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# BMJ Open

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

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5 2 **model based on two independent surveillance systems**  
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## 112 **ABSTRACT**

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

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

122 **Results:** The sensitivity of the two combined surveillance systems was 88.5% (85.0-92.0). SDR  
123 had greater sensitivity than the MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0). In 2014-2015, the  
124 sensitivity of both systems was higher (80.6%; 73.2-87.9 vs. 73.4%; 65.2-81.6) than in 2011-  
125 2013 (59.3%; 52.6-66.0 vs. 58.3%; 51.6-65.1). In private centres, the sensitivity was higher for  
126 SDR than for MRS (100%; 100-100 vs. 4.8%; -4.4-13.9). The adjusted estimate of cases was  
127 lower than that obtained using the Chapman formula (279; 266-296 vs. 313; 295-330). The  
128 estimated adjusted incidence of IMD was 0.7/100,000 persons-year.

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

132

### 133 **Keywords:**

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

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### 136 **Strengths and limitations of this study**

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



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3 139 2. Statutory disease reporting system had greater sensitivity than Microbiological reporting  
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5 140 system.

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7 141 3. Two surveillance sources was higher sensitivity than sources individually.

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9 142 4. Factors associated with under-reporting should be analysed for invasive pneumococcal  
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11 143 disease surveillance.

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17 146 **BACKGROUND**

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19 147 Invasive meningococcal disease (IMD) continues to be an important cause of morbidity and  
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21 148 mortality, mainly in children aged < 4 years and adolescents. [1]

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23 149 In the European regions, the incidence rate of confirmed IMD cases is around 0.6/100,000

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25 150 persons, [2] similar to Spain (0.58/100,000 persons). [3] The highest incidence is for

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27 151 meningococcal serogroup B, accounting for 51.5% of confirmed IMD cases. The case fatality

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29 152 rate is around 10-15% [3, 4] and long-term sequelae occur in 10-20% of cases. [5]

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31 153 IMD is an urgent notifiable disease and its early notification is essential to provide an adequate

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33 154 public health response in patients and their close contacts to prevent further cases.

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35 155 Epidemiological surveillance allows monitoring of the impact of public health interventions,

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37 156 including vaccination programmes. Therefore, a robust epidemiological and microbiological

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39 157 system with timely and accurate surveillance providing information on the frequency of cases

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41 158 and the distribution of circulating serogroups is crucial.

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46 160 Evaluations of surveillance systems should be conducted regularly to increase their utility. [6-8]

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48 161 There are two reporting systems for the epidemiological surveillance of communicable disease

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50 162 in Catalonia: the statutory disease reporting system (SDR) and the microbiological reporting

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52 163 system (MRS). [9]

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57 165 The capture-recapture method is a statistical method for estimating the real incidence of

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59 166 diseases in a population with two or more information sources. [10, 11] The method is valid if

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3 167 four conditions are met: 1) the population under study has to be closed, i.e., there should be no  
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5 168 changes during the study period; 2) there must be a method of determining whether an  
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7 169 individual identified by one source is the same as an individual identified by the other; 3) each  
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9 170 individual must have the same probability of being captured by either system; 4) the systems  
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11 171 must be independent.  
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16 173 The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia  
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18 174 (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD.  
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## 21 176 **METHODS**

### 22 177 **Information sources**

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26 178 Catalonia is a region in the northeast of Spain with a population of 7,508,106 in 2015. [12]  
27

28 179 The SDR is a passive surveillance system through which health professionals declare all  
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30 180 infectious diseases subject to surveillance. The reporting of cases to the Public Health Agency  
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32 181 of Catalonia (PHAC) is mandatory and includes confirmed cases of IMD and is regulated by a  
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34 182 Decree. [9, 13]  
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39 184 The MRS is a surveillance system that consists of microbiologists notifying laboratory  
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41 185 confirmed microorganisms that cause infectious diseases. The main objectives of the MRS are  
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43 186 to confirm suspected cases of infectious diseases through the identification of the  
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45 187 microorganisms and serogroups involved and to determine trends and changes in  
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47 188 epidemiological patterns and microbiological resistance. [14]  
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49 189 The MRS was non-compulsory until 2015 and involved 50 health care centres representing over  
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51 190 83% of acute hospital beds. [15] Confirmed IMD cases were reported by microbiologists  
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53 191 including sex, age, clinical presentation, serogroup and diagnostic method.  
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58 193 Both systems belong to the PHAC epidemiological surveillance network and, since 2014,  
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60 194 transfer information automatically, but the independence of the sources is maintained.

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**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.

201

**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.

208

Estimates were made for the entire 5-year period and by age, sex, year of report, size of municipality (<10,000 and  $\geq$ 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).

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**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).

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224 **Patient and public involvement**

225 No patient involved

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227 **Statistical methods**

228 The total number of IMD cases was estimated using the two-source capture-recapture method,

229 which uses Chapman's formula, [16] developed to reduce bias due to small samples:

$$230 \quad N = \frac{(L1 + 1)(L2 + 1)}{a + 1} - 1$$

$$231 \quad 95\%CI = N \pm 1.96 \sqrt{\frac{(L1 + 1)(L2 + 1)(L1 - a)(L2 - a)}{(a + 1)^2(a + 2)}}$$

232

233 where L1 is the number of cases in the SDR dataset, L2 is the number of cases reported to MRS,

234 and **a** is the number of cases captured by both systems. The sensitivity (Se) of case

235 ascertainment by the two sources was also calculated as the proportion of true cases detected by

236 each source, i.e. Se (1) =L1/N for source 1 and Se (2) =L2/N for source 2. The sensitivity of

237 bothsources combined was calculated as the proportion of cases detected by one of the two

238 sources or both, i.e., Se (1, 2) =(L1+L2-a)/N.

239

240 The independence of the sources was considered when applying the capture-recapture method.

241 [17, 18] In the two-by-two table, where **a** represents cases reported by two sources or242 combinations of sources, **b** and **c** cases reported exclusively by either of the two sources and **x**

243 the estimated non-reported cases by either of the sources, the odds ratio (OR = ax/bc) should not

244 differ from one.

245

246 A multinomial logit model was used to evaluate patient characteristics and the probability of

247 capture by different sources, which allows more precise estimates of the number of cases. [19,

248 20] We used a backwards stepwise procedure (using likelihood ratio tests, with a P-value &gt;0.2

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3 249 as the criterion for removing variables from the model), [21, 22] starting with a full model  
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5 250 including all potential covariates, and we used the parameter estimates from the model to  
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7 251 estimate the sizes of population subgroups and their 95% confidence intervals (CI). All analyses  
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9 252 were made using R software version 3.0.1.  
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## 15 255 **RESULTS**

### 17 256 **Patient characteristics**

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20 257 Patient characteristics by source are shown in Table 1. From 2011 to 2015, 212 IMD cases were  
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22 258 reported to the SDR and 202 cases to the MRS, representing an incidence of 0.56 and 0.54  
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24 259 /100,000 persons-year, respectively. IMD due to serogroup B was the most-frequently reported  
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26 260 serogroup (77.4% and 75.7% in the SDR and MRS, respectively). Around 63% of patients were  
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28 261 aged < 15 years; the mean age was 21.4 for the SDR and 20.5 years for the MRS. Male sex was  
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30 262 more frequent in the SDR (52.4%) than in the MRS (49%). The SDR presented the most cases  
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32 263 in 2015 (48 cases; 22.6%) and the MRS (61 cases; 30.2%) in 2011. The SDR reported that 84%  
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34 264 of patients lived in a municipality of  $\geq 10,000$  people compared with 73% in the MRS. In both  
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36 265 sources, the number of cases declared in a hospital of  $\geq 200$  beds were around 70%. The main  
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38 266 clinical form in both sources was meningitis (54.7% and 64.8%, respectively) and sepsis (38.7%  
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40 267 and 32.7%, respectively). Reports from private centres represented 10% of cases in the SDR and  
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42 268 0.5% in the MRS. Twenty-two cases (10.4%) cases reported by the SDR died compared with 11  
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44 269 cases (5.4%) reported by the MRS .  
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277**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)
<b>Age groups</b>		
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%)
<b>Sex, n (%)</b>		
Male	111 (52.4%)	99 (49.0%)
Female	101 (47.6%)	103 (51.0%)
<b>Year of report, n (%)</b>		
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%)
<b>Size of municipality, n (%)</b>		
<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%)
<b>Country of birth, n (%)</b>		
Spain	194 (91.5%)	188 (93.1%)
Other countries	18 (8.5%)	14 (6.9%)
<b>Number of hospital beds, n (%)</b>		
<200	60 (28.3%)	65 (32.2%)
≥200	149 (70.3%)	137 (67.8%)
NAs	3 (1.4%)	0 (0.0%)
<b>Clinical form, n (%)</b>		
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%)
<b>Serogroup, n (%)</b>		
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%)
<b>Type of reporting centre</b>		
Private	21 (10.0%)	1 (0.5%)
Public	190 (90.0%)	201 (99.5%)

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

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3 280 **Capture-recapture analysis**

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5 281 The odds ratio (OR) was 1.01 (95%CI 0.62-1.66), reinforcing the independence of the two  
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7 282 sources.

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9 283 During the period studied, 212 and 202 IMD cases were reported by the SDR and MRS,  
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11 284 respectively. One hundred thirty-seven cases (43.8%) coincided in both sources and 36 cases  
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13 285 (11.5%) were not reported to either source. The estimated number of cases was 313 (95% CI  
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15 286 295–330) (Table 2) and the estimated incidence rate was 0.83/100,000 persons-year.

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19 288 **Table 2. Capture–recapture analysis of two datasets to estimate the total number of**  
20 289 **invasive meningococcal disease cases, Catalonia 2011-2015**  
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		SDR		Total
		Identified	Not identified	
MRS	Identified	137	65	202
	Not identified	75	36	111
Total		212	101	313

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28 SDR: Statutory disease reporting  
MRS: Microbiological reporting system

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31 292 The sensitivity of the SDR was 67.9% (95%CI 62.7-73.1) and that of the MRS was 64.7%  
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33 293 (95%CI 59.4-70.0) (P-<0.001) (Table 3). The sensitivity increased to 88.5% (95%CI 85.0-92.0)  
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35 294 when the datasets were combined.  
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306 **Table 3. Capture–recapture analysis of all invasive meningococcal disease cases reported to the SDR and MRS stratified by characteristics, Catalonia**  
 307 **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
<b>All cases</b>	212	202	137	36	313 (295, 330)	67.9 (62.7, 73.1)	64.7 (59.4, 70.0)	3.2	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
2011-2013	122	120	71	35	206 (187, 226)	59.3 (52.6, 66.0)	58.3 (51.6, 65.1)	1.0	<b>&lt;0.001</b>
2014-2015	90	82	66	6	112 (106, 118)	80.6 (73.2, 87.9)	73.4 (65.2, 81.6)	7.2	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	
<b>Type of reporting centre</b>									
Private	21	1	1	0	21 (21, 21)	100 (100, 100)	4.8 (-4.4, 13.9)	95.2	<b>0.002</b>
Public	190	201	136	26	281 (267, 295)	67.7 (62.2, 73.2)	71.6 (66.4, 76.9)	-3.9	

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



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3 309 There were no differences in sensitivity between in <15 years and  $\geq 15$  years age groups (P-  
4 value=0.468) in either source although it was higher in the <15 years (69.1%;  
5 310  
6 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  
7 311  
8 the highest sensitivity were 2-4 years in the SDR, with 80.3% (95%CI 68.5-92.1), and 35-44  
9 312  
10 years in the MRS, with 80.5% (95%CI 60.4-100.0) (figure 1).  
11 313  
12 In 2011-2013, sensitivity for the SDR and the MRS were 59.3% (95%CI 52.6-66) and 58.3%  
13 314  
14 (95%CI 51.6-65.1), respectively, lower than that in 2014-2015 (80.6%; 95%CI 73.2-87.9, for  
15 315  
16 the SDR and 73.4%; 95%CI 65.2-81.6, for the MRS (P<0.001)) (Table 3). 2014 showed the  
17 316  
18 highest sensitivity for both sources: 91.3% (95%CI 83.2-99.4) for the SDR and 73.9% (95%CI  
19 317  
20 61.2-86.6) for the MRS (Figure 2). 2011 was the only year in which the MRS had a higher  
21 318  
22 sensitivity than the SDR (56.4%; 95%CI 47.1-65.8 and 39.8%; 95%CI 30.6-49.0, respectively).  
23 319  
24 In private centres the sensitivity of the SDR was 100% (95%CI 100-100) and that of the MRS  
25 320  
26 was 4.8% (95%CI -4.4-13.9). No differences were found in other characteristics analysed.  
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32 323 For l meningitis, 116 and 131 cases were reported by the SDR and the MRS, respectively. The  
33 324  
34 estimated number of meningitis cases was 181, and 18 cases were not reported by either source.  
35 325  
36 The highest sensitivity was detected in the MRS (72.5%; 95% CI 66-79) compared with the  
37 326  
38 SDR (64.2%; 95%CI 57.2-71.2) (P<0.001) (Table 4). 2014-2015 showed a higher sensitivity in  
39 327  
40 both sources compared with 2011-2013: 82.4% (95%CI 72.7-92) in the MRS and 75.6%  
41 328  
42 (95%CI 64.7-86.5) in the SDR. Public centres had a higher sensitivity in the MRS (77.7%;  
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44 95%CI 71.4-84.0) and in the SDR (63.9%; 95%CI 56.6-71.2) (P<0.037).  
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332 **Table 4. Capture–recapture analysis of meningococcal meningitis reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015**

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	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
<b>All cases</b>	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
2011-2013	71	82	47	18	124 (111, 137)	57.5 (48.8, 66.2)	66.4 (58.1, 74.7)	-8.9	<b>0.013</b>
2014-2015	45	49	37	3	60 (56, 64)	75.6 (64.7, 86.5)	82.4 (72.7, 92.0)	-6.7	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Type of reporting centre</b>									
Private	9	1	1	0	9 (9, 9)	100.0 (100.0, 100.0)	11.1 (-9.4, 31.6)	88.9	<b>0.037</b>
Public	107	130	83	14	168 (158, 178)	63.9 (56.6, 71.2)	77.7 (71.4, 84.0)	-13.7	

