4–100.0) (Figure 2).

In 2011-2013, sensitivity for the SDR and the MRS were 59.3% (95%CI 52.6-66) and 58.3% (95%CI 51.6-65.1), respectively, lower than that in 2014-2015 (80.6%; 95%CI 73.2-87.9, for the SDR and 73.4%; 95%CI 65.2-81.6, for the MRS (P<0.001)) (Table 2). 2014 showed the highest sensitivity for both sources: 91.3% (95%CI 83.2-99.4) for the SDR and 73.9% (95%CI 61.2-86.6) for the MRS (Figure 3). 2011 was the only year in which the MRS had a higher sensitivity than the SDR (56.4%; 95%CI 47.1-65.8 and 39.8%; 95%CI 30.6-49.0, respectively). In private centres the sensitivity of the SDR was 100% (95%CI 100-100) and that of the MRS was 4.8% (95%CI -4.4-13.9). No differences were found in other characteristics analysed.

For meningitis, 116 and 131 cases were reported by the SDR and the MRS, respectively. The estimated number of meningitis cases was 181, and 18 cases were not reported by either source. The highest sensitivity was detected in the MRS (72.5%; 95% CI 66-79) compared with the SDR (64.2%; 95%CI 57.2-71.2) (P<0.001) (Table 3). 2014-2015 showed a higher sensitivity in both sources compared with 2011-2013: 82.4% (95%CI 72.7-92) in the MRS and 75.6% (95%CI 64.7-86.5) in the SDR. Public centres had a higher sensitivity in the MRS (77.7%; 95%CI 71.4-84.0) and in the SDR (63.9%; 95%CI 56.6-71.2) (P<0.037).

Table 3. Capture–recapture analysis of meningococcal meningitis reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	***<0.001***
Age group									
<15 years	72	81	51	13	115 (104, 125)	63.1 (54.3, 72.0)	71.0 (62.7, 79.3)	-7.9	*0.682*
≥15 years	43	49	32	6	66 (60, 73)	65.5 (53.9, 77.0)	74.6 (64.1, 85.1)	-9.1	
Sex									
Male	62	69	47	7	91 (84, 98)	68.2 (58.6, 77.8)	75.9 (67.1, 84.7)	-7.7	*0.245*
Female	54	62	37	12	91 (81, 101)	59.9 (49.8, 70.0)	68.7 (59.2, 78.3)	-8.9	
Year of report									
2011-2013	71	82	47	18	124 (111, 137)	57.5 (48.8, 66.2)	66.4 (58.1, 74.7)	-8.9	***0.013***
2014-2015	45	49	37	3	60 (56, 64)	75.6 (64.7, 86.5)	82.4 (72.7, 92.0)	-6.7	
Size of municipality									
<10,000 people	19	20	16	1	24 (22, 26)	80.2 (64.1, 96.2)	84.4 (69.8, 99.0)	-4.2	*0.165*
≥10,000 people	93	93	65	12	133 (124, 143)	70.0 (62.2, 77.8)	70.0 (62.2, 77.8)	0.0	
Country of birth									
Spain	107	120	77	17	167 (155, 179)	64.3 (57.0, 71.5)	72.1 (65.3, 78.9)	-7.8	*0.862*
Other countries	9	11	7	1	14 (12, 17)	64.3 (39.2, 89.4)	78.6 (57.1, 100.0)	-14.3	
Number of hospital beds									
<200	31	40	23	6	54 (47, 61)	57.7 (44.5, 70.9)	74.5 (62.8, 86.2)	-16.8	*0.516*
≥200	84	91	61	11	126 (116, 135)	67.1 (58.9, 75.4)	72.7 (64.9, 80.5)	-5.6	
Type of reporting centre									
Private	9	1	1	0	9 (9, 9)	100.0 (100.0, 100.0)	11.1 (-9.4, 31.6)	88.9	***0.037***
Public	107	130	83	14	168 (158, 178)	63.9 (56.6, 71.2)	77.7 (71.4, 84.0)	-13.7	
Serogrup									
B	91	100	70	9	130 (122, 138)	70.1 (62.2, 77.9)	77.0 (69.7, 84.2)	-6.9	*0.641*
C	16	16	11	2	23 (19, 27)	69.3 (50.4, 88.1)	69.3 (50.4, 88.1)	0	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

For septicaemia, 82 cases and 66 cases were reported by the SDR and the MRS, respectively. The sensitivity was higher for the SDR (75.9%; 95%CI 67.9-84) than the MRS (61.1%; 95%CI 51.9-70.3) (Table 4). There were 108 estimated cases and 10 cases were not reported by either source. The sensitivity was higher in the <15 years than in the ≥15 years in both sources, but higher in the SDR (81.1%; 95%CI 71.1-91.1 versus 71%; 95%CI 59.4-82.5 for the MRS; P=0.036), and higher in 2014-2015 than in 2011-2013 (87.6%; 95%CI 78-97.3 for the SDR and 71.9%; 95%CI 58.7-85.1 for the MRS) (P<0.015).

Serogroup B (Supplementary Table 1) showed the sensitivity of the SDR was higher than that of the MRS (74.6%; 95%CI 68.8-80.3 and 69.6%; 95%CI 63.5-75.6, respectively). There were differences according to the period and the type of centre. In 2014-2015, the sensitivity was 87.1% (95%CI 79.7-94.5) for the SDR and 78.3% (95%CI 69.2-87.4) for the MRS (P<0.002). In private centres, the sensitivity in SDR was 100% compared with 7.1% (95%CI -6.4-20.6) (P=0.004) in MRS. The sensitivity was higher for IMD serogroup C cases in SDR than in MRS (76.7%; 95%CI 62.5-90.9 and 62%; 95%CI 45.6-78.3, respectively) (Supplementary Table 2).

All 22 deaths were reported in the SDR (CFR: 10.4%), and the sensitivity of the SDR was higher than that of the MRS (100%; 95CI% 100-100 vs 50%; 95%CI 29.1-70.9, P=0.104). No differences were found in other characteristics analysed (Supplementary Table 3).

Table 4. Capture–recapture analysis of meningococcal septicaemia reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	***<0.001***
Age at notification, years									
<15 years	48	42	34	4	60 (55, 64)	81.1 (71.1, 91.1)	71.0 (59.4, 82.5)	10.1	***0.036***
≥15 years	34	23	16	8	49 (40, 58)	70.3 (57.4, 83.1)	47.5 (33.4, 61.6)	22.7	
Sex									
Male	43	27	22	5	53 (47, 59)	81.8 (71.3, 92.2)	51.3 (37.8, 64.8)	30.4	*0.315*
Female	39	39	28	5	55 (49, 60)	72.0 (60.0, 83.9)	72.0 (60.0, 83.9)	0.0	
Year of report									
2011-2013	43	34	22	11	66 (56, 77)	65.2 (53.6, 76.7)	51.5 (39.5, 63.6)	13.6	***0.015***
2014-2015	39	32	28	2	45 (42, 48)	87.6 (78.0, 97.3)	71.9 (58.7, 85.1)	15.7	
Size of municipality									
<10,000 people	7	7	5	1	10 (8, 12)	72.2 (44.0, 100.0)	72.2 (44.0, 100.0)	0.0	*0.918*
≥10,000 people	71	52	43	6	86 (80, 93)	82.9 (74.9, 90.8)	60.7 (50.3, 71.0)	22.2	
Country of birth									
Spain	73	63	47	9	98 (90, 106)	74.7 (66.1, 83.3)	64.5 (55.0, 74.0)	10.2	*0.275*
Other countries	9	3	3	0	9 (9, 9)	100.0 (100.0, 100.0)	33.3 (2.5, 64.1)	66.7	
Number of hospital beds									
<200	25	23	16	4	36 (31, 42)	70.0 (55.0, 85.1)	64.4 (48.7, 80.1)	5.6	*0.831*
≥200	56	43	34	6	71 (65, 78)	79.2 (69.7, 88.7)	60.8 (49.4, 72.2)	18.4	
Type of reporting centre									
Private	9	0	0	0	9 (9, 9)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.988*
Public	73	66	50	8	97 (89, 104)	75.9 (67.3, 84.4)	68.6 (59.3, 77.9)	7.3	
Serogrup									
B	66	51	43	4	78 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	*0.661*
C	8	4	4	0	8 (8, 8)	100 (100, 100)	50.0 (15.4, 84.7)	50.0	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

The results of the multivariate model for all cases are shown in Table 5. The variables considered to define the sensitivity of the two sources were year of report (2011-2013 versus 2014-2015) and size of municipality. With these variables in the model, the adjusted estimate of the total number of cases was 279 cases (95%CI 266-296) and the estimated incidence rate was 0.7/100,000 persons-year.

Table 5. Variables defining the sensitivity of the SDR and MRS in detecting invasive meningococcal diseases cases. Multivariate model.

	OR (95%CI)	*p-value*
Year of report (2014-2015)	2.29 (1.35, 3.89)	***0.002***
Size of municipality (≥10,000 people)	0.51 (0.23, 1.12)	*0.093*

OR: odds ratio; n estimate: 279 (266, 296)

DISCUSSION

The sensitivity obtained by combining the two surveillance system for IMD cases was 88.5%, greater than for each source. Globally, the SDR showed higher sensitivity than the MDR, mainly for cases of sepsis, serogroup B and serogroup C, although for meningitis the sensitivity of the MDR was higher than that of the SDR.

