Author's response to reviews

Title: Clinical outcome of pneumococcal meningitis during the emergence of penicillin-resistant Streptococcus pneumoniae: an observational study

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Author's response to reviews: see over
Clinical outcome of pneumococcal meningitis during the emergence of penicillin-resistant Streptococcus pneumoniae: an observational study

Dear Editors,

Thank you for considering our manuscript for publication in *BMC Infectious Diseases*, and for sending the referees’ suggestions.

We have addressed the reviewers’ comments and suggestions in revising the manuscript as follows:

Comments from Referee 1:

Major revision

1. There are few datasets in which outcomes of meningitis, susceptibility data and treatments given are recorded so this is a potentially important report. The main finding is an increased risk in an adjusted multivariable model of mortality associated with increased penicillin MIC - this association apparently disappeared when ceftriaxone was given as presumptive primary therapy - although the regression data are shown for the association of increased pen MIC with mortality - the basis for the analysis with primary ceftriaxone therapy alone is not shown - nor is the analysis shown of all cases in which ceftriaxone was not primary therapy - these analyses should be shown.

Response: We analyzed the data as Dr. Klugman suggested by running the final Cox proportional hazards model with two groups of patients: those who received initial ceftriaxone therapy and those who received initial antibiotic therapy other than ceftriaxone.

The association between penicillin-resistance and case-fatality remained significant only in the group that RECEIVED initial ceftriaxone therapy, suggesting that initial penicillin therapy was not the main cause of the increased case-fatality. We added Table 3 to present the results of the final multivariable Cox proportional hazards model stratified according to initial ceftriaxone or other antibiotic therapy. Because the model did not converge when the model was run with five age categories for the group of patients that received initial antibiotic therapy other than ceftriaxone, two of the age categories were combined.

We updated the abstract and results based on the new results.

2. The analysis of discordant therapy was not significant - the inference from the conclusion above and in fact the conclusion reached by the authors is that penicillin therapy failed when intermediately susceptible strains were treated with penicillin - while this is biologically plausible the authors need to explain why the discordant analysis was not significant - is it a question of small numbers? – a related question is the mortality which is high in Table 1 for
unknown or "other" treatment - while the unknown therapy is a worry as we cannot make any inferences about these cases - is the failure of other therapy a driver of the overall association with failure?

**Response:** We have added a sentence in the first paragraph of the Discussion stating that the number of patients who received discordant therapy was too small to have statistical power to detect an effect on mortality. We observed higher mortality among patients with penicillin-resistant isolates (formerly classified as intermediate resistance), but we cannot say that penicillin therapy failed when patients with resistant isolates received penicillin therapy. In fact, the stratified analysis shows that even the patients with penicillin-resistant isolates who received initial ceftriaxone treatment had significantly higher mortality. However, initial ceftriaxone therapy was not assigned randomly, and younger patients with higher case-fatality were more likely to receive ceftriaxone when supplies were limited. We have revised our Conclusions accordingly.

Of the 33 patients in Table 1 with other/unknown initial antibiotic therapy, antibiotic was not recorded only in 13 patients. Removing 13 patients with unknown therapy from the analysis did not change the findings.

**Minor comments**

1. Hazard ratio is 1.63 in abstract and 1.62 in results table. **Corrected**
2. 21 discordant cases in text and 22 discordant in table 2. **Corrected**

**Comments from Referee 2:**

**Discretionary Revisions**

1.- Abstract: I suggest to add the value of hazard ratio and its 95% CI in the last sentence of the Results paragraph (e.g., “Penicillin-resistance was not associated with higher case-fatality when initial therapy included ceftriaxone” (hazard ratio and confidence interval). The conclusion is based on this finding, so it should be quantified in the Results.

**Response:** Agreed. Note that the association between penicillin-resistance and case-fatality remained significant in the stratified analysis for patients whose initial therapy included ceftriaxone. We updated the abstract and included the hazard ratio and confidence interval from the stratified analysis.

2.- Results section, first paragraph.
The first phrase of the results only comments that 548 pneumococcal meningitis cases were included in the analysis. Below, the second phrase directly comments the results about penicillin-resistant strains observed in the study. I believe that a paragraph describing characteristics of the 548 study subjects would be welcome at the beginning of the Results section.

**Response:** Agreed. We have moved the description of the patients to the beginning of the Results section.

3.- Results section, second paragraph
The authors comment that “serotypes included in the 10-valent pneumococcal conjugate vaccine accounted for 271 (49%) of 548 cases”. It would be possible also include a phrase reporting serotype coverage for the PCV13?
Response: We have added the percentages corresponding to the 13-valent vaccine formulation.

4.- Results.
Last sentence of the Results section (“Penicillin-resistance was not associated with higher case-fatality when initial therapy included ceftriaxone”): Same commentary that suggested for Abstract

Response: We have added Table 3. We have not included the hazard ratios and confidence intervals for the stratified analyses according to initial antibiotic therapy because they are shown in the table.

5.- References
Reference 2 does not contain authors. I suggest revise it.

Response: Corrected.

We have highlighted with red font all changes made in revising the manuscript, with the exception of the addition of Table 3, which is new.

I will serve as the corresponding author during the submission process. Dr. Albert Ko will serve as corresponding author should the manuscript be accepted for publication.

Thank you on behalf of all the authors,

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