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

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3 336 For sepsis, 82 cases and 66 cases were reported by the SDR and the MRS, respectively. The  
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5 337 sensitivity was higher for the SDR (75.9%; 95%CI 67.9-84) than the MRS (61.1%; 95%CI  
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7 338 51.9-70.3) (Table 5). There were 108 estimated cases and 10 cases were not reported by either  
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9 339 source. The sensitivity was higher in the <15 years than in the  $\geq 15$  years in both sources, but  
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11 340 higher in the SDR (81.1%; 95%CI 71.1-91.1 versus 71%; 95%CI 59.4-82.5 for the MRS;  
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13 341  $P=0.0036$ ), and higher in 2014-2015 than in 2011-2013 (87.6%; 95%CI 78-97.3 for the SDR  
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15 342 and 71.9%; 95%CI 58.7-85.1 for the MRS) ( $P<0.015$ ).  
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19 344 Serogroup B (Supplementary Table 1) showed the sensitivity of the SDR was higher than that of  
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21 345 the MRS (74.6%; 95%CI 68.8-80.3 and 69.6%; 95%CI 63.5-75.6, respectively). There were  
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23 346 differences according to the period and the type of centre. In 2014-2015, the sensitivity was  
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25 347 87.1% (95%CI 79.7-94.5) for the SDR and 78.3% (95%CI 69.2-87.4) for the MRS ( $P<0.002$ ).  
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27 348 In private centres, the sensitivity in SDR was 100% compared with 7.1% (95%CI -6.4-20.6)  
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29 349 ( $P=0.004$ ) in MRS. The sensitivity was higher for IMD serogroup C cases in SDR than in MRS  
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31 350 (76.7%; 95%CI 62.5-90.9 and 62%; 95%CI 45.6-78.3, respectively) (Supplementary Table 2).  
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33 351 All 22 deaths were reported in the SDR (CFR: 10.4%), and the sensitivity of the SDR was  
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35 352 higher than that of the MRS (100%; 95%CI 100-100 vs 50%; 95%CI 29.1-70.9,  $P=0.104$ )  
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37 353 (Supplementary Table 3).  
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354 **Table 5. Capture–recapture analysis of meningococcal septicaemia reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015**  
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	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
<b>All cases</b>	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	<b>&lt;0.001</b>
<b>Age at notification, years</b>									
<15 years	48	42	34	4	60 (55, 64)	81.1 (71.1, 91.1)	71.0 (59.4, 82.5)	10.1	<b>0.036</b>
≥15 years	34	23	16	8	49 (40, 58)	70.3 (57.4, 83.1)	47.5 (33.4, 61.6)	22.7	
<b>Sex</b>									
Male	43	27	22	5	53 (47, 59)	81.8 (71.3, 92.2)	51.3 (37.8, 64.8)	30.4	<b>0.315</b>
Female	39	39	28	5	55 (49, 60)	72.0 (60.0, 83.9)	72.0 (60.0, 83.9)	0.0	
<b>Year of report</b>									
2011-2013	43	34	22	11	66 (56, 77)	65.2 (53.6, 76.7)	51.5 (39.5, 63.6)	13.6	<b>0.015</b>
2014-2015	39	32	28	2	45 (42, 48)	87.6 (78.0, 97.3)	71.9 (58.7, 85.1)	15.7	
<b>Size of municipality</b>									
<10,000 people	7	7	5	1	10 (8, 12)	72.2 (44.0, 100.0)	72.2 (44.0, 100.0)	0.0	<b>0.918</b>
≥10,000 people	71	52	43	6	86 (80, 93)	82.9 (74.9, 90.8)	60.7 (50.3, 71.0)	22.2	
<b>Country of birth</b>									
Spain	73	63	47	9	98 (90, 106)	74.7 (66.1, 83.3)	64.5 (55.0, 74.0)	10.2	<b>0.275</b>
Other countries	9	3	3	0	9 (9, 9)	100.0 (100.0, 100.0)	33.3 (2.5, 64.1)	66.7	
<b>Number of hospital beds</b>									
<200	25	23	16	4	36 (31, 42)	70.0 (55.0, 85.1)	64.4 (48.7, 80.1)	5.6	<b>0.831</b>
≥200	56	43	34	6	71 (65, 78)	79.2 (69.7, 88.7)	60.8 (49.4, 72.2)	18.4	
<b>Type of reporting centre</b>									
Private	9	0	0	0	9 (9, 9)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	<b>0.988</b>
Public	73	66	50	8	97 (89, 104)	75.9 (67.3, 84.4)	68.6 (59.3, 77.9)	7.3	

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

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3 359 The results of the multinomial logit model for all cases are shown in Table 6. The variables  
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5 360 considered significant in defining the sensitivity of the two sources were year of report (2011-  
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7 361 2013 versus 2014-2015) and size of municipality. With these variables in the model, the  
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9 362 adjusted estimate of the total number of cases was 279 cases (95%CI 266-296) and the  
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11 363 estimated incidence rate was 0.7/100,000 persons-year.  
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16 365 **Table 6. Variables defining the sensitivity of the SDR and MRS in detecting invasive**  
17 366 **meningococcal diseases cases. Multinomial logit model**  
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	<b>OR (95%CI)</b>	<b>p-value</b>
<b>Year of report (2014-2015)</b>	2.29 (1.35, 3.89)	<b>0.002</b>
<b>Size of municipality (<math>\geq 10,000</math> people)</b>	0.51 (0.23, 1.12)	0.093

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23 369 OR: odds ratio; n estimate: 279 (266, 296)  
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## 26 27 371 DISCUSSION

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29 372 The sensitivity obtained by combining the two surveillance system for IMD cases was 88.5%,  
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31 373 greater than for each source s (67.9% and 64.7%, respectively). Globally, the SDR showed  
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33 374 higher sensitivity than the MDR, mainly for cases of sepsis, I serogroup B and serogroup C,  
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35 375 although for meningitis the sensitivity of the MDR was higher than that of the SDR.  
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37 376 Similar studies found greater sensitivities by combining data systems than we did. Baldovin et  
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39 377 al. [23] in Italy, reported an overall sensitivity of 94.7% by combining four data sources  
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41 378 (mandatory notification system, laboratory surveillance, invasive bacterial surveillance and  
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43 379 hospital discharge). Jansson et al. [24], in Sweden, found a global sensitivity of 98.7%, 91.1%  
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45 380 for clinical notification and 85.4% for laboratory reporting. In Austria a good agreement  
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47 381 between the National Reference Center for meningococci and the hospital discharge was found,  
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49 382 although a clinical review of hospital discharge data was necessary to detect false positive cases  
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51 383 recorded. [25]  
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55 385 The sensitivity was similar in children aged <15 years than in persons aged  $\geq 15$  years in both  
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57 386 sources (69.1% for the SDR and 66.5% for the MRS; P=0.468). Gibson et al., [26] in Australia,  
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3 387 analysed IMD sensitivity in children aged < 15 years in three sources: notifiable system,  
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5 388 hospitalized patients and mortality data. They found a greater sensitivity (99.5%) than we did,  
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7 389 although 15% of hospitalized children were false-positive cases.  
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11 391 We found a greater sensitivity for meningitis in the MRS than in the SDR (72.5% vs 64.2%). A  
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13 392 possible explanation is that meningitis is considered a more serious disease and, therefore,  
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15 393 microbiologists are more sensitive to its reporting. It is difficult to compare our results with  
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17 394 those of other studies, since other sources of information were used or the independence of data  
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19 395 sources was presumed but not demonstrated, [25] which is essential when using the capture-  
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21 396 recapture method.  
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26 398 Notification of confirmed cases of IMD by laboratories is essential in epidemiological  
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28 399 surveillance. [27] Molecular information on circulating serogroups that is required to implement  
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30 400 public health measures such as vaccination is essential to control the disease [28] and evaluate  
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32 401 the impact of available vaccines.  
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37 403 In the absence of automated electronic reporting, monitoring and increasing the speed of  
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39 404 laboratory reports may allow the public health department to administer chemoprophylaxis and  
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41 405 vaccination to contacts. [28] Although a higher sensitivity has been reported for electronic  
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43 406 reporting than for paper-based reports by some authors, [29] during the study period, electronic  
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45 407 surveillance was used in the SDR but not in the MDR, which may explain, at least in part, why  
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47 408 the MDR had a lower sensitivity than the SDR. [30]  
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51 410 In the multinomial model, the 2014-2015 period and the size of the municipality show a higher  
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53 411 sensitivity in the SDR, suggesting that IMD was well recorded in the two surveillance systems,  
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55 412 although 36 cases (11.5%) were not captured by either source. This suggests there was  
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57 413 underreporting, despite the clinical severity of the disease. It is very important to improve  
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3 414 reporting by all physicians and microbiologists to the SDR and MDR to assess the impact of  
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5 415 interventions such as immunization.  
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9 417 The estimated IMD incidence rate of 0.7/100, 000 persons-year found in the multinomial model  
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11 418 is less than that found using capture-recapture (0.83/100,000 persons-year) but higher than that  
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13 419 calculated using the SDR (0.56/100,000 persons-year) or MDR data (0.54/100,000 persons-  
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15 420 year). Other European studies showed incidence rates of between 0.39 [23] and 1.18/100,000  
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17 421 persons-year. [25]  
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21 423 The sensitivity of the two sources were intermediate (67.9% for the SDR and 64.7% for the  
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23 424 MRS). The lower sensitivity of the MRS may be due to the fact that the MRS is a sentinel  
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25 425 system with a coverage of 82% of acute hospital beds and without private centres. In our series,  
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27 426 21 cases (10%) included in the SDR were reported by private centres, while only one case  
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29 427 (0.5%) was reported to the MSR; this patient was finally transferred to a public hospital. The  
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31 428 inclusion of cases that have an equal probability of selection in one source might lead to an  
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33 429 overestimation. Other authors have reported this limitation when the hospital discharge data set  
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35 430 includes probable cases which are not included in the reference centre. [25]  
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39 432 Death was registered in 22 cases (10.5%), similar to that reported in other European countries  
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41 433 (ECDC) but slightly lower than that observed in Italy (14%) using the capture-recapture  
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43 434 method. [23] All cases were reported to the SDR but only 50% were reported to the MRS,  
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45 435 indicating that clinical data are better in the SDR than in the MRS. Other authors have used  
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47 436 mortality data for capture-recapture analysis and concluded that all deaths were reported in  
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49 437 notifiable systems. [26]  
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55 439 The sensitivity of the sources studied for the surveillance of IMD cannot be generalized to other  
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57 440 diseases because physicians' or microbiologists' perception of the importance of IMD differs  
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59 441 from that of other diseases. [29]  
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5 443 The main strength of this study is that the two sources had wide coverage. The SDR is a  
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7 444 universal epidemiological surveillance source and, unlike the MDR, is a sentinel source, with a  
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9 445 high coverage of 83%. Cases with PIC accounted for 85.5% of all cases reported to detect  
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11 446 whether cases were coincident or not. In addition, the independence of the two sources was  
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13 447 demonstrated, complying with the premise of the capture-recapture method.  
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18 449 A limitation of the study was that not all cases had the same probability of being selected from a  
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20 450 given source. Cases diagnosed in private centres or public centres that did not participate in the  
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22 451 MRS could not be reported by this system and this may explain, at least in part, the lower  
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24 452 sensitivity than the SDR. This highlights the importance of including public and private centres  
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26 453 to increase the robustness of the MRS. Another limitation was that we did not analyse the role  
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28 454 of the electronic surveillance system, although a previous study detected greater sensitivity of  
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30 455 the SDR when electronic surveillance was introduced. [30]  
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## 34 457 **CONCLUSIONS**

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36 458 The sensitivity of enhanced surveillance through the combination of two complementary  
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38 459 sources (statutory reporting by physicians and microbiological reporting by microbiologists)  
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40 460 was higher than that of the individual sources. These systems are complementary and constitute  
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42 461 the basic sources of information necessary for adequate epidemiological surveillance of IMD.  
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44 462 Specific studies to estimate the factors associated with under-reporting are needed to reinforce  
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46 463 epidemiological surveillance of this disease.  
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## 53 54 55 466 **DECLARATIONS**

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58 467 **Ethics approval and consent to participate**  
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1  
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3 468 Not applicable  
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6 469 **Consent of publication**  
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9 470 Not applicable  
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12 471 **Availability of data and materials**  
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15 472 The datasets used and analysed during the current study available from the corresponding author  
16  
17 473 on reasonable request.