Sensitivity of SDR was 67.9%, very close to that of 66.5% found by Andrianou et al. in Italy in a study carried out in 2018 using the hospital discharge records system as the external source. [31] Other studies found greater sensitivities by combining data systems than we did. Baldovin et al. [32] in Italy, reported an overall sensitivity of 94.7% by combining four data sources (mandatory notification system, laboratory surveillance, invasive bacterial surveillance and hospital discharge). Jansson et al. [33], in Sweden, found a global sensitivity of 98.7%, 91.1% for clinical notification and 85.4% for laboratory reporting. In Austria a good agreement between the National Reference Center for meningococci and the hospital discharge was found, although a clinical review of hospital discharge data was necessary to detect false positive cases recorded. [34]

Globally, the sensitivity was similar in children aged <15 years than in persons aged ≥15 years in both sources (69.1% for the SDR and 66.5% for the MRS; P=0.468). The differences could be because there is greater sensibilitazion to declare pediatric cases than adult cases or because there are differences on IMD incidence according to age. [9] Gibson et al., [35] in Australia, analysed IMD sensitivity in children aged < 15 years in three sources: notifiable system, hospitalized patients and mortality data. They found a greater sensitivity (99.5%) than we did, although 15% of hospitalized children were false-positive cases.

Sensitivity was higher in 2014-2015 than in 2011-2013 for both sources (SDR and MRS). SDR had overall higher sensitivity for IMD cases, septicaemia cases as well as serogroup B and C cases, but not for meningitis cases for which MRS had higher sensitivity. The improvement in notification in the years 2014-2015 may be due to different causes, one could be that there is greater awareness for the notification of infectious diseases to public health surveillance systems, although it should be analyzed in subsequent studies. In a different way, Andrianou et al [31] compared the surveillance of the Italian IMD with the registry of hospital discharges, and found a lower sensitivity in 2018 compared to 2015-2017. This yearly evaluation allows the detection of problems in the notification process.

We found a greater sensitivity for meningitis in the MRS than in the SDR (72.5% vs 64.2%) but not for septicaemia (61.1% vs 75.9%). Multiple reasons could explain this fact. A possible explanation is that meningitis has a specific section in MRS for reporting while septicaemia is reported in bacteraemia of unknown focus section and it could be confused. It is important to determine the reason for this lower sensitivity to septicaemia in order to improve the completeness of MRS reporting. It is difficult to compare our results with those of other studies, since other sources of information were used or the independence of data sources was presumed but not demonstrated, [34] which is essential when using the capture-recapture method.

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Notification of confirmed cases of IMD by laboratories is essential in epidemiological surveillance. [36] Molecular information on circulating serogroups that is required to implement public health measures such as vaccination is essential to control the disease [37] and evaluate the impact of available vaccines.

In the absence of automated electronic reporting, monitoring and increasing the speed of laboratory reports may allow the public health department to administer chemoprophylaxis and vaccination to contacts. [27] Although a higher sensitivity has been reported for electronic reporting than for paper-based reports by some authors, [38] during the study period, electronic surveillance was used in the SDR but not in the MDR, which may explain, at least in part, why the MDR had a lower sensitivity than the SDR. [39]

In the multivariate model, the 2014-2015 period and the size of the municipality show a higher sensitivity in the SDR, suggesting that IMD was well recorded in the two surveillance systems, although 36 cases (11.5%) were not captured by either source. This suggests there was underreporting, despite the clinical severity of the disease. Other authors have also found underreporting of this disease. [40] It is very important to improve reporting by all physicians and microbiologists to the SDR and MDR to assess the impact of interventions such as immunization.

The estimated IMD incidence rate of 0.7/100, 000 persons-year found in the multivariate model is less than that found using capture-recapture (0.83/100,000 persons-year) but higher than that calculated using the SDR (0.56/100,000 persons-year) or MDR data (0.54/100,000 persons-year). Other European studies showed incidence rates of between 0.39 [32] and 1.18/100,000 persons-year. [34]

The sensitivity of the two sources were intermediate (67.9% for the SDR and 64.7% for the MRS). The lower sensitivity of the MRS may be due to the fact that the MRS is a sentinel system with a coverage of 83% of acute hospital beds and without private centres. In our series, 21 cases (10%)

included in the SDR were reported by private centres, while only one case (0.5%) was reported to the MSR; this patient was finally transferred to a public hospital. The inclusion of cases that have an equal probability of selection in one source might lead to an overestimation. Other authors have reported this limitation when the hospital discharge data set includes probable cases which are not included in the reference centre. [34]

Death was registered in 22 cases (10.5%), similar to that reported in other European countries [2] but slightly lower than that observed in Italy (14%) using the capture-recapture method. [32] All cases were reported to the SDR but only 50% were reported to the MRS, indicating that clinical data are better in the SDR than in the MRS. Other authors have used mortality data for capture-recapture analysis and concluded that all deaths were reported in notifiable systems. [34]

The sensitivity of the sources studied for the surveillance of IMD cannot be generalized to other diseases because physicians' or microbiologists' perception of the importance of IMD differs from that of other diseases. [38]

The main strength of this study is that the two sources had wide coverage. The SDR is a universal epidemiological surveillance source and, unlike the MDR, is a sentinel source, with a high coverage of 83%. Cases with PIC accounted for 85.5% of all cases reported to detect whether cases were coincident or not. In addition, the independence of the two sources was demonstrated, complying with the premise of the capture-recapture method.

A limitation of the study was that not all cases had the same probability of being selected from a given source. Cases diagnosed in private centres or public centres that did not participate in the MRS could not be reported by this system and this may explain, at least in part, the lower sensitivity than the SDR. This highlights the importance of including public and private centres to increase the robustness of the MRS. Another limitation was that we did not analyse the role of

the electronic surveillance system, although a previous study detected greater sensitivity of the SDR when electronic surveillance was introduced. [39]

CONCLUSIONS

The sensitivity of enhanced surveillance through the combination of two complementary sources (statutory reporting by physicians and microbiological reporting by microbiologists) was higher than that of the individual sources. These systems are complementary and constitute the basic sources of information necessary for adequate epidemiological surveillance of IMD. Specific studies to estimate the factors associated with under-reporting are needed to reinforce epidemiological surveillance of this disease.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent of publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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PC analyzed and interpreted data, studied conception and design of the study and writes the manuscript; MV and NS did statistical analysis; GC revised and collected data; TG,SH,LR collected data; MJ revised the study and AD did critical revision and got funding.

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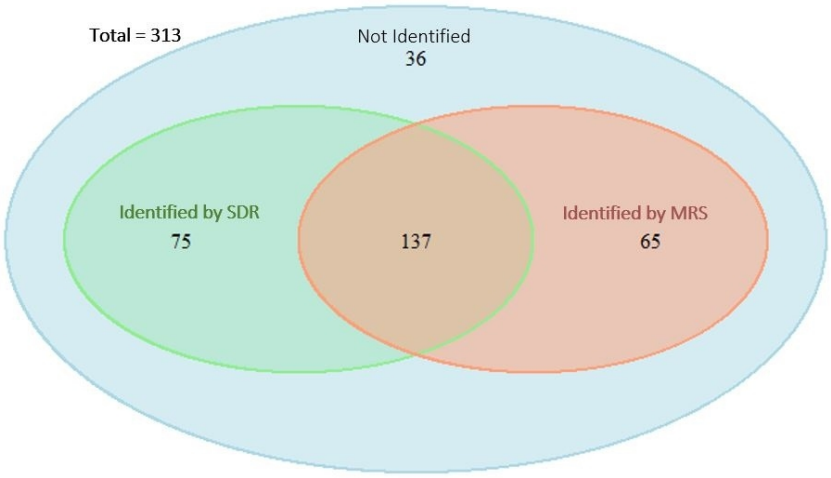
Figure 1. Venn diagram of the capture–recapture analysis of two datasets to estimate the total number of invasive meningococcal disease cases, Catalonia 2011-2015



Venn diagram of the capture–recapture analysis of two datasets to estimate the total number of invasive meningococcal disease cases, Catalonia 2011-2015

189x117mm (144 x 144 DPI)

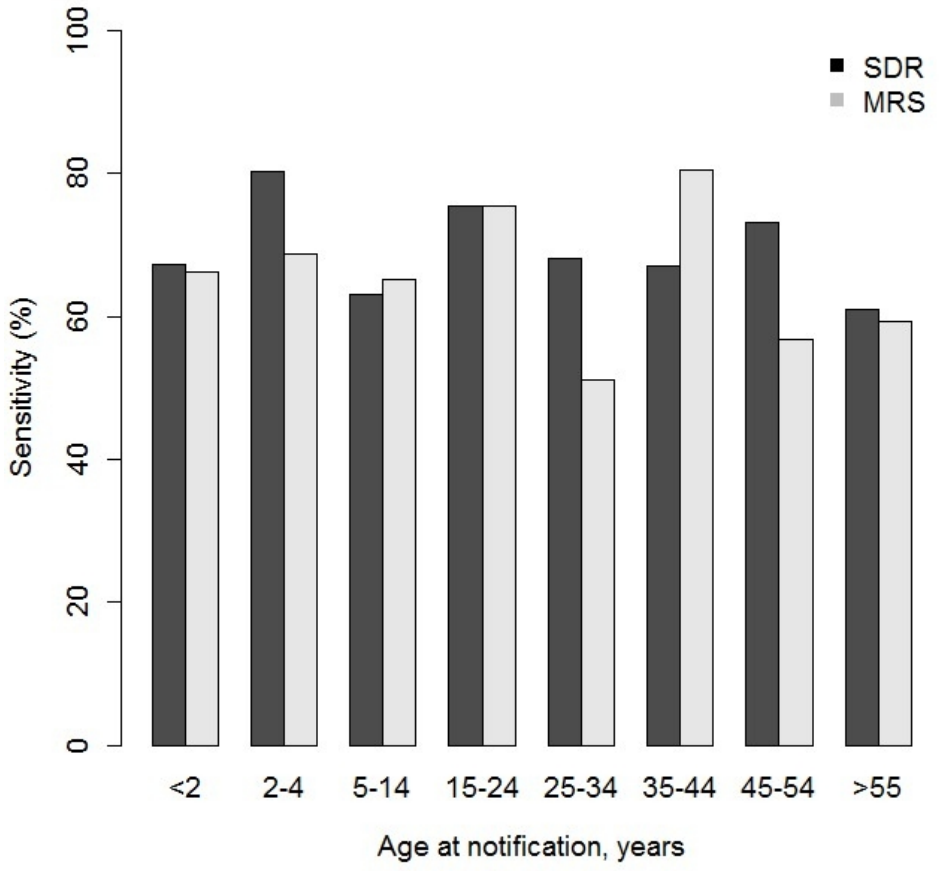


Figure 2. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

176x172mm (96 x 96 DPI)

