PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Estimation of the incidence of invasive meningococcal disease using a capture-recapture model based on two independent surveillance systems, in Catalonia, Spain
AUTHORS	Ciruela, Pilar; Vilaró, Marta; Carmona, Gloria; Jané, Mireia; Soldevila, Núria; Garcia, Tomás; Hernández, Sergi; Ruiz, Laura; Dominguez, Angela

VERSION 1 – REVIEW

REVIEWER	Ladomenou , Fani Venizeleion General Hospital, Department of Pediatrics
REVIEW RETURNED	30-Jan-2022

GENERAL COMMENTS	This is a well written manuscript on invasive meningococcal disease. The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia 174 (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD. They found that the sensitivity of enhanced surveillance through the combination of two complementary sources (statutory reporting by physicians and microbiological reporting by microbiologists) was higher than that of the individual sources The main flaw of this study is its retrospective character. Moreover, there is a comparison between a compulsory (SDR) and a non-compulsory (MRS) system, which means that information may have been lost through the non-compulsory reporting system. Moreover, cases diagnosed in private centres or public centres that did not participate in the MRS could not be reported by this system and this may explain, at least in part, the lower sensitivity than the SDR. Most of the references used are quite old. I would suggest the authors update and use more recent.

REVIEWER	Wang, Bing The University of Adelaide, Robinson Research Institute and Adelaide Medical School
REVIEW RETURNED	07-Feb-2022

GENERAL COMMENTS	Thanks for inviting me to review this manuscript. The manuscript is presented interesting results. There are a few suggestion for authors to consider which may improve the quality of the manuscript. Methods Subgroup analysis: nothing was mentioned here. In Table 3, year of report and type of reporting centre were significant, and clinical form was not significant. But author did subgroup analysis by

	clinical form. Serogroup was not included in Table 3. But author looked at serogroup B separately. Can authors add justification for those subgroup analyses? Lines 246-252: can authors add more information about multinominal logit model? What is the outcome measure? What are potential covariates included in the model? Line 237: space between two words “both” and “sources” Results: Line 285: can authors check the estimated number? Is it 312? Line 311: “MR)S”-typo? Line 323: “For 1 meningitis”-typo? Line 341: p=0.0036. Table 5 says p=0.036. Table 2: I think an overlapping circle chart (Venn diagram) could be easier and clearer for readers to understand. It took me a while to figure out those numbers presented in the table. Table 3: • For all cases, year of report and type of reporting centre, differences in sensitives were significant. What kind of statistical analysis did author use to compare those differences? • As I mentioned previously, authors presented subgroup analyses by clinical form in Tables 4 and 5, although clinical form was not significant in Table 4. Any clinical or statistical justification? • None of those cases were reported as meningitis with septicaemia. Meningitis with septicaemia seems very uncommon. Were clinical forms classified based on early clinical symptoms or administrative coding? Table 6: • Authors stated that “a multinomial logit model was used to evaluate patient characteristics and the probability of capture by different sources, which allows more precise estimates of the number of cases”. If authors think the adjusted estimate of cases is more precise, why did authors only use the Chapman figures - 88.5% (277/313) in the discussion? • Size of municipality was deemed significant in the multinominal logit model. What are the criteria of significance? P value? Discussion: Lines 392-393: Authors said “A possible explanation is that meningitis is considered a more serious disease and, therefore, microbiologists are more sensitive to its reporting.” Meningococcal septicaemia can result in amputation and skin necrosis. I cannot agree with authors on this point. Although all cases were laboratory confirmed IMD cases, there were 75 cases reported through SDR but not identified by MRS. The MRS was non-compulsory until 2015 - which might be reason for the lower sensitivity of MRS? Authors did not discuss the implications and potential reasons of other significant differences between two reporting systems such as year of report, age at notification. Line 425: Lines 190 says MRS covered 83% of acute hospital beds. Line 425 says MRS has a coverage of 82% acute hospital beds and without private centres. Lines 432-437: the results section didn’t say anything about mortality or deaths. But death was mentioned in the discussion section. Can authors add more information about death to the results section? My apologies if I missed anything in the results sec

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Ms. Fani Ladomenou , Venizeleion General Hospital

