Author’s response to reviews

Title: World Health Organization (WHO) antibiotic regimen against other regimens for the treatment of leprosy: A systematic review and meta-analysis

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Diana Machado

Editor
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Subject: Responses to the comments on the manuscript

"World Health Organization (WHO) antibiotic regimen against other regimens for the treatment of leprosy: A systematic review and meta-analysis”
Reference: Manuscript Number: INFD-D-19-01127
Dear Diana Machado

Thank you for your review of the manuscript "World Health Organization (WHO) antibiotic regimen against other regimens for the treatment of leprosy: A systematic review and meta-analysis"

The authors wish to express their gratitude to the editor and reviewers for their time invested in reading our manuscript. We are also thankful for their enriching comments which will result in a much improved manuscript.

Please find our point-by-point response to comments provided below. We had focussed in the major concerns and related commentaries from the reviewers. All changes have been included in the manuscript with track changes and we are submitting a version without track changes, as well.

We want to thank the editor and the reviewer and we are glad you found this manuscript overall interesting.

We look forward to hearing from you.

Sincerely,

German Malaga in behalf of the authors

POINT BY POINT ANSWER

Reviewer 1:

Nora Cardona-Castro, M.D., MSc., Ph.D. (Reviewer 1):

This is a meta-analysis about the efficacy of the World Health Organization (WHO) antibiotic regimen against other regimens for the treatment of leprosy.

The study has limitations for the low number of studies included (n=24), however, the reasons that the authors exposed are related to the lack of quality, confounders, data not available, not the inclusion of several variables important to define the outcome, etc.

This study calls for more research in leprosy and mentioned the importance of research to improve control of the disease.
1. There are several spelling mistakes along with the text. ie: Line 434, 421.
   Answer: Thank you for your comment. We asked to a native English speaker to review the article.

2. Leprosy in upper case in the middle of the text is not correct.
   Answer: We corrected the upper cases in the middle of the text

3. Table PB, line 45 is not well referenced.
   Answer: I was trying to find the observation that you point-out, but I could not find it. I reviewed again the table of PB to avoid mistakes.

4. Figures lack of resolution.
   Answer: Thank you for your suggestion. We worked to improve the quality of the figures.

5. Please explain at the end of supplementary material 2, the values of the Newcastle-Otawa scale.
   Answer: We added the values of the Newcastle-Ottawa scale in the Supplementary Material 2.

Reviewer 2:

Emmanuelle Cambau, MD, PhD (Reviewer 2)
The authors performed a systematic review and meta-analysis of all therapeutical regimens for leprosy including the standard multidrug therapy (MDT) recommended by WHO as a control. The methods were done according to standard rules and by authors with such expertise.
The choice of the studies published between 1982 and 2018 was justified by the WHO recommendations being published in 1982 but it could have been extended to papers previous 1982 since leprosy studies are scarce and the standard MDT relies on studies done before.
Among 135 papers, 24 studies were selected, mostly randomized controlled trials (RCT). The authors tried to present all the data from these studies. However, the disparity of the outcome criteria and the definitions used in these studies make it very difficult to follow. This is a great work but only few relevant conclusions are obtained from it.

The authors should rely and discuss their findings with regard to the recent systematic review done under the umbrella of a WHO guideline group following GRADE recommendations (WHO guidelines for the diagnosis, treatment and prevention, 2018, details of the literature review).
Answer: We add a paragraph discussing about the new guideline of WHO, and its statement about treatment “The same 3-drug regimen of rifampicin, dapsone and clofazimine may be used for all leprosy patients, with a duration of treatment of 6 months for PB leprosy and of 12 months for MB leprosy. (Strength: conditional, quality of evidence: low)” However, they mentioned that “evidence on the potential benefits and harms of a shorter (6-month) 3-drug regimen was limited and inconclusive, with a potential increase in the risk of relapse. Therefore, the GDG determined that there was not enough evidence of equivalent outcomes to support a recommendation to shorten the treatment duration for MB leprosy.”
Major comments:
1. There are many studies comparing the ROM regimen (rifampicin, ofloxacin and minocycline combination) to the standard MDT. The authors need to detail if the ROM combination is giving daily, monthly and how many doses in total. It is not clear in the table 1, e.g. for Kumar 2015 study, and lines 243-246.
   Answer: We appreciate your comment. We specified the doses of the different ROM regimen in table 1 and 2.