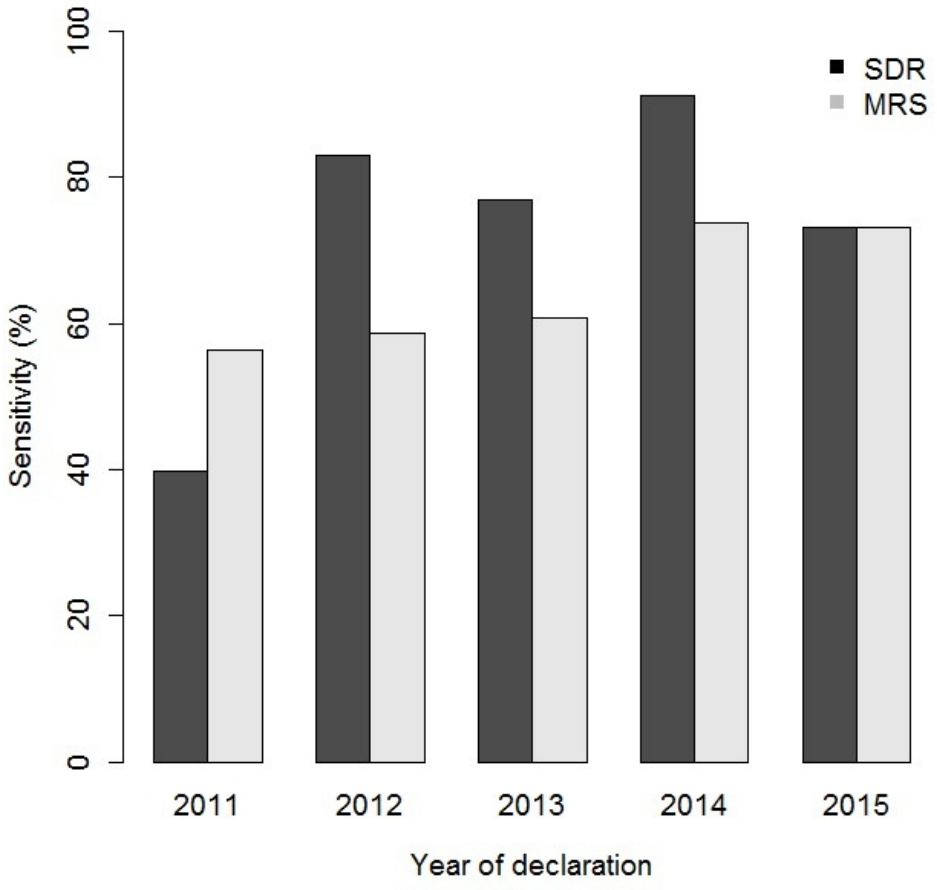


Figure 3. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

172x172mm (96 x 96 DPI)

Supplementary table 1. Capture–recapture analysis of serogroup B meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*p-value*
All cases	164	153	114	17	220 (209, 232)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	***<0.001***
Age group									
<15 years	110	110	78	13	155 (146, 165)	71.0 (63.8, 78.1)	71.0 (63.8, 78.1)	0.0	*0.656*
≥15 years	53	42	35	4	64 (59, 69)	83.5 (74.3, 92.6)	66.1 (54.5, 77.8)	17.3	
Sex									
Male	86	76	62	6	106 (100, 112)	81.7 (74.3, 89.1)	72.2 (63.6, 80.7)	9.5	*0.099*
Female	78	77	52	13	116 (106, 126)	67.7 (59.1, 76.2)	66.8 (58.2, 75.4)	0.9	
Year of report									
2011-2013	95	91	60	18	144 (132, 157)	66.1 (58.3, 73.8)	63.3 (55.4, 71.2)	2.8	***0.002***
2014-2015	69	62	54	3	80 (76, 83)	87.1 (79.7, 94.5)	78.3 (69.2, 87.4)	8.8	
Size of municipality									
<10,000 people	22	24	20	1	27 (26, 28)	83.3 (69.1, 97.6)	90.9 (79.9, 100.0)	-7.6	*0.059*
≥10,000 people	137	114	91	12	172 (163, 181)	79.9 (73.9, 85.9)	66.5 (59.4, 73.5)	13.4	
Country of birth									
Spain	152	144	107	16	205 (194, 215)	74.4 (68.4, 80.4)	70.4 (64.2, 76.7)	3.9	*0.631*
Other countries	12	9	7	2	16 (13, 19)	78.9 (58.4, 99.5)	59.2 (34.5, 83.9)	19.7	
Number of hospital beds									
<200	49	52	33	9	77 (69, 86)	63.7 (53.0, 74.5)	67.6 (57.2, 78.1)	-3.9	*0.095*

>=200	113	101	81	8	141 (134, 148)	80.3 (73.7, 86.8)	71.7 (64.3, 79.2)	8.5	
Clinical form									
Meningitis	91	100	70	9	130 (122, 138)	70.1 (62.2, 77.9)	77.0 (69.7, 84.2)	-6.9	*0.972*
Septicaemia	66	51	43	5	79 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	
Type of reporting centre									
Private	14	1	1	0	14 (14, 14)	100 (100, 100)	7.1 (-6.4, 20.6)	92.9	***0.004***
Public	149	152	113	13	201 (192, 210)	74.4 (68.4, 80.4)	75.9 (70, 81.8)	-1.5	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

Supplementary table 2. Capture–recapture analysis of serogroup C meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*p-value*
All cases	26	21	16	3	34 (30, 39)	76.7 (62.5, 90.9)	62.0 (45.6, 78.3)	14.8	***0.035***
Age group									
<15 years	4	4	4	0	4 (4, 4)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0	*0.992*
≥15 years	22	17	12	4	31 (25, 37)	71.4 (55.5, 87.4)	55.2 (37.6, 72.8)	16.2	
Sex									
Male	13	11	7	3	20 (15, 26)	65.0 (44.1, 85.9)	55.0 (33.2, 76.8)	10.0	*0.368*
Female	13	10	9	1	15 (13, 16)	90.3 (75.0, 100.0)	69.4 (45.7, 93.2)	20.8	
Year of report									
2011-2013	12	10	6	4	20 (14, 26)	61.9 (40.2, 83.5)	51.6 (29.3, 73.8)	10.3	*0.110*
2014-2015	14	11	10	1	16 (14, 17)	90.9 (76.6, 100.0)	71.4 (48.9, 94.0)	19.5	
Size of municipality									
<10,000 people	3	2	2	0	3 (3, 3)	100.0 (100.0, 100.0)	66.7 (13.3, 100.0)	33.3	*0.591*
≥10,000 people	21	15	12	3	27 (23, 30)	80.5 (65.3, 95.7)	57.5 (38.5, 76.4)	23.0	
Country of birth									
Spain	22	19	14	3	30 (26, 35)	74.1 (58.3, 89.8)	64.0 (46.7, 81.2)	10.1	*0.945*
Other countries	4	2	2	0	4 (4, 4)	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	50.0	
Number of hospital beds									

<200	7	5	5	0	7 (7, 7)	100.0 (100.0, 100.0)	71.4 (38.0, 104.9)	28.6	*0.283*
≥200	18	16	11	3	26 (22, 31)	69.5 (51.8, 87.2)	61.8 (43.1, 80.5)	7.7	
Clinical form									
Meningitis	16	16	11	3	24 (20, 27)	69.3 (50.4, 88.1)	69.3 (50.4, 88.1)	0.0	*0.908*
Septicaemia	8	4	4	0	8 (8, 8)	100.0 (100.0, 100.0)	50.0 (15.4, 84.7)	50.0	
Type of reporting centre									
Private	4	0	0	0	4 (4, 4)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.992*
Public	22	21	16	2	29 (26, 33)	76.4 (60.9, 91.9)	72.9 (56.7, 89.2)	3.5	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

Supplementary table 3. Capture–recapture analysis of all deaths due to meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*p-value*
All cases	22	11	11	0	22 (22, 22)	100.0 (100.0, 100.0)	50.0 (29.1, 70.9)	50.0	*0.104*
Age group									
<15 years	6	4	4	0	6 (6, 6)	100.0 (100.0, 100.0)	66.7 (28.9, 100.0)	33.3	*0.346*
≥15 years	16	7	7	0	16 (16, 16)	100.0 (100.0, 100.0)	43.8 (19.4, 68.1)	56.3	
Sex									
Male	16	7	7	0	16 (16, 16)	100.0 (100.0, 100.0)	43.8 (19.4, 68.1)	56.2	*0.346*
Female	6	4	4	0	6 (6, 6)	100.0 (100.0, 100.0)	66.7 (29.0, 100.0)	33.3	
Year of report									
2011-2013	16	6	6	0	16 (16, 16)	100.0 (100.0, 100.0)	31.3 (8.5, 54.0)	68.8	*0.080*
2014-2015	6	5	5	0	6 (6, 6)	100.0 (100.0, 100.0)	83.3 (53.5, 100.0)	16.7	
Size of municipality									
<10,000 people	3	3	3	0	3 (3, 3)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0	*0.991*
≥10,000 people	19	8	8	0	19 (19, 19)	100.0 (100.0, 100.0)	42.1 (19.9, 64.3)	57.9	
Country of birth									
Spain	20	10	10	0	20 (20, 20)	100.0 (100.0, 100.0)	50.0 (28.1, 71.9)	50.0	*1.000*
Other countries	2	1	1	0	2 (2, 2)	100.0 (100.0, 100.0)	50.0 (0.0, 100.0)	50.0	
Number of hospital beds									
<200	4	2	2	0	4 (4, 4)	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	50.0	*0.822*
≥200	16	9	9	0	16 (16, 16)	100.0 (100.0, 100.0)	56.3 (31.9, 80.6)	43.7	
Clinical form									
Meningitis	7	4	4	0	7 (7, 7)	100.0 (100.0, 100.0)	57.1 (20.5, 93.8)	42.9	*0.648*
Septicaemia	15	7	7	0	15 (15, 15)	100.0 (100.0, 100.0)	46.7 (21.4, 71.9)	53.3	

Type of reporting centre									
Private	2	0	0	0	2 (2, 2)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.992*
Public	20	11	11	0	20 (20, 20)	100.0 (100.0, 100.0)	55 (33.2, 76.8)	45	
Serogrup									
B	17	9	9	0	17 (17, 17)	100.0 (100.0, 100.0)	52.9 (29.2, 76.7)	47.1	*0.332*
C	4	1	1	0	4 (4, 4)	100.0 (100.0, 100.0)	25.0 (0.0, 67.4)	75.0	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,11,12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	5,14,15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Estimation of the incidence of invasive meningococcal disease using a capture-recapture model based on two independent surveillance systems, in Catalonia, Spain

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ABSTRACT

Objectives: Invasive meningococcal disease (IMD) is an urgent notifiable disease and its early notification is essential to prevent cases. The objective of the study was to assess the sensitivity of two independent surveillance systems, and to estimate the incidence of IMD.