18  
19 474 **Competing interests**  
20

21 475 The authors declare that they have no competing interests.  
22

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32 480 design of the study and collection, analysis, and interpretation of data and in writing the  
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34 481 manuscript.  
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37 482 **Author contributions**  
38

39 483 PC analyzed and interpreted data, studied conception and design of the study and writes the  
40  
41 484 manuscript; MV and NS did statistical analysis; GC revised and collected data; TG,SH,LR  
42  
43 485 collected data; MJ revised the study and AD did critical revision and got funding.  
44  
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46

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48

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3 931 Figure 1. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015  
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5 932 Figure 2. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015  
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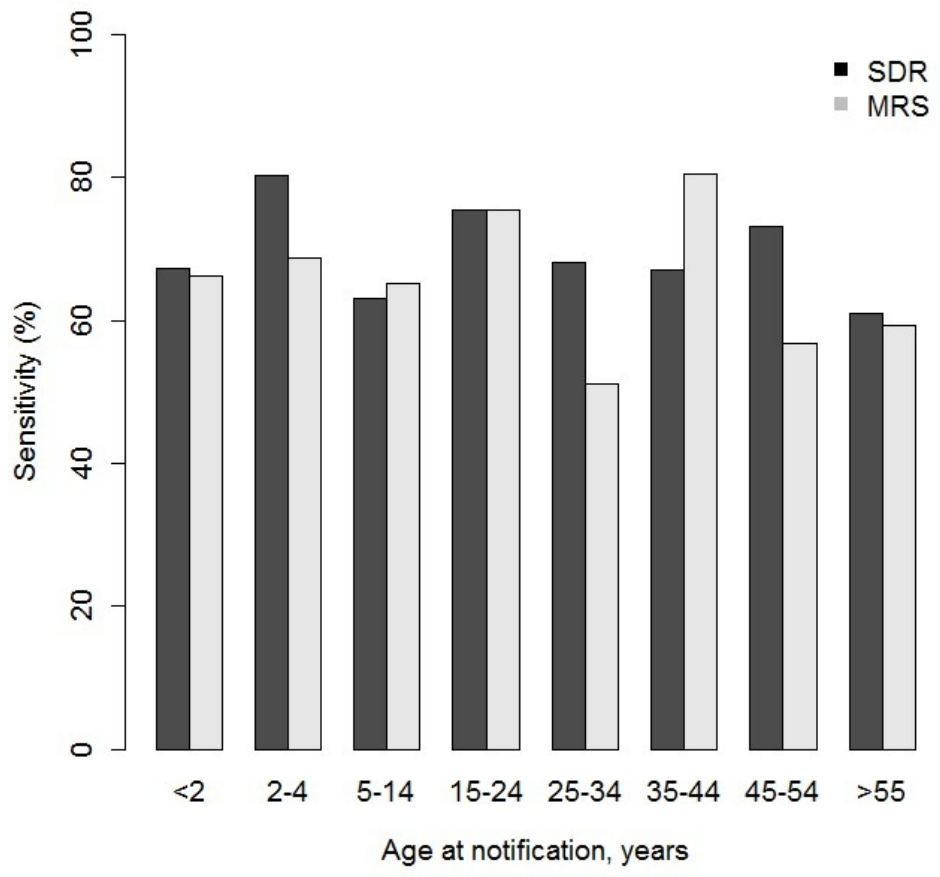


Figure 1. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

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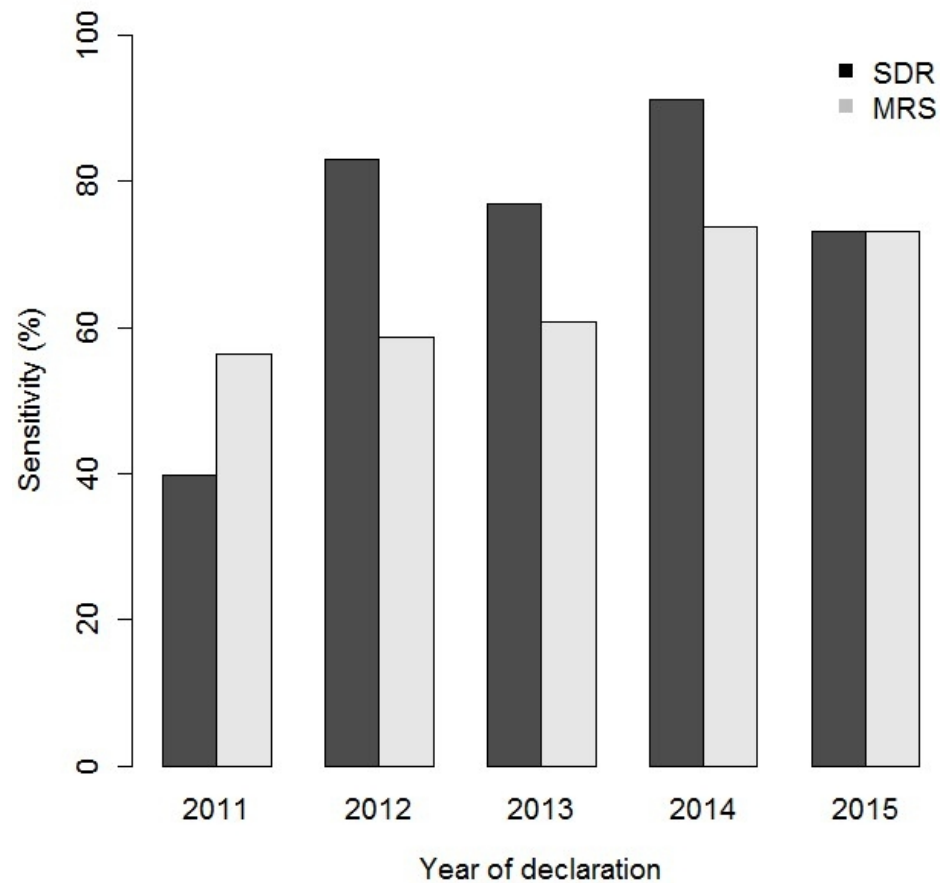


Figure 2. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

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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
<b>All cases</b>	164	153	114	17	220 (209, 232)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
2011-2013	95	91	60	18	144 (132, 157)	66.1 (58.3, 73.8)	63.3 (55.4, 71.2)	2.8	<b>0.002</b>
2014-2015	69	62	54	3	80 (76, 83)	87.1 (79.7, 94.5)	78.3 (69.2, 87.4)	8.8	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	
<b>Type of reporting centre</b>									
Private	14	1	1	0	14 (14, 14)	100 (100, 100)	7.1 (-6.4, 20.6)	92.9	<b>0.004</b>
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
<b>All cases</b>	26	21	16	3	34 (30, 39)	76.7 (62.5, 90.9)	62.0 (45.6, 78.3)	14.8	<b>0.035</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	
<b>Type of reporting centre</b>									
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
<b>All cases</b>	22	11	11	0	22 (22, 22)	100.0 (100.0, 100.0)	50.0 (29.1, 70.9)	50.0	0.104
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	
<b>Type of reporting centre</b>									
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

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Continued on next page

<b>Results</b>			
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	10
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 (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	10,11,12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

## 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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Secondary Subject Heading:	Infectious diseases, Public health
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3 1 **Estimation of the incidence of invasive meningococcal disease using a capture-recapture**  
4 **model based on two independent surveillance systems, in Catalonia, Spain**  
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3 112 **ABSTRACT**  
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5 113 **Objectives:** Invasive meningococcal disease (IMD) is an urgent notifiable disease and its early  
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7 114 notification is essential to prevent cases. The objective of the study was to assess the sensitivity  
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9 115 of two independent surveillance systems, and to estimate the incidence of IMD.  
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11 116 **Design:** We used capture-recapture model based on two independent surveillance systems, the  
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13 117 statutory disease reporting system (SDR) and the microbiological reporting system (MRS) of the  
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15 118 Public Health Agency of Catalonia, between 2011 and 2015. The capture-recapture analysis and  
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17 119 95% confidence intervals were calculated using the Chapman formula. Multivariate vector  
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19 120 generalized linear model was performed for adjusted estimation.  
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22 121 **Measures:** The variables collected were age, sex, year of report, size of municipality (< 10,000  
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24 122 and  $\geq$  10,000), clinical form, death, serogroup, country of birth and type of reporting centre  
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26 123 (private and public).  
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28 124 **Results:** The sensitivity of the two combined surveillance systems was 88.5% (85.0-92.0). SDR  
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30 125 had greater sensitivity than the MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0). In 2014-2015, the  
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32 126 sensitivity of both systems was higher (80.6%; 73.2-87.9 vs. 73.4%; 65.2-81.6) than in 2011-  
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34 127 2013 (59.3%; 52.6-66.0 vs. 58.3%; 51.6-65.1). In private centres, the sensitivity was higher for  
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36 128 SDR than for MRS (100%; 100-100 vs. 4.8%; -4.4-13.9). The adjusted estimate of IMD cases  
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38 129 was lower than that obtained using the Chapman formula (279; 266-296 vs. 313; 295-330). The  
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40 130 estimated adjusted incidence of IMD was 0.7/100,000 persons-year.  
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43 131 **Conclusions:** The sensitivity of enhanced surveillance through the combination of two  
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45 132 complementary sources was higher than for the sources individually. Factors associated with  
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47 133 under-reporting in different systems should be analysed to improve IMD surveillance.  
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51 135 **Keywords:**

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53 136 Meningococcal disease, Capture-recapture, estimated incidence, surveillance systems.  
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58 138 **Strengths and limitations of this study**  
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3 140 • Early notification of Invasive meningococcal disease is essential to prevent cases.  
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5 141 • This study was strengthened by a wide coverage by means of two epidemiological surveillance  
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7 142 sources: The Statutory Disease Reporting System (SDR), based on passive reporting of health  
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9 143 professionals, and the Microbiological Reporting System (MRS), based on confirmed-  
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11 144 laboratory cases.  
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13 145 • SDR had greater sensitivity than MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0) but the  
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15 146 sensitivity of both surveillance sources together was higher than each source individually.  
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17 147 • Factors associated with under-reporting should be analysed for invasive meningococcal  
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19 148 disease (IMD) surveillance.  
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## 26 151 **BACKGROUND**

28 152 Invasive meningococcal disease (IMD) continues to be an important cause of morbidity and  
29  
30 153 mortality, mainly in children aged < 4 years and adolescents. [1]  
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32 154 In the European regions, the incidence rate of confirmed IMD cases was 0.62/100,000 persons-  
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34 155 year in 2018 [2], and in Spain it was 0.86/100,000 persons. [3] Six serogroups (A, B, C, W, X,  
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36 156 Y) currently cause almost all cases of this life-threatening disease worldwide. Case fatality rate is  
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38 157 about 10% in developed countries [4-6], and 40-65% present with meningitis, but  
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40 158 meningococemia and pneumonia are also frequent [4], being the serogroup involved related both  
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42 159 with the case fatality rate [7] and the predominant clinical form. [8] Serogroup B causes more  
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44 160 than a third part of IMD [4,9] but in some countries or population groups the proportion is even  
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46 161 higher. [10,11] In Spain, from 2009 to 2018, serogroup B accounted for 64% of IMD cases. [12]  
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48 162 A high proportion, up to 60% [13] of IMD cases, are affected by a range of sequelae and health  
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50 163 related impairment in the quality of life of survivors and their families. [14]  
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52 164 IMD is an urgent notifiable disease and its early notification is essential to provide an adequate  
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54 165 public health response in patients and their close contacts to prevent further cases.  
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56 166 Epidemiological surveillance allows monitoring of the impact of public health interventions,  
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58 167 including vaccination programmes. Therefore, a robust epidemiological and microbiological  
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3 168 system with timely and accurate surveillance providing information on the frequency of cases and  
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5 169 the distribution of circulating serogroups is crucial.  
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9 171 Evaluations of surveillance systems should be conducted regularly to increase their utility. [15-  
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11 172 17] There are two reporting systems for the epidemiological surveillance of communicable  
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13 173 disease in Catalonia: the statutory disease reporting system (SDR) and the microbiological  
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15 174 reporting system (MRS). [18]  
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20 176 The capture-recapture method is a statistical method for estimating the real incidence of diseases  
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22 177 in a population with two or more information sources. [19, 20] The method is valid if four  
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24 178 conditions are met: 1) the population under study has to be closed, i.e., there should be no changes  
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26 179 during the study period; 2) there must be a method of determining whether an individual identified  
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28 180 by one source is the same as an individual identified by the other; 3) each individual must have  
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30 181 the same probability of being captured by either system; 4) the systems must be independent.  
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34 183 The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia  
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36 184 (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD.  
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## 39 186 **METHODS**

### 40 187 **Information sources**

41 188 Catalonia is a region in the northeast of Spain with a population of 7,508,106 in 2015. [21]

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43 189 The SDR is a passive surveillance system through which health professionals report all infectious  
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45 190 diseases subject to surveillance. The reporting of cases to the Public Health Agency of Catalonia  
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47 191 (PHAC) is mandatory and includes confirmed cases of IMD and is regulated by a Decree. [18,  
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53 194 The MRS is a surveillance system that consists of microbiologists notifying laboratory confirmed  
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55 195 microorganisms that cause infectious diseases. The main objectives of the MRS are to confirm  
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3 196 suspected cases of infectious diseases through the identification of the microorganisms and  
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5 197 serogroups involved and to determine trends and changes in epidemiological patterns and  
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7 198 microbiological resistance. [23]

9 199 The MRS was non-compulsory until 2015 and involved 50 health care centres representing over  
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11 200 83% of acute hospital beds. [24] Confirmed IMD cases were reported by microbiologists  
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13 201 including sex, age, clinical presentation (meningitis, bacteraemia of unknown focus and other  
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15 202 clinical presentations), serogroup and diagnostic method.

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20 204 Both systems belong to the PHAC epidemiological surveillance network and, since 2014, transfer  
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22 205 information automatically, but the independence of the sources is maintained.

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26 207 **Cases definition, inclusion, and exclusion criteria**

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28 208 A confirmed case of IMD was defined as laboratory confirmed if at least one of the following  
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30 209 criteria was fulfilled: isolation in cultures or detection of *Neisseria meningitidis* DNA by PCR in  
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32 210 a normally sterile site, detection of gram-negative diplococci or *N. meningitidis* antigen in  
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34 211 cerebrospinal fluid.

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39 213 **Data collection**

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41 214 We made a retrospective study of confirmed IMD cases in Catalonia from January 2011 to  
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43 215 December 2015. We extracted all IMD records from the MRS and SDR and linked the databases  
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45 216 using the personal identification code (PIC). When the PIC was not available, data on notification,  
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47 217 age and sex were used to identify duplicates between the two sources. In cases with inconclusive  
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49 218 matching, the hospital was used as a fifth matching criterion.

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53 220 Estimates were made for the entire 5-year period and by age, sex, year of report, size of  
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55 221 municipality (<10,000 and  $\geq$ 10,000), country of birth, number of hospital beds, clinical form  
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57 222 (meningitis, with or without sepsis, sepsis, and others), serogroup, death and reporting centre  
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59 223 (private or public).

