Author's response to reviews

Title: Oral prednisolone for acute otitis media in children: a pilot, pragmatic, randomised, open-label, controlled study (OPAL study)

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Comment from Reviewer #1
Given the over prescribing of antibiotics and the potential for antibiotic resistance, the objectives of the study are worth investigation. In regard to feasibility, the authors have learned much as how to design a large RCT, and your statistical analysis is robust. Reducing potential bias, blinding the patients, parents, and nurses would have added strength to the design and more creditability to the findings. However, the researchers recruited children in a way that minimized selection bias.

Response to Reviewer #1
Thank you for recognizing it is a well-conducted study. This was a challenging study as we assessed effectiveness of corticosteroids for AOM in a developing country, we also introduced the option of withholding antibiotics for mild AOM and the importance of conducting clinical research with Indonesian health practitioners and parents.

Comment from Reviewer #2
Thank you for the opportunity to read this interesting pilot study testing the feasibility of an RCT to assess the efficacy of oral prednisolone on acute otitis media. Overall, this was a well-presented study, provides a good discussion of the limitations and addresses many important aspects of feasibility which will benefit a future trial.

Response to Reviewer #2
Thank you for recognizing the important aspects of our pilot study and the obstacles regarding feasibility, as well as your constructive feedback. Please find our response to your comments and feedback below.

Comment from Reviewer #2.1
The main rationale for this study appears to be a concern about overuse of antibiotics and risk of antimicrobial resistance. However, the majority of children recruited were classified with severe disease and therefore received antibiotics regardless. Given these findings, is your original rationale for the RCT still valid? Alternatively, would you consider conducting the trial only in children with mild disease where there is greater potential to reduce antimicrobial use?

Response to Reviewer #2.1
Our original rationale for our proposed RCT is to assess the effectiveness of corticosteroids, both as a monotherapy for mild AOM and as an add-on therapy to antibiotics for severe AOM. In doing so, we hoped to also find an alternative for antibiotics in those patients (mild disease) for whom it has previously been shown that antibiotics are not beneficial. Since we believe this is an important issue, we will include children with both mild and severe AOM. We will include more primary care centres in our main RCT, that will improve the recruitment rate of the children with mild AOM in particular and therefore will allow us to identify the effectiveness of corticosteroids for both mild and severe AOM.

Comment from Reviewer #2.2.1
I was unclear why your sample size calculations for the main RCT were based on a secondary outcome rather than your planned primary endpoint of pain reduction by a clinical important amount. However, after reading the protocol for the RCT (appendix 2) I believe you have changed the primary outcome to children with ongoing pain. I think this should be made clear in the main text.

Response to Reviewer #2.2.1
We did not use the secondary outcome to calculate our sample size for the main RCT. We calculated the sample size for the pilot study based on the mechanistic outcome (middle ear inflammation). Thank you for identifying this. We have added the additional information on the ‘Discussion’ section (Line 637-643):
“Our original primary outcome was the proportion of children with ongoing pain that has not reduced by the minimum clinically important amount (VAS score of 10 mm) by Day 3. However, our pilot study demonstrated that the majority of the children had their pain significantly improved at Day 3. Therefore, we will change the primary outcome in the main RCT to be the proportion of children with persisting pain (defined as the VAS score greater than 5 mm). We will retain the secondary outcome, that is the reduction of pain intensity using VAS, which will allow us to identify the effectiveness of oral prednisolone to improve pain by the previously-defined minimum clinically important amount.”

Comment from Reviewer #2.2.2
Your calculations use all cases of AOM combined. For the RCT you plan to stratify by health facility level and severity so may wish to account for this in the sample size calculations. In
addition, recruiting more children from primary care could increase the number of mild cases and alter the proportion with ongoing pain at day 3.

Response to Reviewer #2.2.2
For the main RCT, we calculated the sample size by using the proportion of children with both mild and severe AOM with persisting pain at Day 3, and weighting these by the expected proportion of mild and severe patients. We have estimated the main RCT sample size in different settings (see Table 4, Line 499-502). If we are able to recruit more children with mild AOM in the main RCT as a result of adding more primary care centres, we may increase the proportion of children with mild AOM to 43%, which will increase our sample size to 570.

Comment from Reviewer #2.3
Your pilot identified more children with severe disease than expected. Have you explored the possible reasons for this? Were most diagnoses based on subjective symptoms such as pain or objective signs such as perforation?