Design: We used **c**apture-recapture model based on two independent surveillance systems**,** the statutory disease reporting system (SDR) and the microbiological reporting system (MRS) of the Public Health Agency of Catalonia, between 2011 and 2015. The capture-recapture analysis and 95% confidence intervals were calculated using the Chapman formula. Multivariate vector generalized linear model was performed for adjusted estimation.

Measures: The variables collected were age, sex, year of report, size of municipality (< 10,000 and ≥ 10,000), clinical form, death, serogroup, country of birth and type of reporting centre (private and public).

Results: The sensitivity of the two combined surveillance systems was 88.5% (85.0-92.0). SDR had greater sensitivity than the MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0). In 2014-2015, the sensitivity of both systems was higher (80.6%; 73.2–87.9 vs. 73.4%; 65.2–81.6) than in 2011-2013 (59.3%; 52.6–66.0 vs. 58.3%; 51.6–65.1). In private centres, the sensitivity was higher for SDR than for MRS (100%; 100–100 vs. 4.8%; -4.4–13.9). The adjusted estimate of IMD cases was lower than that obtained using the Chapman formula (279; 266–296 vs. 313; 295–330). The estimated adjusted incidence of IMD was 0.7/100,000 persons-year.

Conclusions: The sensitivity of enhanced surveillance through the combination of two complementary sources was higher than for the sources individually. Factors associated with under-reporting in different systems should be analysed to improve IMD surveillance.

Keywords:

Meningococcal disease, Capture-recapture, estimated incidence, surveillance systems.

Strengths and limitations of this study

- The use of two surveillance sources as universal statutory disease reporting (SDR) system based on passive reporting and sentinel microbiological reporting system (MRS) covering 83% of acute hospital beds, offer a wide coverage.
- The independence of the two sources was demonstrated by complying with the premise of the capture-recapture method.
- Not all centres participate in the MRS, thus not all cases diagnosed had the same probability of being selected from a given source.
- The role of the automated electronic reporting of data that might be associated to a greater sensitivity was not analysed.

BACKGROUND

Invasive meningococcal disease (IMD) continues to be an important cause of morbidity and mortality, mainly in children aged < 4 years and adolescents. [1]

In the European regions, the incidence rate of confirmed IMD cases was 0.62/100,000 persons-year in 2018, [2] and in Spain it was 0.86/100,000 persons. [3] Six serogroups (A, B, C, W, X, Y) currently cause almost all cases of this life-threatening disease worldwide. Case fatality rate is about 10% in developed countries [4-6], and 40-65% present with meningitis, but meningococcemia and pneumonia are also frequent [4], being the serogroup involved related both with the case fatality rate [7] and the predominant clinical form. [8] Serogroup B causes more than a third part of IMD [4,9] but in some countries or population groups the proportion is even higher. [10,11] In Spain, from 2009 to 2018, serogroup B accounted for 64% of IMD cases. [12] A high proportion, up to 60% [13] of IMD cases, are affected by a range of sequelae and health related impairment in the quality of life of survivors and their families. [14]

IMD is an urgent notifiable disease and its early notification is essential to provide an adequate public health response in patients and their close contacts to prevent further cases.

Epidemiological surveillance allows monitoring of the impact of public health interventions, including vaccination programmes. Therefore, a robust epidemiological and microbiological

system with timely and accurate surveillance providing information on the frequency of cases and the distribution of circulating serogroups is crucial.

Evaluations of surveillance systems should be conducted regularly to increase their utility. [15-17] There are two reporting systems for the epidemiological surveillance of communicable disease in Catalonia: the statutory disease reporting system (SDR) and the microbiological reporting system (MRS). [18]

The capture-recapture method is a statistical method for estimating the real incidence of diseases in a population with two or more information sources. [19, 20] The method is valid if four conditions are met: 1) the population under study has to be closed, i.e., there should be no changes during the study period; 2) there must be a method of determining whether an individual identified by one source is the same as an individual identified by the other; 3) each individual must have the same probability of being captured by either system; 4) the systems must be independent.

The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD.

METHODS

Information sources

Catalonia is a region in the northeast of Spain with a population of 7,508,106 in 2015. [21]

The SDR is a passive surveillance system through which health professionals report all infectious diseases subject to surveillance. The reporting of cases to the Public Health Agency of Catalonia (PHAC) is mandatory and includes confirmed cases of IMD and is regulated by a Decree. [18, 22]

The MRS is a surveillance system that consists of microbiologists notifying laboratory confirmed microorganisms that cause infectious diseases. The main objectives of the MRS are to confirm suspected cases of infectious diseases through the identification of the microorganisms and serogroups involved and to determine trends and changes in epidemiological patterns and microbiological resistance. [23]

The MRS was non-compulsory until 2015 and involved 50 health care centres representing over 83% of acute hospital beds. [24] Confirmed IMD cases were reported by microbiologists including sex, age, clinical presentation (meningitis, bacteraemia of unknown focus and other clinical presentations), serogroup and diagnostic method.

Both systems belong to the PHAC epidemiological surveillance network and, since 2014, transfer information automatically, but the independence of the sources is maintained.

Cases definition, inclusion, and exclusion criteria

A confirmed case of IMD was defined as laboratory confirmed if at least one of the following criteria was fulfilled: isolation in cultures or detection of *Neisseria meningitidis* DNA by PCR in a normally sterile site, detection of gram-negative diplococci or *N. meningitidis* antigen in cerebrospinal fluid.

Data collection

We made a retrospective study of confirmed IMD cases in Catalonia from January 2011 to December 2015. We extracted all IMD records from the MRS and SDR and linked the databases using the personal identification code (PIC). When the PIC was not available, data on notification, age and sex were used to identify duplicates between the two sources. In cases with inconclusive matching, the hospital was used as a fifth matching criterion.

Estimates were made for the entire 5-year period and by age, sex, year of report, size of municipality (<10,000 and ≥10,000), country of birth, number of hospital beds, clinical form (meningitis, with or without sepsis, sepsis, and others), serogroup, death and reporting centre (private or public).

Ethics statement

The study was not submitted for research ethics approval as the activities described were conducted as part of the legislated mandate of the Health Department of Catalonia, the competent authority for surveillance of communicable diseases according to Decree 203/2015

of the 15 September which created the epidemiological surveillance network of Catalonia. [18] All the study activities formed part of public health surveillance and did not require informed consent. Personal data were used only for the matching process and measures to protect the confidentiality of personal data were applied (access to the data restricted to the personnel involved in data analysis, and removal of personal data from the datasets after matching).

Patient and public involvement

No patient involved

Statistical methods

The total number of IMD cases was estimated using the two-source capture-recapture method, which uses Chapman's formula, [25] developed to reduce bias due to small samples:

$$N = \frac{(L1+1)(L2+1)}{a+1} - 1$$

$$95\%CI = N \pm 1.96\sqrt{\frac{(L1+1)(L2+1)(L1-a)(L2-a)}{(a+1)^2(a+2)}}$$

where L1 is the number of cases in the SDR dataset, L2 is the number of cases reported to MRS, and **a** is the number of cases captured by both systems. The sensitivity (Se) of case ascertainment by the two sources was also calculated as the proportion of true cases detected by each source, i.e. Se (1) =L1/N for source 1 and Se (2) =L2/N for source 2. The sensitivity of both sources combined was calculated as the proportion of cases detected by one of the two sources or both, i.e., Se (1, 2) =(L1+L2-**a**)/N.

The independence of the sources was considered when applying the capture-recapture method. [26, 27] In the two-by-two table, where **a** represents cases reported by two sources or combinations of sources, **b** and **c** cases reported exclusively by either of the two sources and **x** the estimated non-reported cases by either of the sources, the odds ratio (OR = ax/bc) should not differ from one.

As a multivariate model, a vector generalized linear model (VGLM) from the generalized additive model (GAM) framework [28] was used to evaluate patient characteristics and the probability of capture by the different sources taking into account the covariates: age (<15 vs ≥15), gender, year of notification (2011-2013 vs 2014-2015), size of the municipality (<10,000 vs ≥10.000), country of birth (Spain vs other), number of hospital beds (<200 vs ≥200) and diagnosis (meningitis vs septicaemia). The outcome for the model is a two column matrix with 0 and 1 indicating if the record is identified by SDR or MRS. We used a backwards stepwise procedure (using likelihood ratio tests, with a p-value >0.2 as the criterion for removing variables from the model) [29, 30] to eliminate covariates, starting with a full model including all described covariates, and we used the parameter estimates from the model to estimate the sizes of population subgroups and calculate incidence rates. The 95% confidence intervals (CI) were calculated, allowing for uncertainty in the total number of cases estimated. For each of the described covariates, VLGM with source notification as outcome was used to test differences in sensitivities. All analyses were made using R software version 3.0.1.