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3 224 **Ethics statement**  
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5 225 The study was not submitted for research ethics approval as the activities described were  
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7 226 conducted as part of the legislated mandate of the Health Department of Catalonia, the competent  
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9 227 authority for surveillance of communicable diseases according to Decree 203/2015 of the 15  
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11 228 September which created the epidemiological surveillance network of Catalonia. [18] All the  
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13 229 study activities formed part of public health surveillance and did not require informed consent.  
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15 230 Personal data were used only for the matching process and measures to protect the confidentiality  
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17 231 of personal data were applied (access to the data restricted to the personnel involved in data  
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19 232 analysis, and removal of personal data from the datasets after matching).  
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24 234 **Patient and public involvement**  
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26 235 No patient involved  
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30 237 **Statistical methods**  
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32 238 The total number of IMD cases was estimated using the two-source capture-recapture method,  
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34 239 which uses Chapman's formula, [25] developed to reduce bias due to small samples:

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$$N = \frac{(L1 + 1)(L2 + 1)}{a + 1} - 1$$
  
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$$95\%CI = N \pm 1.96 \sqrt{\frac{(L1 + 1)(L2 + 1)(L1 - a)(L2 - a)}{(a + 1)^2(a + 2)}}$$
  
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46 243 where L1 is the number of cases in the SDR dataset, L2 is the number of cases reported to MRS,  
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48 244 and **a** is the number of cases captured by both systems. The sensitivity (Se) of case ascertainment  
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50 245 by the two sources was also calculated as the proportion of true cases detected by each source,  
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52 246 i.e. Se (1) =L1/N for source 1 and Se (2) =L2/N for source 2. The sensitivity of both sources  
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54 247 combined was calculated as the proportion of cases detected by one of the two sources or both,  
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56 248 i.e., Se (1, 2) =(L1+L2-a)/N.  
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3 250 The independence of the sources was considered when applying the capture-recapture method.  
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5 251 [26, 27] In the two-by-two table, where **a** represents cases reported by two sources or  
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7 252 combinations of sources, **b** and **c** cases reported exclusively by either of the two sources and **x** the  
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9 253 estimated non-reported cases by either of the sources, the odds ratio ( $OR = ax/bc$ ) should not  
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11 254 differ from one.

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16 256 As a multivariate model, a vector generalized linear model (VGLM) from the generalized additive  
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18 257 model (GAM) framework [28] was used to evaluate patient characteristics and the probability of  
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20 258 capture by the different sources taking into account the covariates: age (<15 vs >=15), gender,  
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22 259 year of notification (2011-2013 vs 2014-2015), size of the municipality (<10,000 vs >=10,000),  
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24 260 country of birth (Spain vs other), number of hospital beds (<200 vs >=200) and diagnosis  
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26 261 (meningitis vs septicaemia). The outcome for the model is a two column matrix with 0 and 1  
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28 262 indicating if the record is identified by SDR or MRS. We used a backwards stepwise procedure  
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30 263 (using likelihood ratio tests, with a p-value >0.2 as the criterion for removing variables from the  
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32 264 model) [29, 30] to eliminate covariates, starting with a full model including all described  
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34 265 covariates, and we used the parameter estimates from the model to estimate the sizes of population  
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36 266 subgroups and calculate incidence rates. The 95% confidence intervals (CI) were calculated,  
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38 267 allowing for uncertainty in the total number of cases estimated. For each of the described  
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40 268 covariates, VLGM with source notification as outcome was used to test differences in  
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42 269 sensitivities. All analyses were made using R software version 3.0.1.

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## 48 49 272 **RESULTS**

### 50 51 273 **Patient characteristics**

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53 274 Patient characteristics by source are shown in Table 1. From 2011 to 2015, 212 IMD cases were  
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55 275 reported to the SDR and 202 cases to the MRS, representing an incidence of 0.56 and 0.54  
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57 276 /100,000 persons-year, respectively. IMD due to serogroup B was the most-frequently reported  
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59 277 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  $\geq 10,000$  people compared with 73% in the MRS. In both sources, the number of cases declared in a hospital of  $\geq 200$  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)
<b>Age groups</b>		
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%)
<b>Sex, n (%)</b>		
Male	111 (52.4%)	99 (49.0%)
Female	101 (47.6%)	103 (51.0%)
<b>Year of report, n (%)</b>		
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%)
<b>Size of municipality, n (%)</b>		
<10,000 people	27 (12.7%)	28 (13.9%)
$\geq 10,000$ people	177 (83.5%)	148 (73.3%)
NAs	8 (3.8%)	26 (12.9%)
<b>Country of birth, n (%)</b>		
Spain	194 (91.5%)	188 (93.1%)
Other countries	18 (8.5%)	14 (6.9%)
<b>Number of hospital beds, n (%)</b>		
<200	60 (28.3%)	65 (32.2%)
$\geq 200$	149 (70.3%)	137 (67.8%)

NAs	3 (1.4%)	0 (0.0%)
<b>Clinical form, n (%)</b>		
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%)
<b>Serogroup, n (%)</b>		
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%)
<b>Type of reporting centre</b>		
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.



308 **Table 2. Capture–recapture analysis of all invasive meningococcal disease cases reported to the SDR and MRS stratified by characteristics, Catalonia**  
 309 **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
<b>All cases</b>	212	202	137	36	313 (295, 330)	67.9 (62.7, 73.1)	64.7 (59.4, 70.0)	3.2	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
2011-2013	122	120	71	35	206 (187, 226)	59.3 (52.6, 66.0)	58.3 (51.6, 65.1)	1.0	<b>&lt;0.001</b>
2014-2015	90	82	66	6	112 (106, 118)	80.6 (73.2, 87.9)	73.4 (65.2, 81.6)	7.2	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	
<b>Type of reporting centre</b>									
Private	21	1	1	0	21 (21, 21)	100 (100, 100)	4.8 (-4.4, 13.9)	95.2	<b>0.002</b>
Public	190	201	136	26	281 (267, 295)	67.7 (62.2, 73.2)	71.6 (66.4, 76.9)	-3.9	
<b>Serogrup</b>									
B	164	153	114	17	220 (209, 231)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	0.636

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<b>C</b>	26	21	16	3	34 (29, 39)	76.7 (62.5, 90.9)	61.9 (45.6, 78.3)	14.8	
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310 SDR: Statutory disease reporting; MDR: Microbiological reporting system

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3 311 There were no differences in sensitivity between in <15 years and  $\geq$ 15 years age group (P-  
4 312 value=0.468) in either source although it was higher in the <15 years (69.1%;  
5 313 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  
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7 314 highest sensitivity were 2-4 years in the SDR, with 80.3% (95%CI 68.5-92.1), and 35-44 years in  
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9 315 the MRS, with 80.5% (95%CI 60.4-100.0) (Figure 2).

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13 316 In 2011-2013, sensitivity for the SDR and the MRS were 59.3% (95%CI 52.6-66) and 58.3%  
14 317 (95%CI 51.6-65.1), respectively, lower than that in 2014-2015 (80.6%; 95%CI 73.2-87.9, for the  
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16 318 SDR and 73.4%; 95%CI 65.2-81.6, for the MRS (P<0.001)) (Table 2). 2014 showed the highest  
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18 319 sensitivity for both sources: 91.3% (95%CI 83.2-99.4) for the SDR and 73.9% (95%CI 61.2-86.6)  
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20 320 for the MRS (Figure 3). 2011 was the only year in which the MRS had a higher sensitivity than  
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22 321 the SDR (56.4%; 95%CI 47.1-65.8 and 39.8%; 95%CI 30.6-49.0, respectively). In private centres  
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24 322 the sensitivity of the SDR was 100% (95%CI 100-100) and that of the MRS was 4.8% (95%CI -  
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26 323 4.4-13.9). No differences were found in other characteristics analysed.

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32 325 For meningitis, 116 and 131 cases were reported by the SDR and the MRS, respectively. The  
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34 326 estimated number of meningitis cases was 181, and 18 cases were not reported by either source.  
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36 327 The highest sensitivity was detected in the MRS (72.5%; 95% CI 66-79) compared with the SDR  
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38 328 (64.2%; 95%CI 57.2-71.2) (P<0.001) (Table 3). 2014-2015 showed a higher sensitivity in both  
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40 329 sources compared with 2011-2013: 82.4% (95%CI 72.7-92) in the MRS and 75.6% (95%CI 64.7-  
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42 330 86.5) in the SDR. Public centres had a higher sensitivity in the MRS (77.7%; 95%CI 71.4-84.0)  
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44 331 and in the SDR (63.9%; 95%CI 56.6-71.2) (P<0.037).

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333 **Table 3. Capture–recapture analysis of meningococcal meningitis reported to the SDR and MRS stratified by characteristics, Catalonia 2011–2015**  
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	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
<b>All cases</b>	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
2011–2013	71	82	47	18	124 (111, 137)	57.5 (48.8, 66.2)	66.4 (58.1, 74.7)	-8.9	<b>0.013</b>
2014–2015	45	49	37	3	60 (56, 64)	75.6 (64.7, 86.5)	82.4 (72.7, 92.0)	-6.7	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Type of reporting centre</b>									
Private	9	1	1	0	9 (9, 9)	100.0 (100.0, 100.0)	11.1 (-9.4, 31.6)	88.9	<b>0.037</b>
Public	107	130	83	14	168 (158, 178)	63.9 (56.6, 71.2)	77.7 (71.4, 84.0)	-13.7	
<b>Serogrup</b>									
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	

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

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3 336 For septicaemia, 82 cases and 66 cases were reported by the SDR and the MRS, respectively. The  
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5 337 sensitivity was higher for the SDR (75.9%; 95%CI 67.9-84) than the MRS (61.1%; 95%CI 51.9-  
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7 338 70.3) (Table 4). There were 108 estimated cases and 10 cases were not reported by either source.  
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9 339 The sensitivity was higher in the <15 years than in the ≥15 years in both sources, but higher in  
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11 340 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  
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13 341 higher in 2014-2015 than in 2011-2013 (87.6%; 95%CI 78-97.3 for the SDR and 71.9%; 95%CI  
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15 342 58.7-85.1 for the MRS) (P<0.015).

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19 344 Serogroup B (Supplementary Table 1) showed the sensitivity of the SDR was higher than that of  
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21 345 the MRS (74.6%; 95%CI 68.8-80.3 and 69.6%; 95%CI 63.5-75.6, respectively). There were  
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23 346 differences according to the period and the type of centre. In 2014-2015, the sensitivity was 87.1%  
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25 347 (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  
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27 348 centres, the sensitivity in SDR was 100% compared with 7.1% (95%CI -6.4-20.6) (P=0.004) in  
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29 349 MRS. The sensitivity was higher for IMD serogroup C cases in SDR than in MRS (76.7%; 95%CI  
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31 350 62.5-90.9 and 62%; 95%CI 45.6-78.3, respectively) (Supplementary Table 2).

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35 352 All 22 deaths were reported in the SDR (CFR: 10.4%), and the sensitivity of the SDR was higher  
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37 353 than that of the MRS (100%; 95%CI 100-100 vs 50%; 95%CI 29.1-70.9, P=0.104). No  
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39 354 differences were found in other characteristics analysed (Supplementary Table 3).  
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355 **Table 4. Capture–recapture analysis of meningococcal septicaemia reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015**  
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	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
<b>All cases</b>	82	66	50	10	108 (99, 117)	75.9 (67.9, 84.0)	61.1 (51.9, 70.3)	14.8	<b>&lt;0.001</b>
<b>Age at notification, years</b>									
<15 years	48	42	34	4	60 (55, 64)	81.1 (71.1, 91.1)	71.0 (59.4, 82.5)	10.1	<b>0.036</b>
≥15 years	34	23	16	8	49 (40, 58)	70.3 (57.4, 83.1)	47.5 (33.4, 61.6)	22.7	
<b>Sex</b>									
Male	43	27	22	5	53 (47, 59)	81.8 (71.3, 92.2)	51.3 (37.8, 64.8)	30.4	<b>0.315</b>
Female	39	39	28	5	55 (49, 60)	72.0 (60.0, 83.9)	72.0 (60.0, 83.9)	0.0	
<b>Year of report</b>									
2011-2013	43	34	22	11	66 (56, 77)	65.2 (53.6, 76.7)	51.5 (39.5, 63.6)	13.6	<b>0.015</b>
2014-2015	39	32	28	2	45 (42, 48)	87.6 (78.0, 97.3)	71.9 (58.7, 85.1)	15.7	
<b>Size of municipality</b>									
<10,000 people	7	7	5	1	10 (8, 12)	72.2 (44.0, 100.0)	72.2 (44.0, 100.0)	0.0	<b>0.918</b>
≥10,000 people	71	52	43	6	86 (80, 93)	82.9 (74.9, 90.8)	60.7 (50.3, 71.0)	22.2	
<b>Country of birth</b>									
Spain	73	63	47	9	98 (90, 106)	74.7 (66.1, 83.3)	64.5 (55.0, 74.0)	10.2	<b>0.275</b>
Other countries	9	3	3	0	9 (9, 9)	100.0 (100.0, 100.0)	33.3 (2.5, 64.1)	66.7	
<b>Number of hospital beds</b>									
<200	25	23	16	4	36 (31, 42)	70.0 (55.0, 85.1)	64.4 (48.7, 80.1)	5.6	<b>0.831</b>
≥200	56	43	34	6	71 (65, 78)	79.2 (69.7, 88.7)	60.8 (49.4, 72.2)	18.4	
<b>Type of reporting centre</b>									
Private	9	0	0	0	9 (9, 9)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	<b>0.988</b>
Public	73	66	50	8	97 (89, 104)	75.9 (67.3, 84.4)	68.6 (59.3, 77.9)	7.3	
<b>Serogrup</b>									
B	66	51	43	4	78 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	<b>0.661</b>
C	8	4	4	0	8 (8, 8)	100 (100, 100)	50.0 (15.4, 84.7)	50.0	

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

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## Meningococcal disease

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

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

	<b>OR (95%CI)</b>	<b><i>p</i>-value</b>
<b>Year of report (2014-2015)</b>	2.29 (1.35, 3.89)	<b>0.002</b>
<b>Size of municipality (<math>\geq 10,000</math> people)</b>	0.51 (0.23, 1.12)	0.093

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

## 372 DISCUSSION

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

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

379 Other studies found greater sensitivities by combining data systems than we did. Baldovin et al.  
 380 [32] in Italy, reported an overall sensitivity of 94.7% by combining four data sources (mandatory  
 381 notification system, laboratory surveillance, invasive bacterial surveillance and hospital  
 382 discharge). Jansson et al. [33], in Sweden, found a global sensitivity of 98.7%, 91.1% for clinical  
 383 notification and 85.4% for laboratory reporting. In Austria a good agreement between the National  
 384 Reference Center for meningococci and the hospital discharge was found, although a clinical  
 385 review of hospital discharge data was necessary to detect false positive cases recorded. [34]



