Author’s response to reviews

Title: Prognostic Factors Related to Sequelae in Childhood Bacterial Meningitis: Data from the Meningitis Registry

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Author’s response to reviews: see over
To the Editor in Chief
Melissa Norton, MD
BMC Infectious Diseases

Dear Editor,

RE: re-submission of revised manuscript [MS: 1070601284411904]

We would like to thank you for the opportunity to consider a revised version of our manuscript entitled “Prognostic Factors for the Determination of Sequelae in Childhood Bacterial Meningitis: Data from the Meningitis Registry” in response to comments made by both reviewers for publication in BMC Infectious Disease.

We have taken into account comments made by both reviewers and have incorporated these changes into the revised manuscript accordingly. However we believe that of the two reviewers reviewing our manuscript it was evident from the comments made that reviewer Francois Brivet has not understood the concept of our manuscript and we therefore kindly request that Francois Brivet not continue with the evaluation. We have no objection for you to introduce a new reviewer for the continuing evaluation. Please find attached point by point answers to both reviewers.

Please do not hesitate to contact me for any further clarifications that may be required.

Yours Sincerely

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Reviewer #1: Allan Tunkel
We would like to thank the reviewer for his comments and suggestions:

This is a revision of the article by Vasilopoulou et al on "Prognostic factors related to sequelae in childhood bacterial meningitis: data from the meningitis registry." The authors have made significant improvement to their manuscript, based on the comments of all of the reviewers, but I continue to have some concerns and comments as follows:

1. In the results section of the abstract, the authors need to add some additional specific information. When discussing rate of acute complications, they need to include the complications being assessed. The same is true for the sequelae. The reason to add it here is that someone just reading the abstract would not have those specifics.

We agree with the reviewer and have added this clarification to the abstract. The abstract now reads as follows:

"The rate of acute complications (arthritis and/or subdural effusion) was estimated at 6.8% (152 out of 2,251 patients, 95%CI 5.8-7.9) while the rate of sequelae (severe hearing loss, ventriculitis, hydrocephalus or seizure disorder) among survivors was estimated at 3.3% (73 out of 2,207 patients, 95%CI 2.6-4.2)."

2. In the background section on page 2, line 5, I don't understand what they mean by the statement that the impact of the vaccines could be 'enlightened' further.

We apologise for the misunderstanding and have substituted the word “enlightened” for “needs to be further investigated during the next few years.”. This change is on page 3 as follows:

“However the impact of these vaccines on the disease epidemiology needs to be further investigated during the next few years.”

3. In the methods section of pages 4 and 5, they discuss the definitions of probable and confirmed bacterial meningitis. They reference an article by Chavez-Bueno and McCracken as including the WHO definitions. However, I pulled the article and cannot find those definitions.

We apologise for this mistake, the citation should have been [8] in the old manuscript and not [7]. Old citation [7] has now been omitted and replaced with the following:

We have also taken the opportunity to add in the following citation as well with respect to our definitions:


For the confirmed cases, did patients have to have evidence of meningitis by CSF examination as that is not included?

We appreciate the reviewers comment. In response to his question the answer is yes, the patients did have to have evidence of meningitis by CSF.

What is Fadebact?

Fabebact is a latex agglutination test (Pharmacia Diagnostics, Sweeden) that consists of specific antibodies against H influenzae type b, S pneumoniae, N meningitides groups A,B,C,Y and W and streptococcus agalactiae. This kit was also known as “Phadebact” We have changed the word “Fabebact” to “Phadebact (latex agglutination)”

4. On page 5 for the definition of acute complications, I find it limiting that only arthritis and subdural effusion were included. Why were other items, such as seizure and hypotension, not included?

According to our definitions we have grouped seizures and hypotension in the category of sequelae and not acute complications. Seizures were classified as chronic sequelae as mentioned because they tend to persist beyond the acute phase. Concerning hypotension, it was included in the admission findings and not in the complications.

5. On page 8, line 3, they mean "confirmed" not "documented" cases. Should stick to the terms in the definition.

This has now been corrected on page 8 of Results line 3.