RESULTS

Patient characteristics

Patient characteristics by source are shown in Table 1. From 2011 to 2015, 212 IMD cases were reported to the SDR and 202 cases to the MRS, representing an incidence of 0.56 and 0.54 /100,000 persons-year, respectively. IMD due to serogroup B was the most-frequently reported serogroup (77.4% and 75.7% in the SDR and MRS, respectively). Around 63% of patients were aged < 15 years; the mean age was 21.4 for the SDR and 20.5 years for the MRS. Male sex was more frequent in the SDR (52.4%) than in the MRS (49%). The SDR presented the most cases in 2015 (48 cases; 22.6%) and the MRS (61 cases; 30.2%) in 2011. The SDR reported that 84% of patients lived in a municipality of ≥10,000 people compared with 73% in the MRS. In both sources, the number of cases declared in a hospital of ≥200 beds were around 70%. The main clinical form in both sources was meningitis (54.7% and 64.8%, respectively) and sepsis (38.7% and 32.7%, respectively). Reports from private centres represented 10% of cases in the SDR and

0.5% in the MRS. Twenty-two cases (10.4%) cases reported by the SDR died compared with 11 cases (5.4%) reported by the MRS.

Table 1. Sociodemographic, clinical and microbiological characteristics of invasive meningococcal disease cases reported to the SDR and MRS, Catalonia 2011-2015

	SDR (n=212)	MRS (n=202)
Age groups		
Mean (SD)	21.4 (27.9)	20.5 (26.7)
Median (IQR)	6 (36)	6 (32.3)
<2 years, n (%)	62 (29.8%)	61 (30.7%)
2 - 4 years, n (%)	35 (16.8%)	30 (15.1%)
5 - 14 years, n (%)	34 (16.3%)	35 (17.6%)
15 - 24 years, n (%)	12 (5.8%)	12 (6.0%)
25 - 34 years, n (%)	12 (5.8%)	9 (4.5%)
35 - 44 years, n (%)	10 (4.8%)	12 (6.0%)
45 - 54 years, n (%)	9 (4.3%)	7 (3.5%)
>55 years, n (%)	34 (16.3%)	33 (16.6%)
NAs	1 (0.5%)	2 (1.0%)
Sex, n (%)		
Male	111 (52.4%)	99 (49.0%)
Female	101 (47.6%)	103 (51.0%)
Year of report, n (%)		
2011	43 (20.3%)	61 (30.2%)
2012	41 (19.3%)	29 (14.4%)
2013	38 (17.9%)	30 (14.9%)
2014	42 (19.8%)	34 (16.8%)
2015	48 (22.6%)	48 (23.8%)
Size of municipality, n (%)		
<10,000 people	27 (12.7%)	28 (13.9%)
≥10,000 people	177 (83.5%)	148 (73.3%)
NAs	8 (3.8%)	26 (12.9%)
Country of birth, n (%)		
Spain	194 (91.5%)	188 (93.1%)
Other countries	18 (8.5%)	14 (6.9%)
Number of hospital beds, n (%)		
<200	60 (28.3%)	65 (32.2%)
≥200	149 (70.3%)	137 (67.8%)
NAs	3 (1.4%)	0 (0.0%)
Clinical form, n (%)		
Meningitis	116 (54.7%)	131 (64.8%)
Septicaemia	82 (38.7%)	66 (32.7%)
Other forms	14 (6.6%)	4 (2.0%)
NAs	0 (0.0%)	1 (0.5%)
Serogroup, n (%)		
A	0 (0.0%)	2 (1.0%)
B	164 (77.4%)	153 (75.7%)
C	26 (12.3%)	21 (10.4%)
W135	4 (1.9%)	6 (3.0%)
Y	5 (2.4%)	2 (1.0%)
Y/ W135	1 (0.5%)	1 (0.5%)
Non-groupable	6 (2.8%)	4 (2.0%)

NAs	6 (2.8%)	13 (6.4%)
Type of reporting centre		
Private	21 (10.0%)	1 (0.5%)
Public	190 (90.0%)	201 (99.5%)

NAs: Not available; SDR: Statutory disease reporting; MDR: Microbiological reporting system

Capture-recapture analysis

The odds ratio (OR) was 1.01 (95%CI 0.62-1.66), reinforcing the independence of the two sources.

During the period studied, 212 and 202 IMD cases were reported by the SDR and MRS, respectively. One hundred thirty-seven cases (43.8%) coincided in both sources and 36 cases (11.5%) were not reported to either source. The estimated number of cases was 313 (95% CI 295–330) (Figure 1) and the estimated incidence rate was 0.83/100,000 persons-year.

The sensitivity of the SDR was 67.9% (95%CI 62.7-73.1) and that of the MRS was 64.7% (95%CI 59.4-70.0) (P<0.001) (Table 2). The sensitivity increased to 88.5% (95%CI 85.0-92.0) when the datasets were combined.

Table 2. Capture–recapture analysis of all invasive meningococcal disease cases reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	212	202	137	36	313 (295, 330)	67.9 (62.7, 73.1)	64.7 (59.4, 70.0)	3.2	***<0.001***
Age group									
<15 years	131	126	87	20	190 (177, 203)	69.1 (62.6, 75.7)	66.5 (59.8, 73.2)	2.6	*0.468*
≥15 years	80	74	49	16	121 (109, 133)	66.4 (58.0, 74.8)	61.4 (52.7, 70.1)	5.0	
Sex									
Male	111	99	71	16	155 (144, 166)	71.8 (64.7, 78.9)	64.0 (56.5, 71.6)	7.8	*0.588*
Female	101	103	66	20	158 (145, 171)	64.2 (56.7, 71.7)	65.5 (58.1, 72.9)	-1.3	
Year of report									
2011-2013	122	120	71	35	206 (187, 226)	59.3 (52.6, 66.0)	58.3 (51.6, 65.1)	1.0	***<0.001***
2014-2015	90	82	66	6	112 (106, 118)	80.6 (73.2, 87.9)	73.4 (65.2, 81.6)	7.2	
Size of municipality									
<10,000 people	27	28	22	2	35 (32, 37)	78.7 (65.0, 92.4)	81.6 (68.7, 94.6)	-2.9	*0.100*
≥10,000 people	177	148	110	23	238 (225, 252)	74.4 (68.9, 80.0)	62.2 (56.1, 68.4)	12.2	
Country of birth									
Spain	194	188	127	32	287 (271, 304)	67.6 (62.2, 73.0)	65.5 (60.0, 71.0)	2.1	*0.696*
Other countries	18	14	10	3	25 (20, 30)	72.3 (54.7, 89.9)	56.2 (36.7, 75.7)	16.1	
Number of hospital beds									
<200	60	65	40	13	97 (87, 108)	61.7 (52.1, 71.4)	66.9 (57.5, 76.2)	-5.1	*0.514*
≥200	149	137	97	22	210 (197, 224)	70.9 (64.7, 77.0)	65.2 (58.7, 71.6)	5.7	
Clinical form									
Meningitis	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	*0.936*
Sepsis	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	
Type of reporting centre									
Private	21	1	1	0	21 (21, 21)	100 (100, 100)	4.8 (-4.4, 13.9)	95.2	***0.002***
Public	190	201	136	26	281 (267, 295)	67.7 (62.2, 73.2)	71.6 (66.4, 76.9)	-3.9	
Serogrup									
B	164	153	114	17	220 (209, 231)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	*0.636*

C	26	21	16	3	34 (29, 39)	76.7 (62.5, 90.9)	61.9 (45.6, 78.3)	14.8	

298 SDR: Statutory disease reporting; MDR: Microbiological reporting system

There were no differences in sensitivity between in <15 years and ≥15 years age group (P-value=0.468) in either source although it was higher in the <15 years (69.1%; 95%CI 62.6-75.7 in the SDR and 66.5%; 95%CI 59.8-73.2 in the MRS). The age groups with the highest sensitivity were 2-4 years in the SDR, with 80.3% (95%CI 68.5-92.1), and 35-44 years in the MRS, with 80.5% (95%CI 60.4–100.0) (Figure 2).

In 2011-2013, sensitivity for the SDR and the MRS were 59.3% (95%CI 52.6-66) and 58.3% (95%CI 51.6-65.1), respectively, lower than that in 2014-2015 (80.6%; 95%CI 73.2-87.9, for the SDR and 73.4%; 95%CI 65.2-81.6, for the MRS (P<0.001)) (Table 2). 2014 showed the highest sensitivity for both sources: 91.3% (95%CI 83.2-99.4) for the SDR and 73.9% (95%CI 61.2-86.6) for the MRS (Figure 3). 2011 was the only year in which the MRS had a higher sensitivity than the SDR (56.4%; 95%CI 47.1-65.8 and 39.8%; 95%CI 30.6-49.0, respectively).

In private centres the sensitivity of the SDR was 100% (95%CI 100-100) and that of the MRS was 4.8% (95%CI -4.4-13.9). No differences were found in other characteristics analysed.

For meningitis, 116 and 131 cases were reported by the SDR and the MRS, respectively. The estimated number of meningitis cases was 181, and 18 cases were not reported by either source. The highest sensitivity was detected in the MRS (72.5%; 95% CI 66-79) compared with the SDR (64.2%; 95%CI 57.2-71.2) (P<0.001) (Table 3). 2014-2015 showed a higher sensitivity in both sources compared with 2011-2013: 82.4% (95%CI 72.7-92) in the MRS and 75.6% (95%CI 64.7-86.5) in the SDR. Public centres had a higher sensitivity in the MRS (77.7%; 95%CI 71.4-84.0) and in the SDR (63.9%; 95%CI 56.6-71.2) (P<0.037).