## Meningococcal disease

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3 387 Globally, the sensitivity was similar in children aged <15 years than in persons aged  $\geq 15$  years in  
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5 388 both sources (69.1% for the SDR and 66.5% for the MRS;  $P=0.468$ ). The differences could be  
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7 389 because there is greater sensibilization to declare pediatric cases than adult cases or because there  
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9 390 are differences on IMD incidence according to age. [9] Gibson et al., [35] in Australia, analysed  
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11 391 IMD sensitivity in children aged < 15 years in three sources: notifiable system, hospitalized  
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13 392 patients and mortality data. They found a greater sensitivity (99.5%) than we did, although 15%  
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15 393 of hospitalized children were false-positive cases.  
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20 395 Sensitivity was higher in 2014-2015 than in 2011-2013 for both sources (SDR and MRS). SDR  
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22 396 had overall higher sensitivity for IMD cases, septicaemia cases as well as serogroup B and C  
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24 397 cases, but not for meningitis cases for which MRS had higher sensitivity. The improvement in  
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26 398 notification in the years 2014-2015 may be due to different causes, one could be that there is  
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28 399 greater awareness for the notification of infectious diseases to public health surveillance systems,  
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30 400 although it should be analyzed in subsequent studies. In a different way, Andrianou et al [31]  
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32 401 compared the surveillance of the Italian IMD with the registry of hospital discharges, and found  
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34 402 a lower sensitivity in 2018 compared to 2015-2017. This yearly evaluation allows the detection  
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36 403 of problems in the notification process.  
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41 405 We found a greater sensitivity for meningitis in the MRS than in the SDR (72.5% vs 64.2%) but  
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43 406 not for septicaemia (61.1% vs 75.9%). Multiple reasons could explain this fact. A possible  
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45 407 explanation is that meningitis has a specific section in MRS for reporting while septicaemia is  
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47 408 reported in bacteraemia of unknown focus section and it could be confused. It is important to  
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49 409 determine the reason for this lower sensitivity to septicaemia in order to improve the completeness  
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51 410 of MRS reporting. It is difficult to compare our results with those of other studies, since other  
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53 411 sources of information were used or the independence of data sources was presumed but not  
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55 412 demonstrated, [34] which is essential when using the capture-recapture method.  
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## Meningococcal disease

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3 414 Notification of confirmed cases of IMD by laboratories is essential in epidemiological  
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5 415 surveillance. [36] Molecular information on circulating serogroups that is required to implement  
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7 416 public health measures such as vaccination is essential to control the disease [37] and evaluate  
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9 417 the impact of available vaccines.  
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13 419 In the absence of automated electronic reporting, monitoring and increasing the speed of  
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15 420 laboratory reports may allow the public health department to administer chemoprophylaxis and  
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17 421 vaccination to contacts. [27] Although a higher sensitivity has been reported for electronic  
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19 422 reporting than for paper-based reports by some authors, [38] during the study period, electronic  
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21 423 surveillance was used in the SDR but not in the MDR, which may explain, at least in part, why  
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23 424 the MDR had a lower sensitivity than the SDR. [39]  
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28 426 In the multivariate model, the 2014-2015 period and the size of the municipality show a higher  
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30 427 sensitivity in the SDR, suggesting that IMD was well recorded in the two surveillance systems,  
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32 428 although 36 cases (11.5%) were not captured by either source. This suggests there was  
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34 429 underreporting, despite the clinical severity of the disease. Other authors have also found  
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36 430 underreporting of this disease. [40] It is very important to improve reporting by all physicians and  
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38 431 microbiologists to the SDR and MDR to assess the impact of interventions such as immunization.  
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43 433 The estimated IMD incidence rate of 0.7/100, 000 persons-year found in the multivariate model  
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45 434 is less than that found using capture-recapture (0.83/100,000 persons-year) but higher than that  
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47 435 calculated using the SDR (0.56/100,000 persons-year) or MDR data (0.54/100,000 persons-year).  
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49 436 Other European studies showed incidence rates of between 0.39 [32] and 1.18/100,000 persons-  
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51 437 year. [34]  
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55 439 The sensitivity of the two sources were intermediate (67.9% for the SDR and 64.7% for the MRS).  
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57 440 The lower sensitivity of the MRS may be due to the fact that the MRS is a sentinel system with a  
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59 441 coverage of 83% of acute hospital beds and without private centres. In our series, 21 cases (10%)

## Meningococcal disease

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3 442 included in the SDR were reported by private centres, while only one case (0.5%) was reported  
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5 443 to the MSR; this patient was finally transferred to a public hospital. The inclusion of cases that  
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7 444 have an equal probability of selection in one source might lead to an overestimation. Other authors  
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9 445 have reported this limitation when the hospital discharge data set includes probable cases which  
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11 446 are not included in the reference centre. [34]  
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15 448 Death was registered in 22 cases (10.5%), similar to that reported in other European countries [2]  
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17 449 but slightly lower than that observed in Italy (14%) using the capture-recapture method. [32] All  
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19 450 cases were reported to the SDR but only 50% were reported to the MRS, indicating that clinical  
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21 451 data are better in the SDR than in the MRS. Other authors have used mortality data for capture-  
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23 452 recapture analysis and concluded that all deaths were reported in notifiable systems. [34]  
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28 454 The sensitivity of the sources studied for the surveillance of IMD cannot be generalized to other  
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30 455 diseases because physicians' or microbiologists' perception of the importance of IMD differs  
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32 456 from that of other diseases. [38]  
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37 458 The main strength of this study is that the two sources had wide coverage. The SDR is a universal  
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39 459 epidemiological surveillance source and, unlike the MDR, is a sentinel source, with a high  
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41 460 coverage of 83%. Cases with PIC accounted for 85.5% of all cases reported to detect whether  
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43 461 cases were coincident or not. In addition, the independence of the two sources was demonstrated,  
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45 462 complying with the premise of the capture-recapture method.  
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49 464 A limitation of the study was that not all cases had the same probability of being selected from a  
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51 465 given source. Cases diagnosed in private centres or public centres that did not participate in the  
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53 466 MRS could not be reported by this system and this may explain, at least in part, the lower  
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55 467 sensitivity than the SDR. This highlights the importance of including public and private centres  
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57 468 to increase the robustness of the MRS. Another limitation was that we did not analyse the role of  
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## Meningococcal disease

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3 469 the electronic surveillance system, although a previous study detected greater sensitivity of the  
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5 470 SDR when electronic surveillance was introduced. [39]

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### 472 **CONCLUSIONS**

11 473 The sensitivity of enhanced surveillance through the combination of two complementary sources  
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13 474 (statutory reporting by physicians and microbiological reporting by microbiologists) was higher  
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15 475 than that of the individual sources. These systems are complementary and constitute the basic  
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17 476 sources of information necessary for adequate epidemiological surveillance of IMD. Specific  
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19 477 studies to estimate the factors associated with under-reporting are needed to reinforce  
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21 478 epidemiological surveillance of this disease.  
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### 30 481 **DECLARATIONS**

#### 33 482 **Ethics approval and consent to participate**

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36 483 Not applicable  
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#### 39 484 **Consent of publication**

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42 485 Not applicable  
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#### 45 486 **Availability of data and materials**

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48 487 The datasets used and analysed during the current study available from the corresponding author  
49  
50 488 on reasonable request.

#### 52 489 **Competing interests**

53  
54 490 The authors declare that they have no competing interests.  
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## Meningococcal disease

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9 495 design of the study and collection, analysis, and interpretation of data and in writing the  
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## Meningococcal disease

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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)

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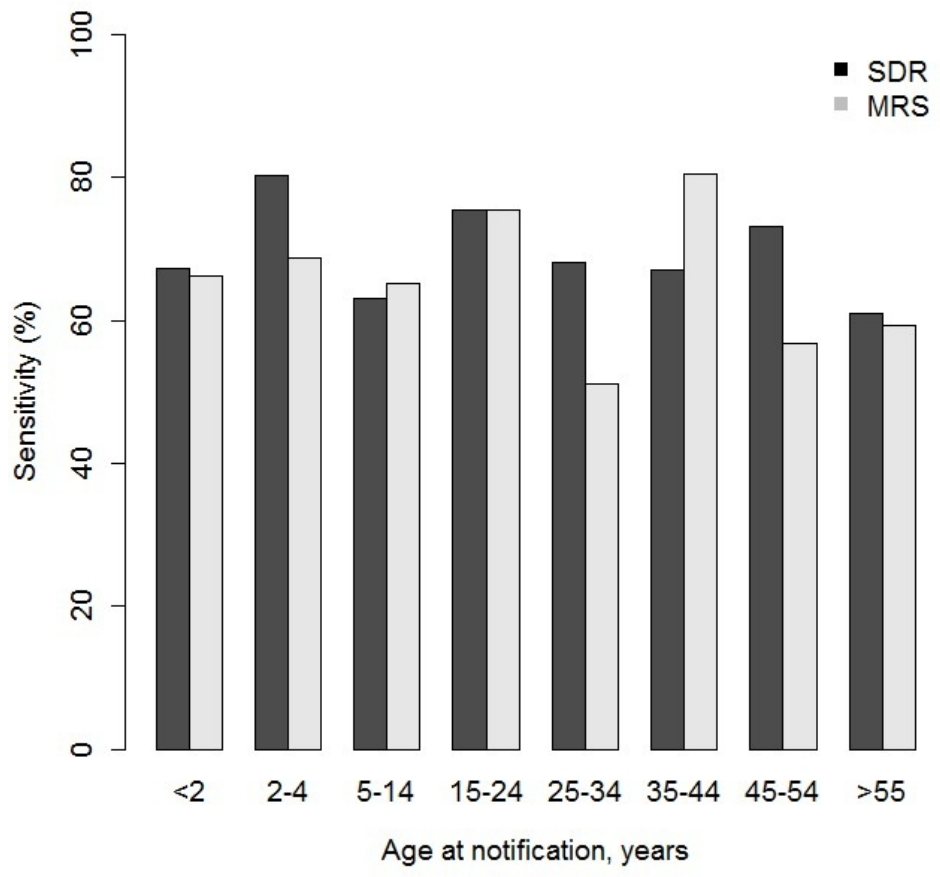


Figure 2. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

176x172mm (96 x 96 DPI)



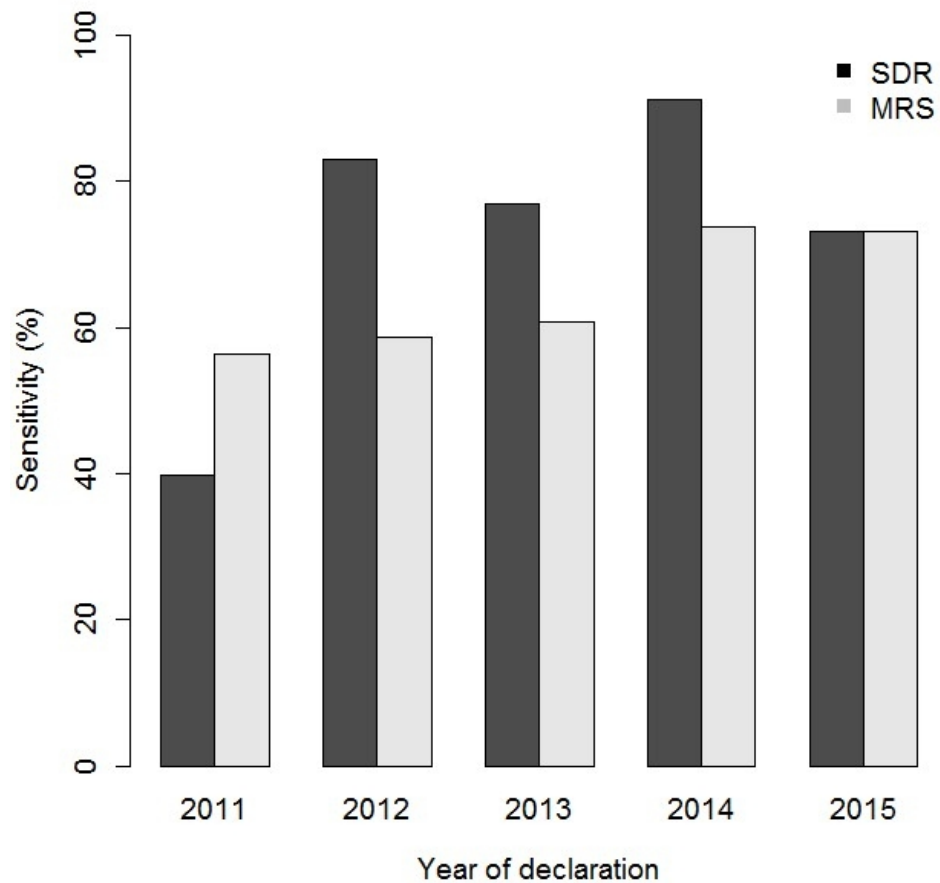


Figure 3. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

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
<b>All cases</b>	164	153	114	17	220 (209, 232)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<200	49	52	33	9	77 (69, 86)	63.7 (53.0, 74.5)	67.6 (57.2, 78.1)	-3.9	0.095

<b>&gt;=200</b>	113	101	81	8	141 (134, 148)	80.3 (73.7, 86.8)	71.7 (64.3, 79.2)	8.5	
<b>Clinical form</b>									
<b>Meningitis</b>	91	100	70	9	130 (122, 138)	70.1 (62.2, 77.9)	77.0 (69.7, 84.2)	-6.9	<i>0.972</i>
<b>Septicaemia</b>	66	51	43	5	79 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	
<b>Type of reporting centre</b>									
<b>Private</b>	14	1	1	0	14 (14, 14)	100 (100, 100)	7.1 (-6.4, 20.6)	92.9	<i>0.004</i>
<b>Public</b>	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 (%)	<i>p</i> -value
<b>All cases</b>	26	21	16	3	34 (30, 39)	76.7 (62.5, 90.9)	62.0 (45.6, 78.3)	14.8	<b>0.035</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									