Comments to the Author:
This is a well written manuscript on invasive meningococcal disease. The aim of this study was to assess the sensitivity of the two surveillance systems in Catalonia
174 (SDR and MRS) using the capture-recapture method and to estimate the incidence of IMD. They found that the sensitivity of enhanced surveillance through the combination of two complementary sources (statutory reporting by physicians and microbiological reporting by microbiologists) was higher than that of the individual sources
The main flaw of this study is its retrospective character. Moreover, there is a comparison between a compulsory (SDR) and a non-compulsory (MRS) system, which means that information may have been lost through the non-compulsory reporting system. Moreover, cases diagnosed in private centres or public centres that did not participate in the
MRS could not be reported by this system and this may explain, at least in part, the lower sensitivity than the SDR.
Most of the references used are quite old. I would suggest the authors update and use more recent.
Response: You are right. The manuscript was prepared before the COVID-19 pandemic. Now we have looked for new studies on capture-recapture of meningococcal disease and we have found only one study (Andrianou) that has included in the discussion section. We have also searched for studies on surveillance of meningoccal disease and we have updated the introduction section with data from new studies about the burden of the disease: incidence, the predominant serogroups, case fatality rate and the sequelae.

Reviewer: 2
Ms. Bing Wang, The University of Adelaide

Comments to the Author:
Thanks for inviting me to review this manuscript. The manuscript is presented interesting results. There are a few suggestion for authors to consider which may improve the quality of the manuscript.

Methods
Subgroup analysis: nothing was mentioned here. In Table 3, year of report and type of reporting centre were significant, and clinical form was not significant. But author did subgroup analysis by clinical form. Serogroup was not included in Table 3. But author looked at serogroup B separately. Can authors add justification for those subgroup analyses? As mentioned in the introduction of the revised version of the manuscript, clinical manifestations varies by serogroup and, therefore, the reporting of the disease by different surveillance systems can also vary. We have included the serogrups in tables 3-5.
Lines 246-252: can authors add more information about multinominal logit model? What is the outcome measure? What are potential covariates included in the model? We did not specify correctly the multivariate analysis used. Now it is corrected, changing the pharagraph as following: “As a multivariate model, a vector generalized linear model (VGLM) from the generalized additive model (GAM) framework [ref Yee...] was used to evaluate patient characteristics and the probability of capture by the different sources taking into account the covariates: age (<15 vs >=15), gender, year of notification (2011-2013 vs 2014-2015), size of the municipality (<10,000 vs >=10.000), country of birth (Spain vs other), number of hospital beds (<200 vs >=200) and diagnosis (meningitis vs septicaemia).

The outcome for the model is a two column matrix with 0 and 1 indicating if the record is identified by SDR or MRS. We used a backwards stepwise procedure (using likelihood ratio tests, with a p-value >0.2 as the criterion for removing variables from the model) [21, 22] to eliminate covariates, starting with a full model including all described covariates, and we used the parameter estimates from the model to estimate the sizes of population subgroups and calculate incidence rates. The 95% confidence intervals (CI) were calculated, allowing for uncertainty in the total number of cases estimated. For each of the described covariates, VLGM with source notification as outcome was used to test differences in sensitivities. All analyses were made using R software version 3.0.1".
Line 237: space between two words "both" and "sources" Thank you. We have done corrected the typo error.