Response to Reviewer #2.3
Clinicians diagnosed AOM based on subjective assessment using VAS and objective assessment using an otoscope. At the initial consultation, there were 60% of children with mild AOM who had mild pain measured using VAS, compared to only 30% of children with severe AOM who had mild pain.

From the otoscope examination (see Table in the word version):

• Out of 15 children with mild AOM:
  o None of them had moderate-severe bulging/suppuration, nor perforation

• Out of 47 children with severe AOM:
  o 30% had mild ear pain: 21% of them had moderate-severe bulging/suppuration and 43% had perforation
  o 70% had moderate-severe ear pain: 48% of them had moderate-severe bulging/suppuration and 39% had perforation

Comment from Reviewer #2.4
You report that all physicians could confirm AOM using an otoscope. Was this self-reported or was it assessed? Can you clarify in the text?

Response to Reviewer #2.4
As this is a pragmatic study, the physicians diagnosed AOM, both objectively and subjectively, based on the clinical expertise using otoscope and VAS score. This process was a self-reported assessment. We have added in the ‘Results’ section, under ‘The successful completion of the study procedures and outcome measures’ sub-section (Line 403) as follows:

“All physicians (100%) successfully recruited and stratified eligible children based on their AOM severity, performed an otoscopic assessment, and measured pain and other relevant symptoms using VAS and AOM-SOS, and reported the findings as self-reported assessment in the CRF”.

Comment from Reviewer #2.5.1
The primary outcome is based on pain scales but it is not clear if you used those completed by parents in symptom diaries or by doctors at study visits.
Response to Reviewer #2.5.1
We have added more information regarding the VAS assessment in the ‘Methods’ section under the ‘Outcomes’ section (Line 269-270) as follows:
“The planned primary outcome of the full RCT is the proportion of children with pain…. The secondary outcomes are…
For the VAS and AOM-SOS assessment, we used data from the symptom diary completed by the parents.”
Regarding the VAS score for assessing the correlation between ear pain and other symptoms with the change of static acoustic admittance (SAA) in tympanometry sub-study, we have clarified that we used VAS and AOM-SOS assessed by the parents in the symptom diary (Line 258-260).

Comment from Reviewer #2.5.2
Did you attempt to look at the reliability of these pain scales, for example, looking at overall variation, trends within children, differences between physicians?

Response to Reviewer #2.5.2
We relied on the literature reports on the reliability of VAS and AOM-SOS as pain scales and other symptoms relevant to AOM. However, in the Appendix 1 (Figure 1 Panel A and B), we have looked at the correlation between pain and other symptoms and tympanometry results that demonstrated a similar trend of the reduction of pain scales in both prednisolone and control groups at Day 3, 7, and 14.

Comment from Reviewer #2.5.3
Did you consider having 2 physicians assess the same child independently to compare responses?

Response to Reviewer #2.5.3
As this is a pragmatic study and we have provided training before the conduct of the study to all clinicians in terms of diagnosing AOM using an otoscope, we did not consider to formally have two physicians assessing the same child independently and compare the response. However, during the conduct of the pilot study, all children recruited from the primary care centres, were assessed by two physicians (the attending physician and the researcher/research assistant for reconfirmation purposes). We did not analyse this because we did not plan this process in the protocol.

Comment from Reviewer #2.5.4
Did you compare parent and doctor responses for the same child?

Response to Reviewer #2.5.4
We had not compared parent and doctor responses for the same child, however we have now done so, as suggested by the reviewer. If the editor wishes, we could add the following to the ‘Discussion’ section (Line 665 forwards) (see the plots in the word version):
“We compared VAS and AOM-SOS assessed by physicians and parents at Day 0 (VAS mean difference (MD) 3.95; AOM-SOS MD 0.38), Day 3 (VAS MD -0.92, AOM-SOS -0.13), and Day 7 (VAS MD 0.07; AOM-SOS MD -0.05) using Bland-Altman analysis and found good agreement between them, except for VAS assessment at the initial visit. At the baseline consultation,
physicians tended to rate pain intensity higher than the parents. They may have rated the worst pain for a child, based on the parent’s information.”

We have also provided the following information which supports the summary above.