2. The definitions of relapse and treatment failure should be discussed and referenced:
   - what does mean "presence of the disease at the completion of the treatment". In leprosy, it is very often observed that the lesions did not disappear after 6 months or 1 year treatment but the lesions cannot progress.
   - what does mean "BI positivity during any time of the treatment". It is very often observed that the BI remains positive even several months after the end of sterilizing treatment.
   Answer: Thank you for your suggestion to clarify the definitions. The new definitions are: i. Relapse: We follow the criteria in the literature and that definition includes clinical or bacteriological or therapeutic criteria. ii. Treatment failure: We deleted the phrase “and positivity in the bacillary index for MB leprosy during any time of the treatment” according to your suggestion. Additionally, we checked that the articles included did not have this definition.

3. The type I and type II reactions cannot be presented as safety outcomes. They are occurring as a part of the disease and are specifically treated. They are not adverse effects of the treatment.
   Answer: Thank you for your comment. We changed the subtitle of safety outcomes by Immunological reactions. New paragraph is: “Regarding safety outcome, we evaluated severe side effects (defined as a side effect that forced the patient to stop the treatment), and mild to moderate side effects. Also, we evaluated immunological reactions: type I (reverse reaction), and type II (erythema nodosum leprosorum - ENL).”

4. In the figure 1, a number of articles were excluded because of unobtainable: How many articles were not available, and for which reasons?
   Answer: We did not find one article for full text: Gallo, M.E.N., Alvim, M.F.S., Nery, J.A.C., Albuquerque, E.C.A., Sarno, E.N. Two multidrug fixed-dosage treatment regimens with multibacillary leprosy patients(1996) Indian Journal of Leprosy, 68 (3), pp. 235-245. Even when we worked with a librarian from Mayo Clinic, we could not access to the article.

Minor comments:
5. All the figures are of poor quality, difficult to read.
   Answer: Thank you for your suggestion. We worked to improve the quality of the figures.

6. The tables are difficult to read and needed to be split at least for PB and MB.
   Answer: According to your suggestion, we separated the table in one table for PB and one table for MB.

7. Figure 3a could be deleted since the figure 3b is gathering the data of all studies with the endpoint at the follow up. In the text (lines 264-267, and 358-361) it is explained that at the completion time there is no difference but one study was added in the figure 3b and this is the
only one with a significant benefit and a very large number of patients included. This has to be explained in the text. The sentence line 268 is not justified.

Answer: We appreciated your comment. The new paragraph is “When the same comparison was evaluated at the end of the study period (Range 6-36 months) in 6 studies ROM showed a statistically significant benefit (RR 1.10, 95%CI 1.01-1.20, p=0.03). However, the study that was added is the only one with a significant benefit and a very large number of patients included.”

8. Since many studies on PB compared the standard MDT versus MDT+clofazimine, can the authors summarized the effects in a figure or a table.

Answer: Thank you for your comment. We found two studies that explore the comparison of MDT vs MDT + clofazamine. However, the outcomes of each study are very different, one of them measure a clinical score (Bathe, 1986), whereas the other measure active disease/ signs of activity, Mitsuda reaction and relapse (Katoch, 1999). This made very difficult to summarize the effect in a figure or table.

9. Table 2: many lines need to be revised: in Fajardo 2009, the study arm does not correspond to what written in table 1; what is the CDC treatment?; In Fajardo and Jadav, is the treatment different from the standard MDT;.

Answer: Thank you for your observation. We unify the name of the treatments in the tables. Fajardo et al had 4 different regimens i) MDT 2y, ii) MDT 1y, iii) 1 month of daily RFP + ofloxacin and MDT 1y + 1 month daily RFP/Ofloxacin. Jadav et al compared MDT 2y vs RFP daily for 9 months and then 1 month till the end of 2 years + dapsone + clofazimine daily. CDC treatment means clarithromycin+ dapsone+ clofazimine.

Reviewer 3:

Bernard Naafs, MD,PhD (Reviewer 3)

I like your paper, though it is very wordy, it is clear and to the point. Congratulations.

It is a clear report of what is already known. (read the discussions over the years on the Leprosy Mailing List). Indeed nearly all papers may have a bias and are analysed to present an opinion. To defend those studies, they are done in the field, often working with mostly dedicated often low educated individuals, where recorded data are not always reliable and many more sophisticated methods of follow-up are not possible, due to lack of money and interest of higher authorities. Thus do not judge to hard from behind a computer or desk in relatively comfortable situation. Though the critic on the weaknesses of the papers are right.