Table 3. Capture–recapture analysis of meningococcal meningitis reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	***<0.001***
Age group									
<15 years	72	81	51	13	115 (104, 125)	63.1 (54.3, 72.0)	71.0 (62.7, 79.3)	-7.9	*0.682*
≥15 years	43	49	32	6	66 (60, 73)	65.5 (53.9, 77.0)	74.6 (64.1, 85.1)	-9.1	
Sex									
Male	62	69	47	7	91 (84, 98)	68.2 (58.6, 77.8)	75.9 (67.1, 84.7)	-7.7	*0.245*
Female	54	62	37	12	91 (81, 101)	59.9 (49.8, 70.0)	68.7 (59.2, 78.3)	-8.9	
Year of report									
2011-2013	71	82	47	18	124 (111, 137)	57.5 (48.8, 66.2)	66.4 (58.1, 74.7)	-8.9	***0.013***
2014-2015	45	49	37	3	60 (56, 64)	75.6 (64.7, 86.5)	82.4 (72.7, 92.0)	-6.7	
Size of municipality									
<10,000 people	19	20	16	1	24 (22, 26)	80.2 (64.1, 96.2)	84.4 (69.8, 99.0)	-4.2	*0.165*
≥10,000 people	93	93	65	12	133 (124, 143)	70.0 (62.2, 77.8)	70.0 (62.2, 77.8)	0.0	
Country of birth									
Spain	107	120	77	17	167 (155, 179)	64.3 (57.0, 71.5)	72.1 (65.3, 78.9)	-7.8	*0.862*
Other countries	9	11	7	1	14 (12, 17)	64.3 (39.2, 89.4)	78.6 (57.1, 100.0)	-14.3	
Number of hospital beds									
<200	31	40	23	6	54 (47, 61)	57.7 (44.5, 70.9)	74.5 (62.8, 86.2)	-16.8	*0.516*
≥200	84	91	61	11	126 (116, 135)	67.1 (58.9, 75.4)	72.7 (64.9, 80.5)	-5.6	
Type of reporting centre									
Private	9	1	1	0	9 (9, 9)	100.0 (100.0, 100.0)	11.1 (-9.4, 31.6)	88.9	***0.037***
Public	107	130	83	14	168 (158, 178)	63.9 (56.6, 71.2)	77.7 (71.4, 84.0)	-13.7	
Serogrup									
B	91	100	70	9	130 (122, 138)	70.1 (62.2, 77.9)	77.0 (69.7, 84.2)	-6.9	*0.641*
C	16	16	11	2	23 (19, 27)	69.3 (50.4, 88.1)	69.3 (50.4, 88.1)	0	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

For septicaemia, 82 cases and 66 cases were reported by the SDR and the MRS, respectively. The sensitivity was higher for the SDR (75.9%; 95%CI 67.9-84) than the MRS (61.1%; 95%CI 51.9-70.3) (Table 4). There were 108 estimated cases and 10 cases were not reported by either source. The sensitivity was higher in the <15 years than in the ≥15 years in both sources, but higher in the SDR (81.1%; 95%CI 71.1-91.1 versus 71%; 95%CI 59.4-82.5 for the MRS; P=0.036), and higher in 2014-2015 than in 2011-2013 (87.6%; 95%CI 78-97.3 for the SDR and 71.9%; 95%CI 58.7-85.1 for the MRS) (P<0.015).

Serogroup B (Supplementary Table 1) showed the sensitivity of the SDR was higher than that of the MRS (74.6%; 95%CI 68.8-80.3 and 69.6%; 95%CI 63.5-75.6, respectively). There were differences according to the period and the type of centre. In 2014-2015, the sensitivity was 87.1% (95%CI 79.7-94.5) for the SDR and 78.3% (95%CI 69.2-87.4) for the MRS (P<0.002). In private centres, the sensitivity in SDR was 100% compared with 7.1% (95%CI -6.4-20.6) (P=0.004) in MRS. The sensitivity was higher for IMD serogroup C cases in SDR than in MRS (76.7%; 95%CI 62.5-90.9 and 62%; 95%CI 45.6-78.3, respectively) (Supplementary Table 2). All 22 deaths were reported in the SDR (CFR: 10.4%), and the sensitivity of the SDR was higher than that of the MRS (100%; 95CI% 100-100 vs 50%; 95%CI 29.1-70.9, P=0.104). No differences were found in other characteristics analysed (Supplementary Table 3).

Table 4. Capture–recapture analysis of meningococcal septicaemia reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*P-value*
All cases	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	***<0.001***
Age at notification, years									
<15 years	48	42	34	4	60 (55, 64)	81.1 (71.1, 91.1)	71.0 (59.4, 82.5)	10.1	***0.036***
≥15 years	34	23	16	8	49 (40, 58)	70.3 (57.4, 83.1)	47.5 (33.4, 61.6)	22.7	
Sex									
Male	43	27	22	5	53 (47, 59)	81.8 (71.3, 92.2)	51.3 (37.8, 64.8)	30.4	*0.315*
Female	39	39	28	5	55 (49, 60)	72.0 (60.0, 83.9)	72.0 (60.0, 83.9)	0.0	
Year of report									
2011-2013	43	34	22	11	66 (56, 77)	65.2 (53.6, 76.7)	51.5 (39.5, 63.6)	13.6	***0.015***
2014-2015	39	32	28	2	45 (42, 48)	87.6 (78.0, 97.3)	71.9 (58.7, 85.1)	15.7	
Size of municipality									
<10,000 people	7	7	5	1	10 (8, 12)	72.2 (44.0, 100.0)	72.2 (44.0, 100.0)	0.0	*0.918*
≥10,000 people	71	52	43	6	86 (80, 93)	82.9 (74.9, 90.8)	60.7 (50.3, 71.0)	22.2	
Country of birth									
Spain	73	63	47	9	98 (90, 106)	74.7 (66.1, 83.3)	64.5 (55.0, 74.0)	10.2	*0.275*
Other countries	9	3	3	0	9 (9, 9)	100.0 (100.0, 100.0)	33.3 (2.5, 64.1)	66.7	
Number of hospital beds									
<200	25	23	16	4	36 (31, 42)	70.0 (55.0, 85.1)	64.4 (48.7, 80.1)	5.6	*0.831*
≥200	56	43	34	6	71 (65, 78)	79.2 (69.7, 88.7)	60.8 (49.4, 72.2)	18.4	
Type of reporting centre									
Private	9	0	0	0	9 (9, 9)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.988*
Public	73	66	50	8	97 (89, 104)	75.9 (67.3, 84.4)	68.6 (59.3, 77.9)	7.3	
Serogrup									
B	66	51	43	4	78 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	*0.661*
C	8	4	4	0	8 (8, 8)	100 (100, 100)	50.0 (15.4, 84.7)	50.0	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

The results of the multivariate model for all cases are shown in Table 5. The variables considered to define the sensitivity of the two sources were year of report (2011-2013 versus 2014-2015) and size of municipality. With these variables in the model, the adjusted estimate of the total number of cases was 279 cases (95%CI 266-296) and the estimated incidence rate was 0.7/100,000 persons-year.

Table 5. Variables defining the sensitivity of the SDR and MRS in detecting invasive meningococcal diseases cases. Multivariate model.

	OR (95%CI)	***p-value***
Year of report (2014-2015)	2.29 (1.35, 3.89)	***0.002***
Size of municipality (≥10,000 people)	0.51 (0.23, 1.12)	*0.093*

OR: odds ratio; n estimate: 279 (266, 296)

DISCUSSION

The sensitivity obtained by combining the two surveillance system for IMD cases was 88.5%, greater than for each source. Globally, the SDR showed higher sensitivity than the MDR, mainly for cases of sepsis, serogroup B and serogroup C, although for meningitis the sensitivity of the MDR was higher than that of the SDR.

Sensitivity of SDR was 67.9%, very close to that of 66.5% found by Andrianou et al. in Italy in a study carried out in 2018 using the hospital discharge records system as the external source. [31]

Other studies found greater sensitivities by combining data systems than we did. Baldovin et al. [32] in Italy, reported an overall sensitivity of 94.7% by combining four data sources (mandatory notification system, laboratory surveillance, invasive bacterial surveillance and hospital discharge). Jansson et al. [33], in Sweden, found a global sensitivity of 98.7%, 91.1% for clinical notification and 85.4% for laboratory reporting. In Austria a good agreement between the National Reference Center for meningococci and the hospital discharge was found, although a clinical review of hospital discharge data was necessary to detect false positive cases recorded. [34]

Globally, the sensitivity was similar in children aged <15 years than in persons aged ≥15 years in both sources (69.1% for the SDR and 66.5% for the MRS; P=0.468). The differences could be because there is greater sensibilization to declare pediatric cases than adult cases or because there are differences on IMD incidence according to age. [9] Gibson et al., [35] in Australia, analysed IMD sensitivity in children aged < 15 years in three sources: notifiable system, hospitalized patients and mortality data. They found a greater sensitivity (99.5%) than we did, although 15% of hospitalized children were false-positive cases.

Sensitivity was higher in 2014-2015 than in 2011-2013 for both sources (SDR and MRS). SDR had overall higher sensitivity for IMD cases, septicaemia cases as well as serogroup B and C cases, but not for meningitis cases for which MRS had higher sensitivity. The improvement in notification in the years 2014-2015 may be due to different causes, one could be that there is greater awareness for the notification of infectious diseases to public health surveillance systems, although it should be analysed in subsequent studies. In a different way, Andrianou et al [31] compared the surveillance of the Italian IMD with the registry of hospital discharges, and found a lower sensitivity in 2018 compared to 2015-2017. This yearly evaluation allows the detection of problems in the notification process.

We found a greater sensitivity for meningitis in the MRS than in the SDR (72.5% vs 64.2%) but not for septicaemia (61.1% vs 75.9%). Multiple reasons could explain this fact. A possible explanation is that meningitis has a specific section in MRS for reporting while septicaemia is reported in bacteraemia of unknown focus section and it could be confused. It is important to determine the reason for this lower sensitivity to septicaemia in order to improve the completeness of MRS reporting. It is difficult to compare our results with those of other studies, since other sources of information were used or the independence of data sources was presumed but not demonstrated, [34] which is essential when using the capture-recapture method.

