Reviewer's report

Title: A randomized controlled trial of hospital versus home based therapy with oral amoxicillin for severe pneumonia in children aged 3 - 59 months: The IndiaCLEN Severe Pneumonia Oral Therapy (ISPOT) Study

Version: 2
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Reviewer: Lilliam Ambroggio

Reviewer's report:

The authors present a compelling research study investigating treatment and costs effects of giving oral amoxicillin at home compared with starting treatment at the hospital for the first 48 hours. The randomized controlled trial was conducted among children 3-59 months who had chest indrawing pneumonia. The main findings included superiority of treatment at home and lower costs with at home care compared with treatment at the hospital.

The major concern is the framing of this study in light of the 2014 publication “Revised WHO classification and treatment of childhood pneumonia at health facilities—Evidence Summaries”. Recommendation 2 specifically states that it is safe to treat chest indrawing pneumonia at home with oral amoxicillin. Since this is the major conclusion from the manuscript submitted by Patel et al. it is unclear the significance this well conducted study has in regards to this body of literature.

Minor Concerns:

Abstract:
1. In the Methods section please change “multicentric” to multi-center as well as throughout the manuscript.
2. The abstract states that a random 20% of the sample was used for cost outcomes however in the text of the manuscript it is 17.2% of the sample. Please match the numbers.
3. The difference in treatment cost between the two groups was statistically significant therefore I would include either the p-value or the phrase in the results section.
4. Reframe the conclusion in light of the 2014 recommendations from the WHO.

Introduction:
The introduction needs to address the gap that home-based administration of amoxicillin with 48 hours is important in the outcome of children. Stating that the majority (69%) of children report receiving appropriate health care and that amoxicillin is effective does not set up the gap that this manuscript is being addressed by home health care compared with hospital care.

Methods:
5. Please specify who administered the oral amoxicillin at home. Was there a
home nurse or was this by the parent?

6. Under “Clinical Outcomes” please include in a supplemental appendix the standard operating procedures that were used to train the physicians in assessing clinical signs.

7. “left against medical advice, voluntary withdrawal of consent from the study or loss to follow up” should not be considered treatment failure as it is unclear whether these individuals would have failed treatment had they stayed in the study. These outcomes should be categorized under a different variable and analyzed separately. Also, what is the equivalent of LAMA in the home population?

8. Has the definition of clinical deterioration being used in previous studies? If so, please cite the study.

9. Please cite references regarding the methods used for micro-costing.

10. Under “Sample Size”, what power did the study have since the final enrollment had fewer than 617 patients per group as needed?

11. Under “economic analysis” it is unclear if cost was normally distributed or not, as t-test was used to compare mean cost and then later OLS is used with or without log transformation. Please specify which costs were normally distributed and which were not.

12. Under “economic analysis” the following statement “and tending (sic) towards significance if they had a two tailed p-value less than 0.1”. This is an incorrect interpretation of the p-value which is dependent on sample size. The authors state 90% power to detect a difference based on the sample size of the clinical trial therefore if no statistical difference was found that it is not statistically significant. There is no “trending” toward significance.

13. Please define “per protocol analysis” in the methods section.

Results:

14. It should be stated that the two intervention group were not statistically different in baseline characteristics, not just that they were similar.

15. What reasons if any were given for the LAMA or voluntary withdrawal from the study? Were the reasons different between the hospital group and home group?

16. Discussion of the boot strap estimates for the cost data should be in the methods section not in the results section.

Discussion:

17. This study was not designed to show effectiveness of amoxicillin as a treatment but rather the effectiveness of home vs. hospital treatment with amoxicillin. A sensitivity analysis should be done restricting the definition of treatment failure to everything BUT LAMA and voluntary withdrawal as that might have nothing to do with the treatment at all.

18. In the limitations section please specify how each of the limitations may have biased the results and in what direction the authors expect the results to shift.
Tables and Figures:
19. Might be worth discussing why some sites were less likely to have patients with treatment failure compared with others (Table 3).
20. Figure 2 should have a dashed line or a lighter line for one of the groups to easily distinguish the groups in the graph when printed in black and white.
21. Figure 3 might be better as a supplemental figure as the text in the manuscript may be sufficient.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.