<b>&lt;200</b>	7	5	5	0	7 (7, 7)	100.0 (100.0, 100.0)	71.4 (38.0, 104.9)	28.6	<i>0.283</i>
<b>≥200</b>	18	16	11	3	26 (22, 31)	69.5 (51.8, 87.2)	61.8 (43.1, 80.5)	7.7	
<b>Clinical form</b>									
<b>Meningitis</b>	16	16	11	3	24 (20, 27)	69.3 (50.4, 88.1)	69.3 (50.4, 88.1)	0.0	<i>0.908</i>
<b>Septicaemia</b>	8	4	4	0	8 (8, 8)	100.0 (100.0, 100.0)	50.0 (15.4, 84.7)	50.0	
<b>Type of reporting centre</b>									
<b>Private</b>	4	0	0	0	4 (4, 4)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	<i>0.992</i>
<b>Public</b>	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
<b>All cases</b>	22	11	11	0	22 (22, 22)	100.0 (100.0, 100.0)	50.0 (29.1, 70.9)	50.0	0.104
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	

<b>Type of reporting centre</b>									
<b>Private</b>	2	0	0	0	2 (2, 2)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	0.992
<b>Public</b>	20	11	11	0	20 (20, 20)	100.0 (100.0, 100.0)	55 (33.2, 76.8)	45	
<b>Serogrup</b>									
<b>B</b>	17	9	9	0	17 (17, 17)	100.0 (100.0, 100.0)	52.9 (29.2, 76.7)	47.1	0.332
<b>C</b>	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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Continued on next page



<b>Results</b>			
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	10
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 (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	10,11,12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

## 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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3 1 **Estimation of the incidence of invasive meningococcal disease using a capture-recapture**  
4 **model based on two independent surveillance systems, in Catalonia, Spain**  
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3 112 **ABSTRACT**  
4

5 113 **Objectives:** Invasive meningococcal disease (IMD) is an urgent notifiable disease and its early  
6  
7 114 notification is essential to prevent cases. The objective of the study was to assess the sensitivity  
8  
9 115 of two independent surveillance systems, and to estimate the incidence of IMD.  
10

11 116 **Design:** We used capture-recapture model based on two independent surveillance systems, the  
12  
13 117 statutory disease reporting system (SDR) and the microbiological reporting system (MRS) of  
14  
15 118 the Public Health Agency of Catalonia, between 2011 and 2015. The capture-recapture analysis  
16  
17 119 and 95% confidence intervals were calculated using the Chapman formula. Multivariate vector  
18  
19 120 generalized linear model was performed for adjusted estimation.  
20  
21

22 121 **Measures:** The variables collected were age, sex, year of report, size of municipality (< 10,000  
23  
24 122 and  $\geq 10,000$ ), clinical form, death, serogroup, country of birth and type of reporting centre  
25  
26 123 (private and public).  
27

28 124 **Results:** The sensitivity of the two combined surveillance systems was 88.5% (85.0-92.0). SDR  
29  
30 125 had greater sensitivity than the MRS (67.9%; 62.7-73.1 vs. 64.7%; 59.4-70.0). In 2014-2015,  
31  
32 126 the sensitivity of both systems was higher (80.6%; 73.2-87.9 vs. 73.4%; 65.2-81.6) than in  
33  
34 127 2011-2013 (59.3%; 52.6-66.0 vs. 58.3%; 51.6-65.1). In private centres, the sensitivity was  
35  
36 128 higher for SDR than for MRS (100%; 100-100 vs. 4.8%; -4.4-13.9). The adjusted estimate of  
37  
38 129 IMD cases was lower than that obtained using the Chapman formula (279; 266-296 vs. 313;  
39  
40 130 295-330). The estimated adjusted incidence of IMD was 0.7/100,000 persons-year.  
41  
42

43 131 **Conclusions:** The sensitivity of enhanced surveillance through the combination of two  
44  
45 132 complementary sources was higher than for the sources individually. Factors associated with  
46  
47 133 under-reporting in different systems should be analysed to improve IMD surveillance.  
48

49 134

50  
51 135 **Keywords:**

52  
53 136 Meningococcal disease, Capture-recapture, estimated incidence, surveillance systems.  
54  
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56 137

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58 138 **Strengths and limitations of this study**  
59

60 139



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2  
3 140 • The use of two surveillance sources as universal statutory disease reporting (SDR) system  
4  
5 141 based on passive reporting and sentinel microbiological reporting system (MRS) covering  
6  
7 142 83% of acute hospital beds, offer a wide coverage.  
8  
9 143 • The independence of the two sources was demonstrated by complying with the premise of  
10  
11 144 the capture-recapture method.  
12  
13 145 • Not all centres participate in the MRS, thus not all cases diagnosed had the same probability  
14  
15 146 of being selected from a given source.  
16  
17 147 • The role of the automated electronic reporting of data that might be associated to a greater  
18  
19 148 sensitivity was not analysed.  
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23 149

## 25 **BACKGROUND**

26  
27 151 Invasive meningococcal disease (IMD) continues to be an important cause of morbidity and  
28  
29 152 mortality, mainly in children aged < 4 years and adolescents. [1]  
30  
31 153 In the European regions, the incidence rate of confirmed IMD cases was 0.62/100,000 persons-  
32  
33 154 year in 2018, [2] and in Spain it was 0.86/100,000 persons. [3] Six serogroups (A, B, C, W, X,  
34  
35 155 Y) currently cause almost all cases of this life-threatening disease worldwide. Case fatality rate  
36  
37 156 is about 10% in developed countries [4-6], and 40-65% present with meningitis, but  
38  
39 157 meningococemia and pneumonia are also frequent [4], being the serogroup involved related  
40  
41 158 both with the case fatality rate [7] and the predominant clinical form. [8] Serogroup B causes  
42  
43 159 more than a third part of IMD [4,9] but in some countries or population groups the proportion is  
44  
45 160 even higher. [10,11] In Spain, from 2009 to 2018, serogroup B accounted for 64% of IMD  
46  
47 161 cases. [12] A high proportion, up to 60% [13] of IMD cases, are affected by a range of sequelae  
48  
49 162 and health related impairment in the quality of life of survivors and their families. [14]  
50  
51 163 IMD is an urgent notifiable disease and its early notification is essential to provide an adequate  
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53 164 public health response in patients and their close contacts to prevent further cases.  
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55 165 Epidemiological surveillance allows monitoring of the impact of public health interventions,  
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57 166 including vaccination programmes. Therefore, a robust epidemiological and microbiological  
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3 167 system with timely and accurate surveillance providing information on the frequency of cases  
4  
5 168 and the distribution of circulating serogroups is crucial.

6  
7 169 Evaluations of surveillance systems should be conducted regularly to increase their utility. [15-  
8  
9 170 17] There are two reporting systems for the epidemiological surveillance of communicable  
10  
11 171 disease in Catalonia: the statutory disease reporting system (SDR) and the microbiological  
12  
13 172 reporting system (MRS). [18]

14  
15 173 The capture-recapture method is a statistical method for estimating the real incidence of  
16  
17 174 diseases in a population with two or more information sources. [19, 20] The method is valid if  
18  
19 175 four conditions are met: 1) the population under study has to be closed, i.e., there should be no  
20  
21 176 changes during the study period; 2) there must be a method of determining whether an  
22  
23 177 individual identified by one source is the same as an individual identified by the other; 3) each  
24  
25 178 individual must have the same probability of being captured by either system; 4) the systems  
26  
27 179 must be independent.

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29  
30 180 The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia  
31  
32 181 (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD.

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## 35 36 183 **METHODS**

### 37 38 184 **Information sources**

39  
40 185 Catalonia is a region in the northeast of Spain with a population of 7,508,106 in 2015. [21]

41  
42 186 The SDR is a passive surveillance system through which health professionals report all  
43  
44 187 infectious diseases subject to surveillance. The reporting of cases to the Public Health Agency  
45  
46 188 of Catalonia (PHAC) is mandatory and includes confirmed cases of IMD and is regulated by a  
47  
48 189 Decree. [18, 22]

49  
50  
51 190 The MRS is a surveillance system that consists of microbiologists notifying laboratory  
52  
53 191 confirmed microorganisms that cause infectious diseases. The main objectives of the MRS are  
54  
55 192 to confirm suspected cases of infectious diseases through the identification of the  
56  
57 193 microorganisms and serogroups involved and to determine trends and changes in  
58  
59 194 epidemiological patterns and microbiological resistance. [23]

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3 195 The MRS was non-compulsory until 2015 and involved 50 health care centres representing over  
4  
5 196 83% of acute hospital beds. [24] Confirmed IMD cases were reported by microbiologists  
6  
7 197 including sex, age, clinical presentation (meningitis, bacteraemia of unknown focus and other  
8  
9 198 clinical presentations), serogroup and diagnostic method.  
10  
11 199 Both systems belong to the PHAC epidemiological surveillance network and, since 2014,  
12  
13 200 transfer information automatically, but the independence of the sources is maintained.  
14  
15  
16 201

### 17 18 202 **Cases definition, inclusion, and exclusion criteria**

19  
20 203 A confirmed case of IMD was defined as laboratory confirmed if at least one of the following  
21  
22 204 criteria was fulfilled: isolation in cultures or detection of *Neisseria meningitidis* DNA by PCR  
23  
24 205 in a normally sterile site, detection of gram-negative diplococci or *N. meningitidis* antigen in  
25  
26 206 cerebrospinal fluid.  
27  
28 207

### 29 30 208 **Data collection**

31  
32 209 We made a retrospective study of confirmed IMD cases in Catalonia from January 2011 to  
33  
34 210 December 2015. We extracted all IMD records from the MRS and SDR and linked the  
35  
36 211 databases using the personal identification code (PIC). When the PIC was not available, data on  
37  
38 212 notification, age and sex were used to identify duplicates between the two sources. In cases with  
39  
40 213 inconclusive matching, the hospital was used as a fifth matching criterion.  
41  
42 214 Estimates were made for the entire 5-year period and by age, sex, year of report, size of  
43  
44 215 municipality (<10,000 and  $\geq$ 10,000), country of birth, number of hospital beds, clinical form  
45  
46 216 (meningitis, with or without sepsis, sepsis, and others), serogroup, death and reporting centre  
47  
48 217 (private or public).  
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50 218

### 51 52 219 **Ethics statement**

53  
54 220 The study was not submitted for research ethics approval as the activities described were  
55  
56 221 conducted as part of the legislated mandate of the Health Department of Catalonia, the  
57  
58 222 competent authority for surveillance of communicable diseases according to Decree 203/2015  
59  
60

1  
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3 223 of the 15 September which created the epidemiological surveillance network of Catalonia. [18]  
4  
5 224 All the study activities formed part of public health surveillance and did not require informed  
6  
7 225 consent. Personal data were used only for the matching process and measures to protect the  
8  
9 226 confidentiality of personal data were applied (access to the data restricted to the personnel  
10  
11 227 involved in data analysis, and removal of personal data from the datasets after matching).  
12  
13  
14 228

### 15 229 *Patient and public involvement*

16  
17  
18 230 No patient involved  
19  
20 231

### 21 232 *Statistical methods*

22  
23  
24 233 The total number of IMD cases was estimated using the two-source capture-recapture method,  
25  
26 234 which uses Chapman's formula, [25] developed to reduce bias due to small samples:

$$27$$

$$28$$

$$29 \quad N = \frac{(L1 + 1)(L2 + 1)}{a + 1} - 1$$

$$30$$

$$31$$

$$32 \quad 95\%CI = N \pm 1.96 \sqrt{\frac{(L1 + 1)(L2 + 1)(L1 - a)(L2 - a)}{(a + 1)^2(a + 2)}}$$

$$33$$

$$34$$

35 237  
36  
37 238 where L1 is the number of cases in the SDR dataset, L2 is the number of cases reported to MRS,  
38  
39 239 and **a** is the number of cases captured by both systems. The sensitivity (Se) of case  
40  
41 240 ascertainment by the two sources was also calculated as the proportion of true cases detected by  
42  
43 241 each source, i.e. Se (1) =L1/N for source 1 and Se (2) =L2/N for source 2. The sensitivity of  
44  
45 242 both sources combined was calculated as the proportion of cases detected by one of the two  
46  
47 243 sources or both, i.e., Se (1, 2) =(L1+L2-a)/N.

48  
49 244 The independence of the sources was considered when applying the capture-recapture method.  
50  
51 245 [26, 27] In the two-by-two table, where **a** represents cases reported by two sources or  
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53 246 combinations of sources, **b** and **c** cases reported exclusively by either of the two sources and **x**  
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55 247 the estimated non-reported cases by either of the sources, the odds ratio (OR = ax/bc) should not  
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57 248 differ from one.  
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3 249 As a multivariate model, a vector generalized linear model (VGLM) from the generalized  
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5 250 additive model (GAM) framework [28] was used to evaluate patient characteristics and the  
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7 251 probability of capture by the different sources taking into account the covariates: age (<15 vs  
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9 252  $\geq 15$ ), gender, year of notification (2011-2013 vs 2014-2015), size of the municipality (<10,000  
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11 253 vs  $\geq 10,000$ ), country of birth (Spain vs other), number of hospital beds (<200 vs  $\geq 200$ ) and  
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13 254 diagnosis (meningitis vs septicæmia). The outcome for the model is a two column matrix with  
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15 255 0 and 1 indicating if the record is identified by SDR or MRS. We used a backwards stepwise  
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17 256 procedure (using likelihood ratio tests, with a p-value  $> 0.2$  as the criterion for removing  
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19 257 variables from the model) [29, 30] to eliminate covariates, starting with a full model including  
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21 258 all described covariates, and we used the parameter estimates from the model to estimate the  
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23 259 sizes of population subgroups and calculate incidence rates. The 95% confidence intervals (CI)  
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25 260 were calculated, allowing for uncertainty in the total number of cases estimated. For each of the  
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27 261 described covariates, VLGGM with source notification as outcome was used to test differences in  
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29 262 sensitivities. All analyses were made using R software version 3.0.1.  
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## 34 264 **RESULTS**

### 35 265 **Patient characteristics**

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38 266 Patient characteristics by source are shown in Table 1. From 2011 to 2015, 212 IMD cases were  
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40 267 reported to the SDR and 202 cases to the MRS, representing an incidence of 0.56 and 0.54  
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42 268 /100,000 persons-year, respectively. IMD due to serogroup B was the most-frequently reported  
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44 269 serogroup (77.4% and 75.7% in the SDR and MRS, respectively). Around 63% of patients were  
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46 270 aged < 15 years; the mean age was 21.4 for the SDR and 20.5 years for the MRS. Male sex was  
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48 271 more frequent in the SDR (52.4%) than in the MRS (49%). The SDR presented the most cases  
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50 272 in 2015 (48 cases; 22.6%) and the MRS (61 cases; 30.2%) in 2011. The SDR reported that 84%  
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52 273 of patients lived in a municipality of  $\geq 10,000$  people compared with 73% in the MRS. In both  
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54 274 sources, the number of cases declared in a hospital of  $\geq 200$  beds were around 70%. The main  
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56 275 clinical form in both sources was meningitis (54.7% and 64.8%, respectively) and sepsis (38.7%  
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58 276 and 32.7%, respectively). Reports from private centres represented 10% of cases in the SDR and  
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277 0.5% in the MRS. Twenty-two cases (10.4%) cases reported by the SDR died compared with 11  
 278 cases (5.4%) reported by the MRS.

