PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sensorineural hearing loss after neonatal meningitis: a single centre retrospective study
AUTHORS	Sharma, Ankur Leaf, James M Thomas, Saumya Cane, Christine Stuart, Claire Tremlett, Catherine Fitzgerald, John Clarke, Paul

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Karel Allegaert Institution and Country: KU Leuven, Belgium Competing interests: None
REVIEW RETURNED	03-Aug-2022

GENERAL COMMENTS	I have read this letter with interest Hearing outcome is indeed a somewhat understudied aspect of neonatal outcome, but the main limitation is the small group, and the incompleteness of the data. In a single center study, 16 meningitis cases were identified, 10 cases with diagnostic audiology (of 14 survivors), and 2/10 cases had SNHL. This is a relevant shortage of the letter, as only reflecting a very small group (perhaps the use of % is not really appropriate), with incomplete data. I have tried to read the reference 2, and perhaps a specific description of the 'meningitis appendix 2' is appropriate ? I understood the current guideline somewhat different (not 'only' testing at 8 months as currently suggested). I understood that only bacterial and fungal meningitis has been considered ? If so, this should be better reflected in the title and abstract, and that we are not discussing the screening tests, but the final audiology outcomes. Can you compare this to the overall hearing outcome in your cohort ? Larger studies are needed is a very 'common' final sentence, any more targeted ideas ? Ehics: I assume that single center, and the specific characteristics make the individual cases identifiable for their relatives ? it is not yet clear how the authors have handled this ? perhaps remove table 1 and provide some additional information in the text is a way to mitigate this (not sure if formal agreement of an IRB or similar, or parents is needed in the UK

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VERSION 1 – AUTHOR RESPONSE

Editors' comments Our Responses

Title amend to "sensorineural hearing loss after neonatal meningitis: a single centre retrospective study"

Amended as requested.

Delete all % - your numbers are small

We have deleted reference to percentages for all the audiological outcomes. However we have retained the percentage rate of definite meningitis, ("the definite meningitis rate was 16/16,070 (0.1%)" as this was a complete figure with no missing microbiological data for whole the period, and an accurate denominator.

Delete Table 1 and replace with a summary table, listing organisms, ranges for age, etc.

As requested we have deleted 'Table 1' and replaced with 'Summary Table' and changed the citation to it in the manuscript accordingly.

Following the comment from the Referee regarding anonymity, we have deleted the column in the Table which provided the completed gestational ages of the babies at birth.

Reviewer's Comments Our Responses

I have read this letter with

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interest

Hearing outcome is indeed a somewhat understudied aspect of neonatal outcome, but the main limitation is the small group, and the incompleteness of the data.

Thank you and we accept the limitation of our incomplete data. We included the reasons for missing definitive audiological data in 6 babies, data which was lacking despite our best efforts to elicit (2 had died, 2 had never been tested, and 2 failed to attend appointments).

In a single center study, 16 meningitis cases were identified, 10 cases with diagnostic audiology (of 14 survivors), and 2/10 cases had SNHL. This is a relevant shortage of the letter, as only reflecting a very small group (perhaps the use of % is not really appropriate), with incomplete data.

As requested, we have deleted reference to percentages for the audiological outcomes. However we have retained the percentage rate of definite meningitis, ("the definite meningitis rate was 16/16,070 (0.1%)" as this was a complete figure with no missing microbiological data for the period.

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I have tried to read the reference 2, and perhaps a specific description of the ‘meningitis appendix 2’ is appropriate ? I understood the current guideline somewhat different (not ‘only’ testing at 8 months as currently suggested).

Thank you for these points and for your diligence in verifying our citation to reference #2.

We have now revised our introductory paragraph to say instead that formal audiological referral is indicated for meningitis cases for “early auditory brainstem response testing and other formal audiological testing”. We could expand further on the specific details of the testing in our letter if the editors felt it imperative to add much further detail, but are mindful of the word count limits and in any case the cited reference guideline (Ref #2) is freely downloadable via the link provided. Moreover, it provides (in Sec. 7) a full detailed description of the prescribed formal audiological testing that is indicated in the UK for babies who have been diagnosed with neonatal bacterial meningitis.

The Reviewer is quite correct to identify that the guideline recommends ‘not only’ testing at 8 months, and we are grateful for this point of detail and apologise for our former error. We have now corrected the manuscript by deleting the clause

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that referred to testing ‘at 8 months’ and have instead substituted it with the more-correct statement that “early auditory brainstem response testing and other formal audiological testing” is indicated.

I understood that only bacterial and fungal meningitis has been considered ? If so, this should be better reflected in the title and abstract,

Yes, that is correct we only studied cases of bacterial and fungal meningitis. This has now been included in the revised abstract. We have also included in the manuscript text that cases of viral meningitis were excluded. We have amended the Title as requested by the Editor.