Results:
Line 285: can authors check the estimated number? Is it 312? The estimated number is 313.
Line 311: "MR)S"-typo? We have corrected it
Line 323: "For 1 meningitis"-typo? We have corrected dit.
Line 341: p=0.0036. Table 5 says p=0.036. You are right. We have corrected it
Table 2: I think an overlapping circle chart (Venn diagram) could be easier and clearer for readers to understand. It took me a while to figure out those numbers presented in the table. Ok. We changed table 2 for figure 1.
Table 3:
• For all cases, year of report and type of reporting centre, differences in sensitives were significant. What kind of statistical analysis did author use to compare those differences? We used the bivariate VGLM to obtain the p-values. We added a phrase in the methods section indicating this point: "For each of the described covariates, VLGM with source notification as outcome was used to test differences in sensitivities."
• As I mentioned previously, authors presented subgroup analyses by clinical form in Tables 4 and 5, although clinical form was not significant in Table 4. Any clinical or statistical justification? As we have explained in the introduction of the revised version of the manuscript, clinical form can vary and serogroup involved related both with the case fatality rate and the predominant clinical form.
• None of those cases were reported as meningitis with septicaemia. Meningitis with septicaemia seems very uncommon. Were clinical forms classified based on early clinical symptoms or administrative coding? In the study cases that presented meningitis could have sepsis or not. This information is in methodology. The information provided by the laboratories depends on the request made by the attending physicians.
Table 6:
• Authors stated that "a multinomial logit model was used to evaluate patient characteristics and the probability of capture by different sources, which allows more precise estimates of the number of cases". If authors think the adjusted estimate of cases is more precise, why did authors only use the Chapman figures -88.5% (277/313) in the discussion? Thank you for bringing up this issue. We have removed this phrase because it can generate confusion. The crude estimate of population size is biased when the sources are not independent. In that case, adjusting for covariates produce less biased estimates. We tested the independence of the sources and we obtained that they can be considered independent, therefore the multivariate analysis may not be more precise than the Chapman.
• Size of municipality was deemed significant in the multinominal logit model. What are the criteria of significance? P value? After backward stepwise procedure (with a p-value >0.2 as the criterion for removing variables) in the multivariate analysis, the variables considered to define the model were size of municipality and year of report. Only year of report was statistically significant ($p<0.05$). We have changed the phrase in the Results section.

Discussion:
Lines 392-393: Authors said "A possible explanation is that meningitis is considered a more serious

disease and, therefore, microbiologists are more sensitive to its reporting." Meningococcal septicaemia can result in amputation and skin necrosis. I cannot agree with authors on this point. Although all cases were laboratory confirmed IMD cases, there were 75 cases reported through SDR but not identified by MRS. The MRS was non-compulsory until 2015 - which might be reason for the lower sensitivity of MRS? MRS had greater sensitivity than SDR in meningitis (in the two periods analyzed) in contrast to septicaemia (greater sensitivity in SDR than MDR, in both periods). We do not know what the reasons may be. A possible explanation is that meningitis has a specific section in MRS for reporting while septicaemia is reported in bacteraemia of unknown focus section and it could be confused. We have included this paragraph in the discussion.

Authors did not discuss the implications and potential reasons of other significant differences between two reporting systems such as year of report, age at notification. Referent to year of report:
You are right. We have included this variable in the discussion.
For age at notification we expand the discussion:
Globally, the sensitivity was similar in children aged <15 years than in persons aged ≥15 years in both sources (69.1% for the SDR and 66.5% for the MRS; P=0.468). The differences could be because there is greater sensibilitazion to declare pediatric cases than adult cases or because there are differences on IMD incidence according to age (Acevedo).

Line 425: Lines 190 says MRS covered 83% of acute hospital beds. Line 425 says MRS has a coverage of 82% acute hospital beds and without private centres. You are right. We have changed 82% by 83% as mentioned the references.

Lines 432-437: the results section didn't say anything about mortality or deaths. But death was mentioned in the discussion section. Can authors add more information about death to the results section? My apologies if I missed anything in the results section. In the results section there was a short description about death and all analyzed information was in supplementary table 3:
"All 22 deaths were reported in the SDR (CFR: 10.4%), and the sensitivity of the SDR was higher than that of the MRS (100%; 95CI% 100-100 vs 50%; 95%CI 29.1-70.9, P=0.104) (Supplementary Table 3)".
We have added: No differences were found in other characteristics analysed.

Thank you very much in advance. We look forward to receiving your decision.

Yours sincerely, on behalf of the authors,

Dr. Pilar Ciruela
Corresponding Author

VERSION 2 – REVIEW

REVIEWER	Wang, Bing The University of Adelaide, Robinson Research Institute and Adelaide Medical School
REVIEW RETURNED	19-Apr-2022

GENERAL COMMENTS	Thanks for inviting me to review the revision. The marked copy is a draft version which has got a comment, highlights and unfinished references. Can the authors submit the correct version of the tracked change copy please?

VERSION 2 – AUTHOR RESPONSE

General	3	R2	The marked copy is a draft version which has got a comment, highlights and unfinished references. Can the authors submit the correct version of the tracked change copy please? We apologize for this error. We send the correct version with the track changes.

VERSION 3 – REVIEW

REVIEWER	Wang, Bing The University of Adelaide, Robinson Research Institute and Adelaide Medical School
REVIEW RETURNED	05-Jun-2022

GENERAL COMMENTS	No further comments.