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

	SDR (n=212)	MRS (n=202)
<b>Age groups</b>		
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%)
<b>Sex, n (%)</b>		
Male	111 (52.4%)	99 (49.0%)
Female	101 (47.6%)	103 (51.0%)
<b>Year of report, n (%)</b>		
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%)
<b>Size of municipality, n (%)</b>		
<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%)
<b>Country of birth, n (%)</b>		
Spain	194 (91.5%)	188 (93.1%)
Other countries	18 (8.5%)	14 (6.9%)
<b>Number of hospital beds, n (%)</b>		
<200	60 (28.3%)	65 (32.2%)
≥200	149 (70.3%)	137 (67.8%)
NAs	3 (1.4%)	0 (0.0%)
<b>Clinical form, n (%)</b>		
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%)
<b>Serogroup, n (%)</b>		
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%)
<b>Type of reporting centre</b>		
Private	21 (10.0%)	1 (0.5%)
Public	190 (90.0%)	201 (99.5%)

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

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### 285 Capture-recapture analysis

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

288 During the period studied, 212 and 202 IMD cases were reported by the SDR and MRS,  
289 respectively. One hundred thirty-seven cases (43.8%) coincided in both sources and 36 cases  
290 (11.5%) were not reported to either source. The estimated number of cases was 313 (95% CI  
291 295–330) (Figure 1) and the estimated incidence rate was 0.83/100,000 persons-year.

292 The sensitivity of the SDR was 67.9% (95%CI 62.7-73.1) and that of the MRS was 64.7%  
293 (95%CI 59.4-70.0) (P<0.001) (Table 2). The sensitivity increased to 88.5% (95%CI 85.0-92.0)  
294 when the datasets were combined.

295

296 **Table 2. Capture–recapture analysis of all invasive meningococcal disease cases reported to the SDR and MRS stratified by characteristics, Catalonia**  
 297 **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
<b>All cases</b>	212	202	137	36	313 (295, 330)	67.9 (62.7, 73.1)	64.7 (59.4, 70.0)	3.2	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
2011-2013	122	120	71	35	206 (187, 226)	59.3 (52.6, 66.0)	58.3 (51.6, 65.1)	1.0	<b>&lt;0.001</b>
2014-2015	90	82	66	6	112 (106, 118)	80.6 (73.2, 87.9)	73.4 (65.2, 81.6)	7.2	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	
<b>Type of reporting centre</b>									
Private	21	1	1	0	21 (21, 21)	100 (100, 100)	4.8 (-4.4, 13.9)	95.2	<b>0.002</b>
Public	190	201	136	26	281 (267, 295)	67.7 (62.2, 73.2)	71.6 (66.4, 76.9)	-3.9	
<b>Serogrup</b>									
B	164	153	114	17	220 (209, 231)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	0.636



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C	26	21	16	3	34 (29, 39)	76.7 (62.5, 90.9)	61.9 (45.6, 78.3)	14.8	
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298 SDR: Statutory disease reporting; MDR: Microbiological reporting system

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3 299 There were no differences in sensitivity between in <15 years and  $\geq 15$  years age group (P-  
4 value=0.468) in either source although it was higher in the <15 years (69.1%;  
5 300 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  
6 301 the highest sensitivity were 2-4 years in the SDR, with 80.3% (95%CI 68.5-92.1), and 35-44  
7 302 years in the MRS, with 80.5% (95%CI 60.4-100.0) (Figure 2).  
8 303  
9 304 In 2011-2013, sensitivity for the SDR and the MRS were 59.3% (95%CI 52.6-66) and 58.3%  
10 305 (95%CI 51.6-65.1), respectively, lower than that in 2014-2015 (80.6%; 95%CI 73.2-87.9, for  
11 306 the SDR and 73.4%; 95%CI 65.2-81.6, for the MRS (P<0.001)) (Table 2). 2014 showed the  
12 307 highest sensitivity for both sources: 91.3% (95%CI 83.2-99.4) for the SDR and 73.9% (95%CI  
13 308 61.2-86.6) for the MRS (Figure 3). 2011 was the only year in which the MRS had a higher  
14 309 sensitivity than the SDR (56.4%; 95%CI 47.1-65.8 and 39.8%; 95%CI 30.6-49.0, respectively).  
15 310 In private centres the sensitivity of the SDR was 100% (95%CI 100-100) and that of the MRS  
16 311 was 4.8% (95%CI -4.4-13.9). No differences were found in other characteristics analysed.  
17 312 For meningitis, 116 and 131 cases were reported by the SDR and the MRS, respectively. The  
18 313 estimated number of meningitis cases was 181, and 18 cases were not reported by either source.  
19 314 The highest sensitivity was detected in the MRS (72.5%; 95% CI 66-79) compared with the  
20 315 SDR (64.2%; 95%CI 57.2-71.2) (P<0.001) (Table 3). 2014-2015 showed a higher sensitivity in  
21 316 both sources compared with 2011-2013: 82.4% (95%CI 72.7-92) in the MRS and 75.6%  
22 317 (95%CI 64.7-86.5) in the SDR. Public centres had a higher sensitivity in the MRS (77.7%;  
23 318 95%CI 71.4-84.0) and in the SDR (63.9%; 95%CI 56.6-71.2) (P<0.037).  
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320 Table 3. Capture–recapture analysis of meningococcal meningitis reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

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	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
<b>All cases</b>	116	131	84	18	181 (169, 193)	64.2 (57.2, 71.2)	72.5 (66.0, 79.0)	-8.3	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
2011-2013	71	82	47	18	124 (111, 137)	57.5 (48.8, 66.2)	66.4 (58.1, 74.7)	-8.9	<b>0.013</b>
2014-2015	45	49	37	3	60 (56, 64)	75.6 (64.7, 86.5)	82.4 (72.7, 92.0)	-6.7	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Type of reporting centre</b>									
Private	9	1	1	0	9 (9, 9)	100.0 (100.0, 100.0)	11.1 (-9.4, 31.6)	88.9	<b>0.037</b>
Public	107	130	83	14	168 (158, 178)	63.9 (56.6, 71.2)	77.7 (71.4, 84.0)	-13.7	
<b>Serogrup</b>									
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	

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

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3 323 For septicaemia, 82 cases and 66 cases were reported by the SDR and the MRS, respectively.  
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5 324 The sensitivity was higher for the SDR (75.9%; 95%CI 67.9-84) than the MRS (61.1%; 95%CI  
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7 325 51.9-70.3) (Table 4). There were 108 estimated cases and 10 cases were not reported by either  
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9 326 source. The sensitivity was higher in the <15 years than in the  $\geq 15$  years in both sources, but  
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11 327 higher in the SDR (81.1%; 95%CI 71.1-91.1 versus 71%; 95%CI 59.4-82.5 for the MRS;  
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13 328  $P=0.036$ ), and higher in 2014-2015 than in 2011-2013 (87.6%; 95%CI 78-97.3 for the SDR and  
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15 329 71.9%; 95%CI 58.7-85.1 for the MRS) ( $P<0.015$ ).  
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17 330 Serogroup B (Supplementary Table 1) showed the sensitivity of the SDR was higher than that of  
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19 331 the MRS (74.6%; 95%CI 68.8-80.3 and 69.6%; 95%CI 63.5-75.6, respectively). There were  
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21 332 differences according to the period and the type of centre. In 2014-2015, the sensitivity was  
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23 333 87.1% (95%CI 79.7-94.5) for the SDR and 78.3% (95%CI 69.2-87.4) for the MRS ( $P<0.002$ ).  
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25 334 In private centres, the sensitivity in SDR was 100% compared with 7.1% (95%CI -6.4-20.6)  
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27 335 ( $P=0.004$ ) in MRS. The sensitivity was higher for IMD serogroup C cases in SDR than in MRS  
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29 336 (76.7%; 95%CI 62.5-90.9 and 62%; 95%CI 45.6-78.3, respectively) (Supplementary Table 2).  
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31 337 All 22 deaths were reported in the SDR (CFR: 10.4%), and the sensitivity of the SDR was  
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33 338 higher than that of the MRS (100%; 95CI% 100-100 vs 50%; 95%CI 29.1-70.9,  $P=0.104$ ). No  
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35 339 differences were found in other characteristics analysed (Supplementary Table 3).  
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340 Table 4. Capture–recapture analysis of meningococcal septicaemia reported to the SDR and MRS stratified by characteristics, Catalonia 2011-2015

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	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	

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

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3 345 The results of the multivariate model for all cases are shown in Table 5. The variables  
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5 346 considered to define the sensitivity of the two sources were year of report (2011-2013 versus  
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7 347 2014-2015) and size of municipality. With these variables in the model, the adjusted estimate of  
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9 348 the total number of cases was 279 cases (95%CI 266-296) and the estimated incidence rate was  
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11 349 0.7/100,000 persons-year.

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16 351 **Table 5. Variables defining the sensitivity of the SDR and MRS in detecting invasive**  
17 352 **meningococcal diseases cases. Multivariate model.**

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	<b>OR (95%CI)</b>	<b><i>p-value</i></b>
<b>Year of report (2014-2015)</b>	2.29 (1.35, 3.89)	<b>0.002</b>
<b>Size of municipality (<math>\geq 10,000</math> people)</b>	0.51 (0.23, 1.12)	0.093

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23 355 OR: odds ratio; n estimate: 279 (266, 296)

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## 26 27 357 **DISCUSSION**

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29 358 The sensitivity obtained by combining the two surveillance system for IMD cases was 88.5%,  
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31 359 greater than for each source. Globally, the SDR showed higher sensitivity than the MDR,  
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33 360 mainly for cases of sepsis, serogroup B and serogroup C, although for meningitis the sensitivity  
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35 361 of the MDR was higher than that of the SDR.

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37 362 Sensitivity of SDR was 67.9%, very close to that of 66.5% found by Andrianou et al. in Italy in  
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39 363 a study carried out in 2018 using the hospital discharge records system as the external source.  
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41 364 [31]

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43 365 Other studies found greater sensitivities by combining data systems than we did. Baldovin et al.  
44  
45 366 [32] in Italy, reported an overall sensitivity of 94.7% by combining four data sources  
46  
47 367 (mandatory notification system, laboratory surveillance, invasive bacterial surveillance and  
48  
49 368 hospital discharge). Jansson et al. [33], in Sweden, found a global sensitivity of 98.7%, 91.1%  
50  
51 369 for clinical notification and 85.4% for laboratory reporting. In Austria a good agreement  
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53 370 between the National Reference Center for meningococci and the hospital discharge was found,  
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55 371 although a clinical review of hospital discharge data was necessary to detect false positive cases  
56  
57 372 recorded. [34]