… and [I understood that] that we are not discussing the screening tests, but the final audiology outcomes.

Our manuscript actually reports both. We report both the neonatal newborn screening tests (OAEs +/- aABRs) where available, and also the definitive audiological testing results.

“For all confirmed [meningitis] cases we reviewed (…) newborn hearing screening results, and later diagnostic audiological testing”.

Of the 16 confirmed meningitis cases, our results section of the manuscript reports screening and final audiology outcome data for:

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i) those 14 babies who underwent a
newborn hearing screening test
ii) those 10 babies who survived and had
definitive audiological outcomes
allowing their classification according to
whether or not they had permanent
SNHL.
Can you compare this to the
overall hearing outcome in your
cohort ?
Thank you for the suggestion but this would be
way beyond the scope of our small study. It would
be a massive undertaking and as such a virtually
impossible task for us to obtain definitive hearing
outcomes for more than 16,000 babies.
Larger studies are needed is a
very 'common' final sentence,
any more targeted ideas?
We have thus revised the final sentences of our
manuscript as follows:
"A large epidemiological study, for example one
linking meningitis cases contained in large infection
surveillance databases with hearing outcomes as
logged in national audiological databases would
provide a more accurate indication of SNHL risk after
neonatal meningitis. Such linking, along with related
biochemical antimicrobial therapeutic drug
monitoring data, may also help to clarify whether
SNHL occurs mainly due to meningitis itself or to its
antimicrobial drug treatment in extremely preterm

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neonates.”

Ehics: I assume that single center, and the specific characteristics make the individual cases identifiable for their relatives ? it is not yet clear how the authors have handled this ? perhaps remove table 1 and provide some additional information in the text is a way to mitigate this (not sure if formal agreement of an IRB or similar, or parents is needed in the UK)

Anonymity:

Neonatal meningitis and permanent hearing loss are both relatively rare diseases. Our study has indeed also shown that the combination is very rare. As such it is accepted that a parent of a baby born in our centre in the past 16 years who ended up deaf and who had a history of neonatal meningitis might themselves theoretically – though in the highly unlikely scenario that they ever read our future published report – possibly suspect that their infant were amongst those reported in the Table. However, we have been very careful to remove all personal patient identifiers and no individual baby could ever conceivably be identifiable to the public at large. Arguably, birth gestational age and implicated organisms causing meningitis are in any case not

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personal identifiers, even along with the rare diseases reported. Nevertheless, on further consideration in the light of the referee's comment we decided to remove the column in the Table that provided linked birth gestational ages. We believe this will further assure regarding the remote risk of loss of anonymity. Further, we have now also removed from the manuscript text all reference to the exact completed gestational ages of the two infants with SNHL; this will also help assure anonymity.

While recognising that 100% anonymity can never be guaranteed, we believe our revised manuscript fully accords with the BMJ's standard on anonymisation https://authors.bmj.com/policies/patient-consentandconfidentiality/#bmjs_standard_on_anonymisation

We would like the Editors to please note that if our revised manuscript is eventually accepted for publication, then publication of our [unredacted] previous (initially-submitted) manuscript version and former Table as a Supplementary file will actually negate these additional steps we have taken in our revision to try to further preserve patient anonymity!

Ethics:

We would like to reassure the reviewer (and Editors) that our study does not and did not require formal ethics approval/waiver in the UK. As a study that has simply collected anonymised routinely- and already-collected data, this project

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did not require formal ethics approval according

to current guidelines. Confirmation of this is

provided from the MRC decision tool “Human

http://www.hra-decisiontools.org.uk/research/

which is provided by NHS Health Research

Authority and based on the Defining Research

table produced by the UK Research Ethics

Service. (please find printout attached as

Supplementary File

VERSION 2 – AUTHOR RESPONSE

Dear Prof Choonara,

Thanks very much for having considered our revised manuscript and for inviting us to submit a new version with minor revision.

Thank you for your further guidance and clarification as to the required revision of the Table. I have now revised accordingly and taken the opportunity to add into the revised table the summarised birth weight data also.

The only other revision to mention since R1 version is that I have added back in the summary rate of permanent hearing loss associated with meningitis, viz. "a rate of SNHL among surviving neonatal meningitis cases of at least 14% (2/14) (95% confidence limits: 2%, 43%)."

I hope this is acceptable. Determining the rate of permanent hearing loss associated with meningitis in our centre was indeed the main point of this project. The wide confidence limits indicated pave the way for the previously revised conclusion that a more accurate rate will only be determined by a large epidemiological study.

Thank you for considering our revised manuscript for publication in BMJ Paediatrics Open.

With best wishes,

Paul Clarke

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