Answer: Thank you for your comment. We apologize, because our intention was not to criticize the authors or judge too hard the studies, and our interest has been to collect all available information to be grouped and serve for decision-making with greater reliability, but we cannot avoid to mention that unfortunately, for the reasons mentioned “working with often low educated individuals, where recorded data are not always reliable and many more sophisticated methods of follow-up are not possible, due to lack of money and interest of higher authorities” many of the included articles have biases that weaken their conclusions. We added this dimensioning to the discussion.
Some remarks:

Please explain that ROM is a one monthly treatment. And the strength of WHO-MDT is the daily dapsone and Clofazimine. You showed that Clofazimine protected against Type II reaction (ENL). It is worthwhile to look also for dapsone in the protection against Type I reaction (Not reverse but reversal reaction). I think with different arrangement it is visible. Only effective during treatment after RFT the protection disappears quickly for dapsone and more slowly for Clofazimine.

Answer: Thank you for your comment in our findings for type II we stated that “This outcome was evaluated in 9 studies (1 PB and 8 MB). We were not able to develop a meta-analysis. In patients with MB the combination of Dapsone, Rifampin and Clofazimine showed a statistically significant reduction in the development of type II reaction. On the other hand, the use of MDT regimen for 2 years increased the development of this outcome in the same population when compared to the use of MDT for 1 year. No other statistically significant differences were observed.”

I agree with the conclusion; No better treatment than WHO-MDT was found. (But the old recommendation for duration: 6-12 month for PB and 2 or longer years for MB were better.)
Answer: Thank you for your comment. As we found there is not evidence to reduce the time of the treatment.

107-108 this pathology? What pathology? The sentence is not needed it is opinion about what?
Answer: We referred to “leprosy”. Now, the paragraph is “On the other hand, research on leprosy is scarce, limiting the development of new strategies.”

117 213,899 is not an estimation. (Though it is most likely wrong)
Answer: We appreciated your suggestion. We included the word “reported” instead of “estimated”
A compliment on the methods.

191 define your "neuritis" . As such unclear as an outcome.
Answer: We include the following “Neuritis was considered if participants reported pain during the interview or when participants complains of pain in one or more peripheral nerve trunks of the limb(s) during the period of the treatment.”

195-196 Type I as well as Type II are immunological reactions.
Answer: We included the term “immunological reaction”, instead of “safety outcomes or adverse reactions”

199 What percentage of the authors responded?
Answer: We contacted two authors and they did not answer. We added a small paragraph “One study was not found for the full text revision and we contacted two authors. However, they did not answer »
244 here you can explain ROM.
Answer: Thank you for your comment. “The most common treatment was a single monthly dose of Rifampin, Ofloxacin and Minocycline (ROM) used in 8 studies (6 of PB and 2 of MB leprosy). »

269 Clofazimine addition to PB MDT not to MB MDT
Answer: Thank you for the comment. We corrected the mistake.

297 Interesting less relapsing in PB ROM. We were only able to study the histopathology in PB relapses in patients who relapsed after ROM treatment. We had no relapses in MDT patients.
Answer: Thank you for your comment. Our findings related to relapse are the following “This outcome was evaluated in 8 studies. Two studies used ROM as their comparison for patients with PB and one for MB. The pooled estimate of the studies in patients with PB showed no difference between both regimes (RR 1.62, 95%CI 0.98-2.67, p=0.06) but there seem to be a tendency to favour ROM (Figure 6). The big difference in follow up periods complicates the interpretation of this estimate (6 months vs. 8 years). Additionally, the study evaluating MB did not report any relapses. None of the regimes evaluated showed any benefit over MDT for patients with PB or MB »

322 Have a look: when you compare all patients who got dapsone with the treatment with the ones without dapsone concerning a type I there could be a difference. (Barnetson at al +/- 1976)
Answer: Thank you for your suggestion. We could not analyse the difference between patients that receive dapsone with those that did not receive dapsone.

329 I am glad you could show the beneficial effect of Clofazimine preventing ENL. Realize that reactions belong to the normal course in leprosy as a disease.
Answer: Thank you for your comment.

422 I think in Bauru Brazil a study of Bedaquiline in MB was started a year ago.
Answer: Thank you for the information. We included some lines about this trial in the paper. “Now, Bedaquiline is being tested in a Phase 2 trial (not started yet) for MB leprosy(29) in Brazil »

431 MDT for PB.
Answer: Thank you for your suggestion. We added PB MDT instead of MDT.