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3 373 Globally, the sensitivity was similar in children aged <15 years than in persons aged  $\geq$ 15 years  
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5 374 in both sources (69.1% for the SDR and 66.5% for the MRS;  $P=0.468$ ). The differences could  
6  
7 375 be because there is greater sensibilization to declare pediatric cases than adult cases or because  
8  
9 376 there are differences on IMD incidence according to age. [9] Gibson et al., [35] in Australia,  
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11 377 analysed IMD sensitivity in children aged < 15 years in three sources: notifiable system,  
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13 378 hospitalized patients and mortality data. They found a greater sensitivity (99.5%) than we did,  
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15 379 although 15% of hospitalized children were false-positive cases.  
16  
17 380 Sensitivity was higher in 2014-2015 than in 2011-2013 for both sources (SDR and MRS). SDR  
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19 381 had overall higher sensitivity for IMD cases, septicaemia cases as well as serogroup B and C  
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21 382 cases, but not for meningitis cases for which MRS had higher sensitivity. The improvement in  
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23 383 notification in the years 2014-2015 may be due to different causes, one could be that there is  
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25 384 greater awareness for the notification of infectious diseases to public health surveillance  
26  
27 385 systems, although it should be analysed in subsequent studies. In a different way, Andrianou et  
28  
29 386 al [31] compared the surveillance of the Italian IMD with the registry of hospital discharges, and  
30  
31 387 found a lower sensitivity in 2018 compared to 2015-2017. This yearly evaluation allows the  
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33 388 detection of problems in the notification process.  
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35 389 We found a greater sensitivity for meningitis in the MRS than in the SDR (72.5% vs 64.2%) but  
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37 390 not for septicaemia (61.1% vs 75.9%). Multiple reasons could explain this fact. A possible  
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39 391 explanation is that meningitis has a specific section in MRS for reporting while septicaemia is  
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41 392 reported in bacteraemia of unknown focus section and it could be confused. It is important to  
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43 393 determine the reason for this lower sensitivity to septicaemia in order to improve the  
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45 394 completeness of MRS reporting. It is difficult to compare our results with those of other studies,  
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47 395 since other sources of information were used or the independence of data sources was presumed  
48  
49 396 but not demonstrated, [34] which is essential when using the capture-recapture method.  
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51 397 Notification of confirmed cases of IMD by laboratories is essential in epidemiological  
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53 398 surveillance. [36] Molecular information on circulating serogroups that is required to implement  
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55 399 public health measures such as vaccination is essential to control the disease [37] and evaluate  
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57 400 the impact of available vaccines.  
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3 401 In the absence of automated electronic reporting, monitoring and increasing the speed of  
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5 402 laboratory reports may allow the public health department to administer chemoprophylaxis and  
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7 403 vaccination to contacts. [27] Although a higher sensitivity has been reported for electronic  
8  
9 404 reporting than for paper-based reports by some authors, [38] during the study period, automated  
10  
11 405 electronic reporting was used in the SDR but not in the MDR, which may explain, at least in  
12  
13 406 part, why the MDR had a lower sensitivity than the SDR. [39]  
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15 407 In the multivariate model, the 2014-2015 period and the size of the municipality show a higher  
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17 408 sensitivity in the SDR, suggesting that IMD was well recorded in the two surveillance systems,  
18  
19 409 although 36 cases (11.5%) were not captured by either source. This suggests there was  
20  
21 410 underreporting, despite the clinical severity of the disease. Other authors have also found  
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23 411 underreporting of this disease. [40] It is very important to improve reporting by all physicians  
24  
25 412 and microbiologists to the SDR and MDR to assess the impact of interventions such as  
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27 413 immunization.  
28  
29 414 The estimated IMD incidence rate of 0.7/100,000 persons-year found in the multivariate model  
30  
31 415 is less than that found using capture-recapture (0.83/100,000 persons-year) but higher than that  
32  
33 416 calculated using the SDR (0.56/100,000 persons-year) or MDR data (0.54/100,000 persons-  
34  
35 417 year). Other European studies showed incidence rates of between 0.39 [32] and 1.18/100,000  
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37 418 persons-year. [34]  
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39 419 The sensitivity of the two sources were intermediate (67.9% for the SDR and 64.7% for the  
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41 420 MRS). The lower sensitivity of the MRS may be due to the fact that the MRS is a sentinel  
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43 421 system with a coverage of 83% of acute hospital beds and without private centres. In our series,  
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45 422 21 cases (10%) included in the SDR were reported by private centres, while only one case  
46  
47 423 (0.5%) was reported to the MSR; this patient was finally transferred to a public hospital. The  
48  
49 424 inclusion of cases that have an equal probability of selection in one source might lead to an  
50  
51 425 overestimation. Other authors have reported this limitation when the hospital discharge data set  
52  
53 426 includes probable cases which are not included in the reference centre. [34]  
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55 427 Death was registered in 22 cases (10.5%), similar to that reported in other European countries  
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57 428 [2] but slightly lower than that observed in Italy (14%) using the capture-recapture method. [32]

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3 429 All cases were reported to the SDR but only 50% were reported to the MRS, indicating that  
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5 430 clinical data are better in the SDR than in the MRS. Other authors have used mortality data for  
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7 431 capture-recapture analysis and concluded that all deaths were reported in notifiable systems.  
8  
9 432 [34]

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11 433 The sensitivity of the sources studied for the surveillance of IMD cannot be generalized to other  
12  
13 434 diseases because physicians' or microbiologists' perception of the importance of IMD differs  
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15 435 from that of other diseases. [38]

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17 436 The main strength of this study is that the two sources had wide coverage. The SDR is a  
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19 437 universal epidemiological surveillance source and, unlike the MDR, is a sentinel source, with a  
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21 438 high coverage of 83%. Cases with PIC accounted for 85.5% of all cases reported to detect  
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23 439 whether cases were coincident or not. In addition, the independence of the two sources was  
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25 440 demonstrated, complying with the premise of the capture-recapture method.

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27 441 A limitation of the study was that not all cases had the same probability of being selected from a  
28  
29 442 given source. Cases diagnosed in private centres or public centres that did not participate in the  
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31 443 MRS could not be reported by this system and this may explain, at least in part, the lower  
32  
33 444 sensitivity than the SDR. This highlights the importance of including public and private centres  
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35 445 to increase the robustness of the MRS. Another limitation was that we did not analyse the role  
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37 446 of the electronic surveillance system, although a previous study detected greater sensitivity of  
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39 447 the SDR when electronic surveillance was introduced. [39]

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#### 44 449 **CONCLUSIONS**

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46 450 The sensitivity of enhanced surveillance through the combination of two complementary  
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48 451 sources (statutory reporting by physicians and microbiological reporting by microbiologists)  
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50 452 was higher than that of the individual sources. These systems are complementary and constitute  
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52 453 the basic sources of information necessary for adequate epidemiological surveillance of IMD.  
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54 454 Specific studies to estimate the factors associated with under-reporting are needed to reinforce  
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56 455 epidemiological surveillance of this disease.  
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6 458 **DECLARATIONS**  
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9 459 **Ethics approval and consent to participate**

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11  
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15 461 **Consent of publication**

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17  
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20  
21 463 **Availability of data and materials**  
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24 464 The datasets used and analysed during the current study available from the corresponding author  
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26 465 on reasonable request.

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29  
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46 474 **Author contributions**  
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22 764 **The Working Group of the Epidemiological Surveillance Network of Catalonia is**  
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24 765 **composed by:**  
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23 955 Figure 1. Venn diagram of the capture–recapture analysis of two datasets to estimate the total  
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25 956 number of invasive meningococcal disease cases, Catalonia 2011-2015  
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28 957 Figure 2. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015  
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31 958 Figure 3. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015  
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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

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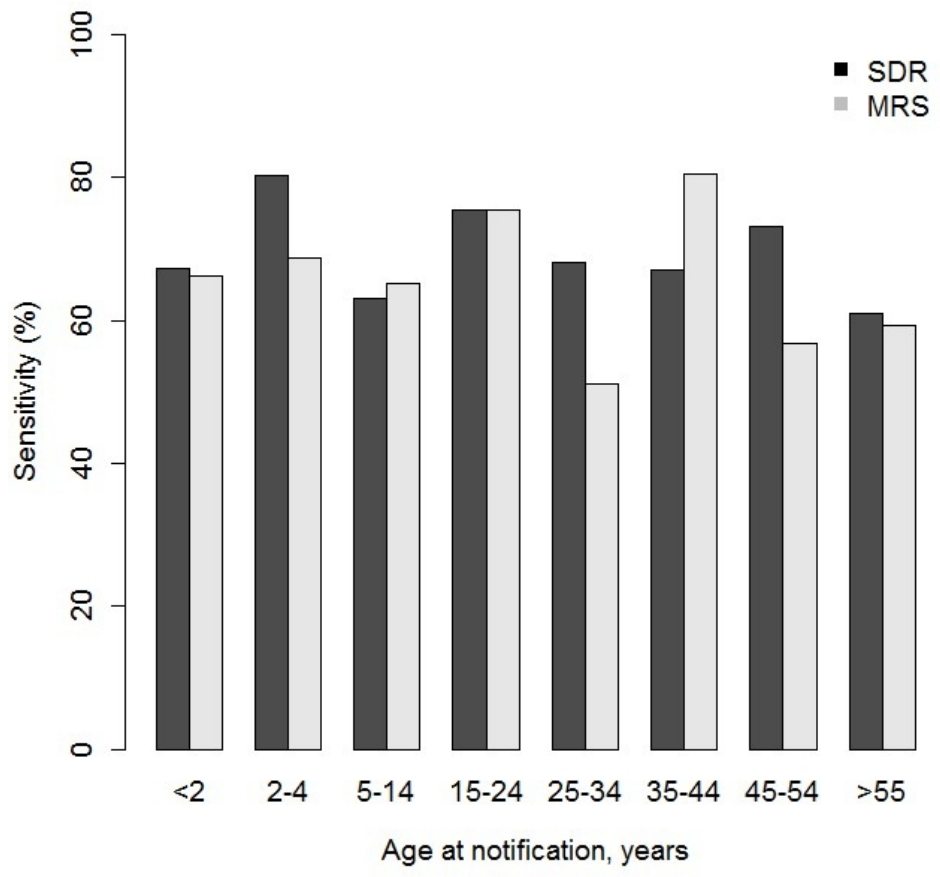


Figure 2. Sensitivities of the SDR and MRS stratified by age groups. Catalonia 2011-2015

176x172mm (96 x 96 DPI)

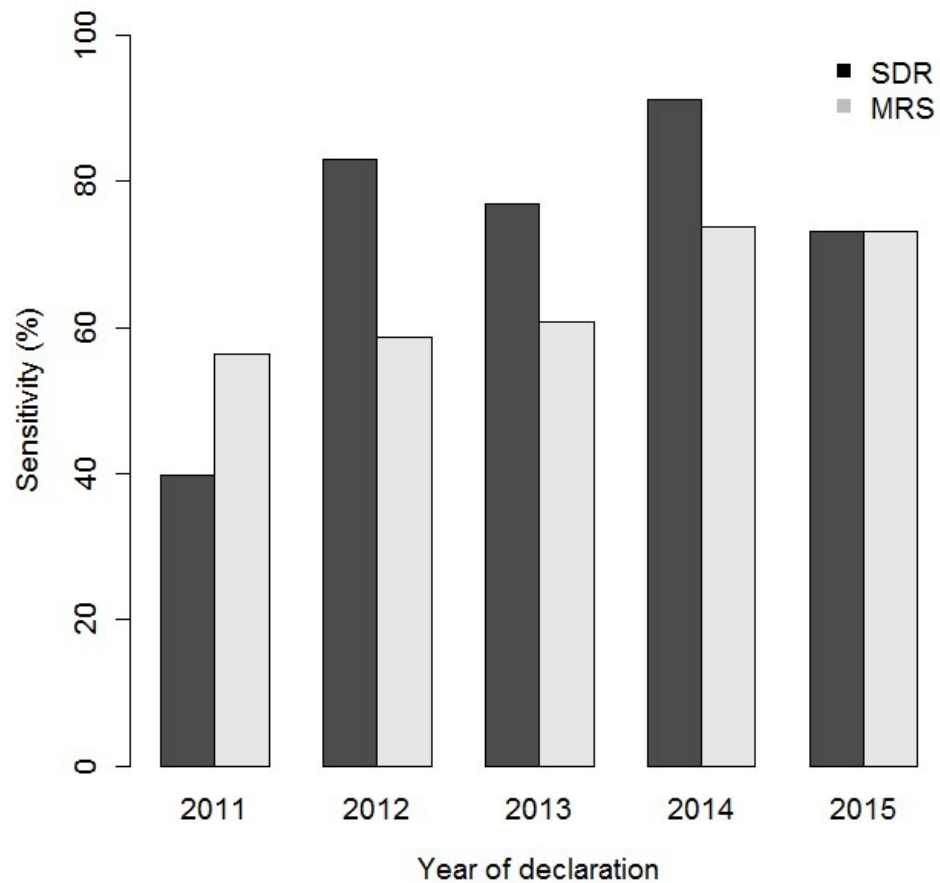


Figure 3. Sensitivities of the SDR and MRS stratified by year of reporting, Catalonia 2011-2015

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
<b>All cases</b>	164	153	114	17	220 (209, 232)	74.6 (68.8, 80.3)	69.6 (63.5, 75.6)	5.0	<b>&lt;0.001</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<200	49	52	33	9	77 (69, 86)	63.7 (53.0, 74.5)	67.6 (57.2, 78.1)	-3.9	0.095

<b>&gt;=200</b>	113	101	81	8	141 (134, 148)	80.3 (73.7, 86.8)	71.7 (64.3, 79.2)	8.5	
<b>Clinical form</b>									
<b>Meningitis</b>	91	100	70	9	130 (122, 138)	70.1 (62.2, 77.9)	77.0 (69.7, 84.2)	-6.9	<i>0.972</i>
<b>Septicaemia</b>	66	51	43	5	79 (73, 84)	84.4 (76.4, 92.4)	65.2 (54.7, 75.8)	19.2	
<b>Type of reporting centre</b>									
<b>Private</b>	14	1	1	0	14 (14, 14)	100 (100, 100)	7.1 (-6.4, 20.6)	92.9	<i>0.004</i>
<b>Public</b>	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 (%)	<i>p</i> -value
<b>All cases</b>	26	21	16	3	34 (30, 39)	76.7 (62.5, 90.9)	62.0 (45.6, 78.3)	14.8	<b>0.035</b>
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									

<b>&lt;200</b>	7	5	5	0	7 (7, 7)	100.0 (100.0, 100.0)	71.4 (38.0, 104.9)	28.6	<i>0.283</i>
<b>≥200</b>	18	16	11	3	26 (22, 31)	69.5 (51.8, 87.2)	61.8 (43.1, 80.5)	7.7	
<b>Clinical form</b>									
<b>Meningitis</b>	16	16	11	3	24 (20, 27)	69.3 (50.4, 88.1)	69.3 (50.4, 88.1)	0.0	<i>0.908</i>
<b>Septicaemia</b>	8	4	4	0	8 (8, 8)	100.0 (100.0, 100.0)	50.0 (15.4, 84.7)	50.0	
<b>Type of reporting centre</b>									
<b>Private</b>	4	0	0	0	4 (4, 4)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	<i>0.992</i>
<b>Public</b>	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
<b>All cases</b>	22	11	11	0	22 (22, 22)	100.0 (100.0, 100.0)	50.0 (29.1, 70.9)	50.0	0.104
<b>Age group</b>									
<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	
<b>Sex</b>									
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	
<b>Year of report</b>									
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	
<b>Size of municipality</b>									
<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	
<b>Country of birth</b>									
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	
<b>Number of hospital beds</b>									
<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	
<b>Clinical form</b>									
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	

<b>Type of reporting centre</b>									
<b>Private</b>	2	0	0	0	2 (2, 2)	100.0 (100.0, 100.0)	0 (0.0, 0.0)	100	0.992
<b>Public</b>	20	11	11	0	20 (20, 20)	100.0 (100.0, 100.0)	55 (33.2, 76.8)	45	
<b>Serogrup</b>									
<b>B</b>	17	9	9	0	17 (17, 17)	100.0 (100.0, 100.0)	52.9 (29.2, 76.7)	47.1	0.332
<b>C</b>	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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Continued on next page

<b>Results</b>			
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	10
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 (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	10,11,12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).