**VAS – Day 0:**
Bland-Altman comparison of Vis0VAS and Diary0VAS
Limits of agreement (Reference Range for difference): -36.856 to 44.756
Mean difference: 3.950 (CI -1.321 to 9.221)
Range: 0.000 to 99.000
Pitman's Test of difference in variance: r = -0.145, n = 60, p = 0.268

**VAS – Day 3:**
Bland-Altman comparison of Vis1VAS and Diary3VAS
Limits of agreement (Reference Range for difference): -21.238 to 19.388
Mean difference: -0.925 (CI -3.549 to 1.699)
Range: 0.000 to 53.750
Pitman's Test of difference in variance: r = -0.083, n = 60, p = 0.529

**VAS – Day-7:**
Bland-Altman comparison of Vis2VAS and Diary7VAS
Limits of agreement (Reference Range for difference): -7.087 to 7.225
Mean difference: 0.069 (CI -0.872 to 1.010)
Range: 0.000 to 39.000
Pitman's Test of difference in variance: r = -0.141, n = 58, p = 0.291

**AOM-SOS – Day 0:**
Bland-Altman comparison of Vis0AOMSTot and Diary0AOMSTot
Limits of agreement (Reference Range for difference): -4.128 to 4.895
Mean difference: 0.383 (CI -0.199 to 0.966)
Range: 0.500 to 14.000
Pitman's Test of difference in variance: r = -0.217, n = 60, p = 0.096

**AOM-SOS – Day-3:**
Bland-Altman comparison of Vis1AOMSTot and Diary3AOMSTot
Limits of agreement (Reference Range for difference): -2.295 to 2.028
Mean difference: -0.133 (CI -0.413 to 0.146)
Range: 0.000 to 5.500
Pitman's Test of difference in variance: r = -0.088, n = 60, p = 0.503

**AOM-SOS – Day 7:**
Bland-Altman comparison of Vis2AOMSTot and Diary7AOMSTot
Limits of agreement (Reference Range for difference): -2.281 to 2.178
Mean difference: -0.052 (CI -0.345 to 0.241)
Range: 0.000 to 4.500
Pitman's Test of difference in variance: r = 0.033, n = 58, p = 0.807
Comment from Reviewer #2.6
You report that symptom diaries were only completed per protocol by 60% of parents. Have you explored the reason for this with parents and do you have ways to improve this for the main RCT or will you rely on interviews? I presume the interview data was collected retrospectively - when was this done and how reliable do you consider it?

Response to Reviewer #2.6
There were 25 parents who did not complete the symptom diary per protocol. We have added more information regarding this in the ‘Results’ section, under ‘The successful completion of the study procedures and outcome measures’ sub-section (Line 413-417):
“One hundred per cent of symptom diary data was completed for analysis…. We regularly checked the completion of the symptom diary of: Day 0 to 3 at the first follow-up visit (Day 3) and Day 4 to 7 at the second visit (Day 7), and after the diary collection at Day 14. We expected this strategy may reduce recall bias. We interviewed the parents directly during the consultation at the follow-up visits and at the follow-up by phone at Day 14.”
We have not formally explored the reason for the diary incompleteness. However, we noticed during the interview that parents rarely missed the completion of the diary but rather missed two to three items. Small fonts and narrow spacing were potential reasons for this. Therefore, we will improve the layout of the symptom diary in the main RCT to help the parents to read and complete the diary adequately. We added this in the ‘Discussion’ section (Line 594) as follows:
“To improve recruitment, future studies could: (1) recruit from more primary care centres; (2) provide incentives for participating healthcare personnel despite insufficient evidence of effects on recruitment rate [41]; and (3) simplify the study process (simplifying and improving the layout of CRFs and symptom diary and allocating research assistants to support study procedures including randomisation).”

Comment from Reviewer #2.7.1
You recognise the low recruitment rate. Do you plan any qualitative work to understand the issues and therefore address the problem before the RCT?

Response to Reviewer #2.7.1
It is very interesting to conduct formal qualitative work to identify and understand the recruitment issue before the conduct of the main RCT. However, we always recognise the recruitment will be more difficult in our setting. In addition to obstacles from the recruiting personnel (e.g. workload, time), the implementation of national coverage insurance in our healthcare system also contributed to a low recruitment rate in our pilot study. Therefore, we believe by allocating research assistants in every recruiting site and including more primary care centres will improve the recruitment rate in our main RCT.

Comment from Reviewer #2.7.2
Was there a difference in recruitment between primary and secondary health facility level?

Response to Reviewer #2.7.2
In the primary care, the proportion of children who were screened was 36 children: 23 of them (64%) were recruited in to the study. Whilst, in the secondary/tertiary care, the number of children who were screened was 125 children: 39 of them (31%) were recruited in to the study. These
findings supported our decision to include more primary care centres into our main RCT in order to improve our recruitment rate.