On the bottom of the same page, they found significant differences with a decrease in the duration of symptoms of the time periods. What is being compared to get this significant difference? Comparing A to B, or A to C, or B to C?
We have compared all periods together and not in pairs. For the reviewer we have also compared groupings of period A to B, A to C, and B to C. In all of these pair-wise comparisons we observed statistically significant differences (Mann-Whitney Test, Bonferroni correction). As shown below. For this reason we have not altered the manuscript in response to this comment.

<table>
<thead>
<tr>
<th>Pair wise comparison of periods</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A to B</td>
<td>0,009</td>
</tr>
<tr>
<td>A to C</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>B to C</td>
<td>0,016</td>
</tr>
</tbody>
</table>

*Mann-Whitney test

By using *Bonferroni correction* the critical value = 0.0166 instead of 0.05

6. On page 9 under clinical data, the authors do explain in the tables why they don’t have data for all the clinical parameters, but how can they say that 93.2% of patients had fever when an initial temperature was only measured in half of their patients? The same is true for some of the other parameters with low denominators. I then find it even more difficult to make comparisons in clinical findings between age groups (Table 2) when the numbers of patients assessed may not be complete. I certainly understand it is based on data in the registry, but if the data are incomplete, perhaps these parameters should not be assessed or compared?

We appreciate the reviewers remarks, however we disagree as it is almost impossible to find a data registry that is 100% completed. In our study we believe that we have large enough denominators that render our results reliable as seen in table 1a. This can further be supported with close confidence interval ranges. With respect to table 2, we agree with the reviewer that some of the age group populations are small however this is unavoidable as some clinical features are associated with certain age groups. Even if we were to regroup them into two age groups and hence increase population size it would not make any difference to our calculations. Nevertheless we believe that these statistics are worth reporting. Moreover, in most of the cases the registry completeness is very high with the exception of the variable for fever where we have approximately 50% completeness. Please note that for the variables such as meningeal signs, headache, bulging fontanelle and grunting, the denominators are not the total population but correspond to a subgroup of the entire population as there are age restrictions for these prognostic factors. However, we do not believe that even for fever the relatively low % of completeness of fever could not be considered as bias as we do not have any information / indication that this was done.
systematically for any particular reason. In addition it is different to have 50% completeness in a total population of say 100, in comparison to that of 50% over total population of 2477 as is the case in our study!

7. On page 10 in the paragraph comparing the time periods, I have the same concern that I have elucidated above. The authors are giving percentages of patients with a clinical presentation, but the registry may not have the complete data.

We appreciate the reviewers concern, however as seen in the results on page 10, p values of seizures, bulging fontanelle, grunting and shock are all < 0.001 while coma and hemorrhagic rash had p values =0.002 and 0.006 respectively, all of which were statistically significant. If our population had been small we would not have statistically significant results and we would therefore argue that this was due to a low population size. However this is not the case in our study, and therefore we believe that our results are reliable. Moreover, the completeness of these variables are quite high and could be considered as representative of the total population (for example: Headache 1112/1330 (83.6%), Meningeal signs 1477/1691 (87.3%), Seizures 1777/2477 (71.7 %), Bulging fontanelle 918/1218 (75.4%), Grunting 952/1218 (78.2%), Poor feeding 1611/2477 (66.4%), Shock 1689/2477 (68.2%) and Coma 1671/2477 (67.5%). As mentioned above we do not believe that even for fever the relatively low % of completeness of fever could not be considered as bias as we do not have any information / indication that this was done systematically for any particular reason. In addition it is different to have 50% completeness in a total population of say 100, in comparison to that of 50% over total population of 2477 as is the case in our study!

8. On page 11 in the paragraph on the rate of acute complications, were arthritis and subdural effusions the only ones and did no patients have both of these complications?

Yes, one patient did have both arthritis and subdural effusions. As well one patient presented both hydrocephalus and ventriculitis, one patient had both hydrocephalus and seizure disorder, two patients had both seizure disorder and ventriculitis, three patients had both seizure disorder and severe hearing loss, and three patients presented both ventriculitis and severe hearing loss. These numbers are very low and, practically, they do not influence our results. However, we believe that this information is not related with the purpose of our study and we do not have any implication in the analysis and the results.
9. Tables 3, 4, and 6 are the most important and perhaps this is the data that should be the primary focus of their paper.