Notification of confirmed cases of IMD by laboratories is essential in epidemiological surveillance. [36] Molecular information on circulating serogroups that is required to implement public health measures such as vaccination is essential to control the disease [37] and evaluate the impact of available vaccines.

In the absence of automated electronic reporting, monitoring and increasing the speed of laboratory reports may allow the public health department to administer chemoprophylaxis and vaccination to contacts. [27] Although a higher sensitivity has been reported for electronic reporting than for paper-based reports by some authors, [38] during the study period, automated electronic reporting was used in the SDR but not in the MDR, which may explain, at least in part, why the MDR had a lower sensitivity than the SDR. [39]

In the multivariate model, the 2014-2015 period and the size of the municipality show a higher sensitivity in the SDR, suggesting that IMD was well recorded in the two surveillance systems, although 36 cases (11.5%) were not captured by either source. This suggests there was underreporting, despite the clinical severity of the disease. Other authors have also found underreporting of this disease. [40] It is very important to improve reporting by all physicians and microbiologists to the SDR and MDR to assess the impact of interventions such as immunization.

The estimated IMD incidence rate of 0.7/100, 000 persons-year found in the multivariate model is less than that found using capture-recapture (0.83/100,000 persons-year) but higher than that calculated using the SDR (0.56/100,000 persons-year) or MDR data (0.54/100,000 persons-year). Other European studies showed incidence rates of between 0.39 [32] and 1.18/100,000 persons-year. [34]

The sensitivity of the two sources were intermediate (67.9% for the SDR and 64.7% for the MRS). The lower sensitivity of the MRS may be due to the fact that the MRS is a sentinel system with a coverage of 83% of acute hospital beds and without private centres. In our series, 21 cases (10%) included in the SDR were reported by private centres, while only one case (0.5%) was reported to the MSR; this patient was finally transferred to a public hospital. The inclusion of cases that have an equal probability of selection in one source might lead to an overestimation. Other authors have reported this limitation when the hospital discharge data set includes probable cases which are not included in the reference centre. [34]

Death was registered in 22 cases (10.5%), similar to that reported in other European countries [2] but slightly lower than that observed in Italy (14%) using the capture-recapture method. [32]

All cases were reported to the SDR but only 50% were reported to the MRS, indicating that clinical data are better in the SDR than in the MRS. Other authors have used mortality data for capture-recapture analysis and concluded that all deaths were reported in notifiable systems. [34]

The sensitivity of the sources studied for the surveillance of IMD cannot be generalized to other diseases because physicians' or microbiologists' perception of the importance of IMD differs from that of other diseases. [38]

The main strength of this study is that the two sources had wide coverage. The SDR is a universal epidemiological surveillance source and, unlike the MDR, is a sentinel source, with a high coverage of 83%. Cases with PIC accounted for 85.5% of all cases reported to detect whether cases were coincident or not. In addition, the independence of the two sources was demonstrated, complying with the premise of the capture-recapture method.

A limitation of the study was that not all cases had the same probability of being selected from a given source. Cases diagnosed in private centres or public centres that did not participate in the MRS could not be reported by this system and this may explain, at least in part, the lower sensitivity than the SDR. This highlights the importance of including public and private centres to increase the robustness of the MRS. Another limitation was that we did not analyse the role of the electronic surveillance system, although a previous study detected greater sensitivity of the SDR when electronic surveillance was introduced. [39]

CONCLUSIONS

The sensitivity of enhanced surveillance through the combination of two complementary sources (statutory reporting by physicians and microbiological reporting by microbiologists) was higher than that of the individual sources. These systems are complementary and constitute the basic sources of information necessary for adequate epidemiological surveillance of IMD. Specific studies to estimate the factors associated with under-reporting are needed to reinforce epidemiological surveillance of this disease.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent of publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

PC analyzed and interpreted data, studied conception and design of the study and writes the manuscript; MV and NS did statistical analysis; GC revised and collected data; TG,SH,LR collected data; MJ revised the study and AD did critical revision and got funding.

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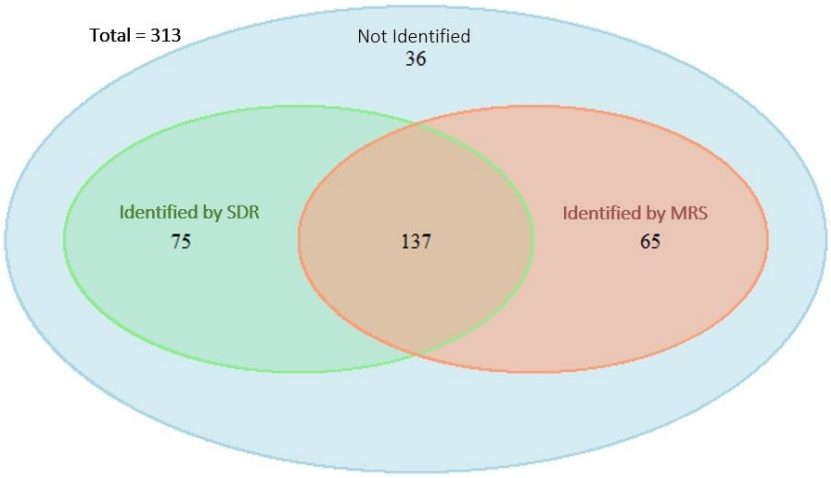
955 Figure 1. Venn diagram of the capture–recapture analysis of two datasets to estimate the total
956 number of invasive meningococcal disease cases, Catalonia 2011-2015

957 Figure 2. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

958 Figure 3. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

Figure 1. Venn diagram of the capture–recapture analysis of two datasets to estimate the total number of invasive meningococcal disease cases, Catalonia 2011-2015



Venn diagram of the capture–recapture analysis of two datasets to estimate the total number of invasive meningococcal disease cases, Catalonia 2011-2015

189x117mm (144 x 144 DPI)

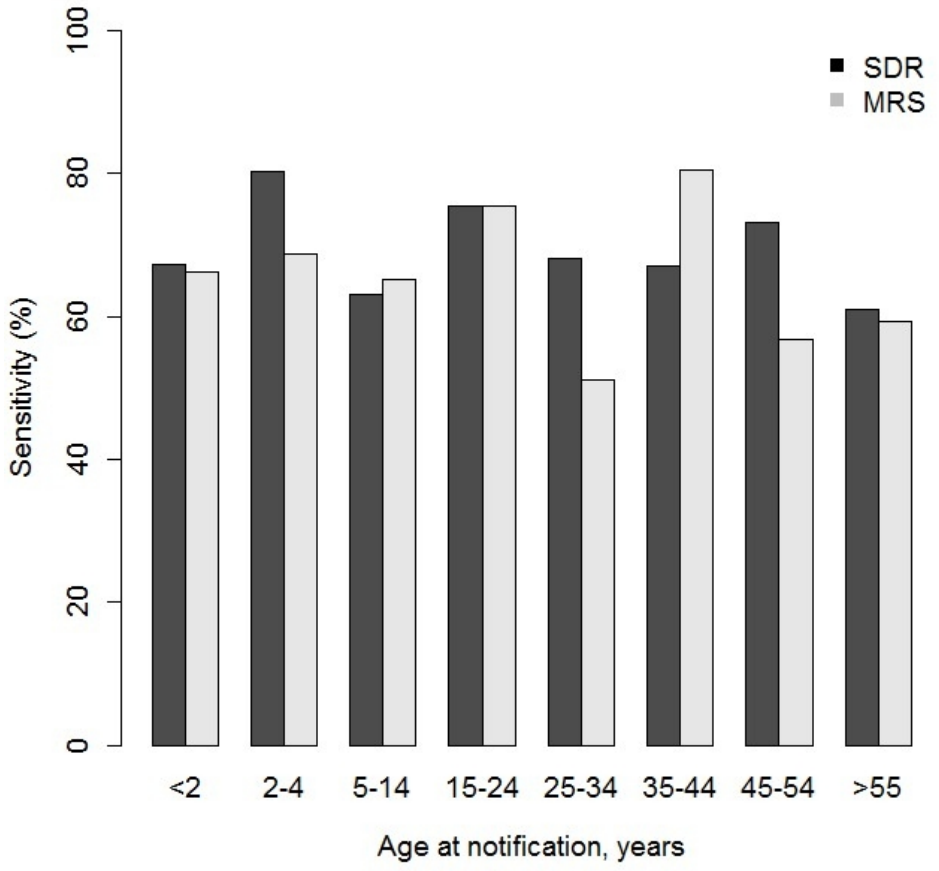


Figure 2. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

176x172mm (96 x 96 DPI)