We also believe that the results presented in the above mentioned tables are important, and for that reason we have included them in the manuscript. We tried not to overwhelm the paper by describing in words all the results of the prognostic factors shown in these tables.

10. I continue to be unclear about the significance of Figure 1. It is not a algorithm but simply shows that the more negative factors you put together increases the risk.

We appreciate the reviewer’s comment with respect to this figure however we believe that this figure may be of some assistance for clinicians.

11. For comparison of the times periods A, B, and C, I think it would have been more interesting to see the decrease in incidence of various pathogens, particularly Hib, rather than extrapolate that Hib must have gone down because symptoms usually attributable to that organism have decreased.

We appreciate the reviewer’s suggestion however I must refer you to a previous paper titled: Maria N Theodoridou et al, Meningitis registry of hospitalized cases in children: epidemiological patterns of acute bacterial meningitis throughout a 32-year period BMC Infectious Diseases 2007, 7:101 doi:10.1186/1471-2334-7-101

12. On page 12, line 6 from bottom, I am not sure what is meant by have ‘appointed’.

We appreciate the reviewer’s attention to detail. We apologise for this mistake. Firstly the error was on page 17 and not 12 and secondly it should have been “pointed” and not “appointed”. This has now been corrected. The paragraph now reads as follows:

“Although current study focuses on short term effects of BM in children, several studies have pointed out the presence of long term neurobehavioural effects.”

13. Table 1a. Not sure of the validity of percentages when denominators are low in many categories.

We appreciate the reviewers remarks, however we disagree as it is almost impossible to find a data registry that is 100% completed. After rechecking table 1a for low denominators, we do not believe that the denominators are that low that they may influence the validity of our results. In our study we believe that we have large enough denominators that render our
results reliable. We do not believe that denominators over 1000 can be considered low. When examining Table 1a, the lowest denominators were that of Bulging fontanelle (denominator n= 918) and Grunting (denominator n= 952). However we must not forget that these parameters are associated with specific age groups (ie. Bulging fontanelle and Grunting - children <2 years old). Secondly, the validity of our results can be supported by the close confidence intervals ranges. In continuation to this comment completeness of these variables are quite high and could be considered as representative of the total population (for example: Headache 1112/1330 (83.6%), Meningeal signs 1477/1691 (87.3%), Seizures 1777/2477 (71.7 %), Bulging fontanelle 918/1218 (75.4%), Grunting 952/1218 (78.2%), Poor feeding 1611/2477 (66.4%), Shock 1689/2477 (68.2%) and Coma 1671/2477 (67.5%).

Reviewer: Francois Brivet

Majors comments

The main problem of this revised version is the statistical analysis. As suggested in the previous comments authors split their population into two groups according to the confirmation or not of the diagnosis of Bacterial Meningitis, but for their analysis of prognostic factors the authors compare the subgroup “confirmed BM” to the all population;
I am not sure that this comparison is adequate and thus that results are correct;

We disagree with the reviewer as we have not made any comparisons between the two populations. We have analysed them separately and have shown their results without comparing them in the same table. Please note that “confirmed” cases have different p values to those of “all cases”.

Authors should describe the all population and then compare the two subgroups “confirmed BM” and “suspected BM; Indeed if we focus on table 3 and particularly the sequelae, at evidence the sequelae occurred mainly in case of confirmed BM

We believe that our analysis is correct. Furthermore, we agree that evidence of sequelae occurred mainly in confirmed BM cases. This is expected and has been described in previous studies. As well in this study: in additional file 1 the sequelae are presented according to etiology. As it is prominent sequelae are more frequent among BM
Streptococcus pneumoniae, Haemophilus influenzae type b (Hib) and Other bacteria which of all them belong to the confirm BM category.

While in a previous publication we have also analysed probable and confirmed population with respect to predetermining bacterial pathogen:


In the confirmed BM case category, pneumococcal and “other pathogens” are included, in which it is well known that sequelae are more frequent than in meningococcal meningitis. As for comparing subgroups of confirmed and probable, our purpose was to examine prognostic factors in a population that present to hospital before confirmation of meningitis (ie, probable and confirmed populations). In our view this would be more valuable to the clinician, rather than looking only at probable and / or confirmed cases of BM. After all, the classification of “confirmed” is usually done afterwards and most of the time this is done for analysis purposes. Furthermore, since we conducted the analysis of prognostic factors separately for the confirmed population and for all population (ie, confirmed and probable cases together), it is therefore obvious that the difference between all cases and confirmed cases is that of probable cases.

In table 4, the analysis of the sequelae according to the pathogens is correct ONLY for the subgroup of confirmed BM with differences in the incidence (estimated CHI2 : 60,2 p< 0.001) whereas the comparison with the all population is in my concern a nonsense.

We disagree with the reviewer, and we believe that the analysis of all population is not nonsense but on the contrary very important as the aim of this study is to identify prognostic factors for sequelae in the population that presents to hospital before diagnosis (as it is this population that includes both probable and confirmed). However we have also included analysis of confirmed cases only whereby we can see that in most cases the same prognostic factors of both populations, show to be statistically significant. Please note that we have not statistically compared them. We have analysed them separately and presented them in the same table.
Furthermore, I am not sure of the usefulness of a logistic regression for each type of acute complications or sequelae.

We would kindly request that the reviewer re-read our manuscript as we have not conducted logistic regression analysis for each type of acute complications nor sequelae.

After the comparison of the two subgroups according to the documentation or not of their BM cases, the results would be more evident that sequelae occur mainly in case of Documented BM.

We agree with the reviewer that sequelae occur mainly in cases of confirmed BM and this finding was presented in our previous study as well as in other studies. However our aim in this study, is to identify prognostic factors in BM cases whether they are confirmed or not.

Minors comments

Even if the journal is a free FULL TEXT journal, authors should improved the Abstract (unchanged since the previous versions) ,the number of documented BM and the case Fatality rate should at least appear, and results may change when using adequate comparison;

We would like to thank the reviewer for the useful to improve the abstract. We have altered it by adding some definitions as requested by reviewer #1. However, Fatality rate has been discussed in a previous paper. It is not the main focus of our paper and therefore we have not added this to our abstract. If the reviewer or the editor feels that it is very important we can include this information.

For the multivariate analysis instead of positive blood culture, authors should recalculate the OR after introducing “confirmed( or not) BM in their model

We appreciate the reviewers’ suggestion. We have recalculated the OR after introducing confirmed (or not) BM in our model, however no difference was seen. These are the results that can be compared to the results in our manuscript (Table 6).

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of Seizures</td>
<td>5.36</td>
<td>2.63-10.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of Hemorrhagic rash</td>
<td>0.21</td>
<td>0.06-0.69</td>
<td>0.011</td>
</tr>
<tr>
<td>CSF Glucose &lt;40mg/dl</td>
<td>5.20</td>
<td>1.68-16.07</td>
<td>0.004</td>
</tr>
<tr>
<td>CSF Protein &gt;100mg/dl</td>
<td>2.98</td>
<td>1.06-8.32</td>
<td>0.038</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>2.69</td>
<td>1.18-6.13</td>
<td>0.019</td>
</tr>
<tr>
<td>Confirmed case</td>
<td>0.98</td>
<td>0.40-2.36</td>
<td>0.957</td>
</tr>
</tbody>
</table>
Table 6 as shown in current manuscript:

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>5.36</td>
<td>2.63-10.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhagic rash</td>
<td>0.21</td>
<td>0.06-0.69</td>
<td>0.011</td>
</tr>
<tr>
<td>CSF Glucose &lt;40mg/dl</td>
<td>5.18</td>
<td>1.69-15.87</td>
<td>0.004</td>
</tr>
<tr>
<td>CSF Protein &gt;100mg/dl</td>
<td>2.97</td>
<td>1.06-8.29</td>
<td>0.038</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>2.66</td>
<td>1.24-5.72</td>
<td>0.012</td>
</tr>
</tbody>
</table>

As can be seen there are no differences in the results thus, we do not believe that it is worth including confirmed status in the analysis model. Therefore no change with respect to this has been made in the manuscript. Moreover, confirmed status (OR 0.98) could not be considered as a prognostic factor for sequelae.