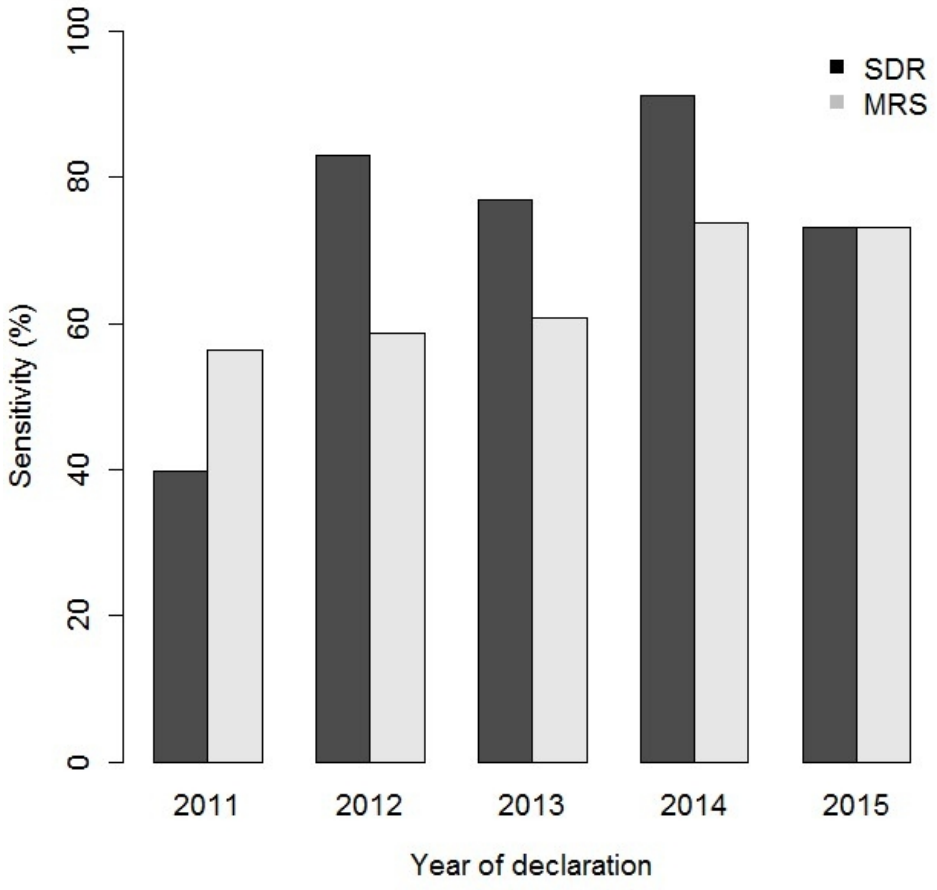


Figure 3. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

172x172mm (96 x 96 DPI)

Supplementary table 1. Capture–recapture analysis of serogroup B meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*p-value*
All cases	164	153	114	17	220 (209, 232)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	***<0.001***
Age group									
<15 years	110	110	78	13	155 (146, 165)	71.0 (63.8, 78.1)	71.0 (63.8, 78.1)	0.0	*0.656*
≥15 years	53	42	35	4	64 (59, 69)	83.5 (74.3, 92.6)	66.1 (54.5, 77.8)	17.3	
Sex									
Male	86	76	62	6	106 (100, 112)	81.7 (74.3, 89.1)	72.2 (63.6, 80.7)	9.5	*0.099*
Female	78	77	52	13	116 (106, 126)	67.7 (59.1, 76.2)	66.8 (58.2, 75.4)	0.9	
Year of report									
2011-2013	95	91	60	18	144 (132, 157)	66.1 (58.3, 73.8)	63.3 (55.4, 71.2)	2.8	***0.002***
2014-2015	69	62	54	3	80 (76, 83)	87.1 (79.7, 94.5)	78.3 (69.2, 87.4)	8.8	
Size of municipality									
<10,000 people	22	24	20	1	27 (26, 28)	83.3 (69.1, 97.6)	90.9 (79.9, 100.0)	-7.6	*0.059*
≥10,000 people	137	114	91	12	172 (163, 181)	79.9 (73.9, 85.9)	66.5 (59.4, 73.5)	13.4	
Country of birth									
Spain	152	144	107	16	205 (194, 215)	74.4 (68.4, 80.4)	70.4 (64.2, 76.7)	3.9	*0.631*
Other countries	12	9	7	2	16 (13, 19)	78.9 (58.4, 99.5)	59.2 (34.5, 83.9)	19.7	
Number of hospital beds									
<200	49	52	33	9	77 (69, 86)	63.7 (53.0, 74.5)	67.6 (57.2, 78.1)	-3.9	*0.095*

>=200	113	101	81	8	141 (134, 148)	80.3 (73.7, 86.8)	71.7 (64.3, 79.2)	8.5	
Clinical form									
Meningitis	91	100	70	9	130 (122, 138)	70.1 (62.2, 77.9)	77.0 (69.7, 84.2)	-6.9	*0.972*
Septicaemia	66	51	43	5	79 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	
Type of reporting centre									
Private	14	1	1	0	14 (14, 14)	100 (100, 100)	7.1 (-6.4, 20.6)	92.9	***0.004***
Public	149	152	113	13	201 (192, 210)	74.4 (68.4, 80.4)	75.9 (70, 81.8)	-1.5	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

Supplementary table 2. Capture–recapture analysis of serogroup C meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*p-value*
All cases	26	21	16	3	34 (30, 39)	76.7 (62.5, 90.9)	62.0 (45.6, 78.3)	14.8	***0.035***
Age group									
<15 years	4	4	4	0	4 (4, 4)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0	*0.992*
≥15 years	22	17	12	4	31 (25, 37)	71.4 (55.5, 87.4)	55.2 (37.6, 72.8)	16.2	
Sex									
Male	13	11	7	3	20 (15, 26)	65.0 (44.1, 85.9)	55.0 (33.2, 76.8)	10.0	*0.368*
Female	13	10	9	1	15 (13, 16)	90.3 (75.0, 100.0)	69.4 (45.7, 93.2)	20.8	
Year of report									
2011-2013	12	10	6	4	20 (14, 26)	61.9 (40.2, 83.5)	51.6 (29.3, 73.8)	10.3	*0.110*
2014-2015	14	11	10	1	16 (14, 17)	90.9 (76.6, 100.0)	71.4 (48.9, 94.0)	19.5	
Size of municipality									
<10,000 people	3	2	2	0	3 (3, 3)	100.0 (100.0, 100.0)	66.7 (13.3, 100.0)	33.3	*0.591*
≥10,000 people	21	15	12	3	27 (23, 30)	80.5 (65.3, 95.7)	57.5 (38.5, 76.4)	23.0	
Country of birth									
Spain	22	19	14	3	30 (26, 35)	74.1 (58.3, 89.8)	64.0 (46.7, 81.2)	10.1	*0.945*
Other countries	4	2	2	0	4 (4, 4)	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	50.0	
Number of hospital beds									

<200	7	5	5	0	7 (7, 7)	100.0 (100.0, 100.0)	71.4 (38.0, 104.9)	28.6	*0.283*
≥200	18	16	11	3	26 (22, 31)	69.5 (51.8, 87.2)	61.8 (43.1, 80.5)	7.7	
Clinical form									
Meningitis	16	16	11	3	24 (20, 27)	69.3 (50.4, 88.1)	69.3 (50.4, 88.1)	0.0	*0.908*
Septicaemia	8	4	4	0	8 (8, 8)	100.0 (100.0, 100.0)	50.0 (15.4, 84.7)	50.0	
Type of reporting centre									
Private	4	0	0	0	4 (4, 4)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.992*
Public	22	21	16	2	29 (26, 33)	76.4 (60.9, 91.9)	72.9 (56.7, 89.2)	3.5	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

Supplementary table 3. Capture–recapture analysis of all deaths due to meningococcal invasive disease reported to the SDR and MRS stratified by different characteristics, Catalonia 2011-2015

	No. records in SDR	No. records in MRS	Matched records	Calculated unreported cases	Estimated total no. of cases (95% CI)	Sensitivity SDR (%) (95% CI)	Sensitivity MRS (%) (95% CI)	*Difference in sensitivities (%)*	*p-value*
All cases	22	11	11	0	22 (22, 22)	100.0 (100.0, 100.0)	50.0 (29.1, 70.9)	50.0	*0.104*
Age group									
<15 years	6	4	4	0	6 (6, 6)	100.0 (100.0, 100.0)	66.7 (28.9, 100.0)	33.3	*0.346*
≥15 years	16	7	7	0	16 (16, 16)	100.0 (100.0, 100.0)	43.8 (19.4, 68.1)	56.3	
Sex									
Male	16	7	7	0	16 (16, 16)	100.0 (100.0, 100.0)	43.8 (19.4, 68.1)	56.2	*0.346*
Female	6	4	4	0	6 (6, 6)	100.0 (100.0, 100.0)	66.7 (29.0, 100.0)	33.3	
Year of report									
2011-2013	16	6	6	0	16 (16, 16)	100.0 (100.0, 100.0)	31.3 (8.5, 54.0)	68.8	*0.080*
2014-2015	6	5	5	0	6 (6, 6)	100.0 (100.0, 100.0)	83.3 (53.5, 100.0)	16.7	
Size of municipality									
<10,000 people	3	3	3	0	3 (3, 3)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0	*0.991*
≥10,000 people	19	8	8	0	19 (19, 19)	100.0 (100.0, 100.0)	42.1 (19.9, 64.3)	57.9	
Country of birth									
Spain	20	10	10	0	20 (20, 20)	100.0 (100.0, 100.0)	50.0 (28.1, 71.9)	50.0	*1.000*
Other countries	2	1	1	0	2 (2, 2)	100.0 (100.0, 100.0)	50.0 (0.0, 100.0)	50.0	
Number of hospital beds									
<200	4	2	2	0	4 (4, 4)	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	50.0	*0.822*
≥200	16	9	9	0	16 (16, 16)	100.0 (100.0, 100.0)	56.3 (31.9, 80.6)	43.7	
Clinical form									
Meningitis	7	4	4	0	7 (7, 7)	100.0 (100.0, 100.0)	57.1 (20.5, 93.8)	42.9	*0.648*
Septicaemia	15	7	7	0	15 (15, 15)	100.0 (100.0, 100.0)	46.7 (21.4, 71.9)	53.3	

Type of reporting centre									
Private	2	0	0	0	2 (2, 2)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	*0.992*
Public	20	11	11	0	20 (20, 20)	100.0 (100.0, 100.0)	55 (33.2, 76.8)	45	
Serogrup									
B	17	9	9	0	17 (17, 17)	100.0 (100.0, 100.0)	52.9 (29.2, 76.7)	47.1	*0.332*
C	4	1	1	0	4 (4, 4)	100.0 (100.0, 100.0)	25.0 (0.0, 67.4)	75.0	

SDR: Statutory disease reporting; MDR: Microbiological reporting system

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,11,12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12,13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	5,14,15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.