**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

**Authors:**

Maria Lazo-Porras (maria.lazo@upch.pe)  
Gabriela J. Prutsky (gapru24@gmail.com)  
Patricia Barrionuevo (patibarrionuevo@gmail.com)  
Jose C. Tapia-Tapia (josecarlostap@gmail.com)  
Cesar Ugarte-Gil (cesar.ugarte@upch.pe)  
Oscar Ponce (oscarp28@gmail.com)  
Ana Acuña-Villaorduña (ana.acuna.vi@gmail.com)  
Juan P. Domecq (jpdomecqg@gmail.com)  
Celso de la Cruz-Luque (cdlcruzI@hotmail.com)  
Larry J. Prokop (Prokop.Larry@mayo.edu)  
German Malaga (gmalaga01@gmail.com)

**Version:** 2  **Date:** 20 Oct 2019

**Author’s response to reviews:**

October 17th, 2019

Diana Machado  
Editor  
BMC Infectious Diseases

Subject: Reponses 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 for your enriching corrections and comments which will result in a much improved manuscript.

Also, we would like to add that the figure 3b and figure 4 were changed because a mistake in the total number of participants was noticed during the corrections. This does not change the message of the study, but it changes some estimations.

Please find our point-by-point response to comments provided below. 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 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

Editor:

Abstract
L70. WHO. Define here. See comment to L94-95
L80-81. Remove italic
L87-88. “Complete cure at 6 months of Multidrug Therapy (MDT) in comparison to Rifampin-Ofloxacin-Minocycline (ROM) found…” revise to “Complete cure at 6 months of multidrug therapy (MDT) in comparison to rifampin-ofloxacin-minocycline (ROM) found…”
L94-95. “World Health Organization”. Should be used in full in line 70 and abbreviated here.

Keywords
Revise to “World Health Organization”

Introduction
L116. Revise to “In 2014, the World Health Organization…”
L122. See comment above.
L123. Revise to “for paucibacillary (PB) leprosy”
L131. (8) - remove italic.
Methods
L162. Revise to “multidrug”
L182. Revise to “study”
L185-189. Remove italics.

Results
L234-235. Revise to “After initial screening, 135 studies were eligible to full text screening.”

Answer: Thank you for your corrections, we included all your revisions in the new version of the manuscript.

L237-238. Revise to “One study does not have the full text available. Two of the authors were contacted but we received no answer.” The two authors contacted were authors of the same study or different studies?

Answer: Two authors were contacted, one was contacted to have access to the full text and we did not get an answer and the other author was contacted to ask him/her to know if the study was a randomized controlled trial or not. The new paragraph reads like this “One study does not have the full text available. and we contacted the corresponding author without getting an answer. Also, another author was contacted to ask the author about the study design without a successful answer. No unpublished studies were identified.”

L242. Revise to “range”
L248. See comment above.
L270-271. Revise to “(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).

Answer: We much appreciated your comments. We corrected the mistakes.

L272-273. “…the study that was added is the only one with a significant benefit and a very large number of patients included. (Figures 3a and 3b).” The meaning of this sentence is not clear. Five studies had information at 6 months and 6 studies had data at the end of the treatment. Is this interpretation correct? Please revise the sentence for clarify. Remove dot after “included”.

Answer: Yes, five studies had information at 6 months and the metanalysis was not significant, and the same comparison was evaluated at the end of the study period (studies had between 6 and 36 months of follow up). We re-checked the analysis and we found that ROM was not better than MDT (RR 1.01, 95%CI 0.78-1.31, p=0.93). We add the following phrase: “A meta-analysis of 5 studies comparing MDT vs. ROM did not show statistically significant difference between them after 6 months of treatment (RR 1.06, 95%CI 0.88-1.27, p=0.56). When the same comparison was evaluated at the end of the study period (range 6-36 months) in 6 studies, ROM was not better than MDT (RR 1.01, 95%CI 0.78-1.31, p=0.93). The studies with more participants that were included in the analysis had significant and contrary results with RR of 1.14 (95%CI 1.02 – 1.27) by Babu et al, 1997 and 0.73 (95% CI 0.69 – 0.77) by Manickam et al, 2012 (Figures 3a and 3b).”
L274; L286, L453. Remove caps from clofazimine.
L274. Revise the sentence according to the comment proposed by Reviewer 3 - The addition of clofazimine to PB MDT did not show significant improvement.”
L289. Revise to “MB leprosy”
L295. Revise to “in PB leprosy”. Place dot at the end of the sentence.
L300. Revise “with PB leprosy and one for MB leprosy.”
L301, L304, L307, L331. See comment above.

Answer: We much appreciated your comments. We corrected the mistakes.

L329 (previous L322). Reviewer 3 – “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.” Any particular reason for not analyzing this data?

Answer: We could not analyse it because Dapsone was provided with different combinations (two provided with RFP + clofazimine and another provided with RFP + clofazimine + acedapsone), different time treatments (6 months and 2 years) and different follow-up periods (2 and 5 years).


Discussion
L357. Revise to “reactions for leprosy. One of”
L360-363. Revise to “follow up. If we add the poor methodological quality of the majority of studies found, this show us a situation that support the denomination and let us understand what leprosy is a neglected disease.”
L366. Delete “be”
L373-374. “other treatments schemes, since most of the magnitudes of these differences are small. However, these schemes had a great success rate after 1 or 2 years of follow-up.”
L377-380. “…others). Together with the lack of resistance pattern of relapse cases, this successful treatment scheme can be jeopardized by the increasing rate of relapse cases and the unknown effect of resistance epidemiology of M. leprae (8, 16, 17).” Remove italics from the citations.
L381-389. Remove italics. The sentences have speech marks.
L393. Revise to “of use”.

Answer: Thank you for your corrections, we included all of them in the manuscript.

L406-408. Revise sentence construction. It is difficult to understand.

Answer: The new phase is “Another limitation of primary studies was the heterogeneous report of treatment outcomes, so a proper comparison between treatments was very difficult, e.g almost
a third part of treatment outcome evaluation was with different clinical scores, which applied diverse items and can be affected by evaluator bias.”

L413. Revise to “of these studies reported antibiotic resistance patterns of M. leprae.”
L414. Revise to “there are reports on drug resistance in leprosy patients (19-23) which can be one”
L421. Revise to “that studies with people”
L430. Revise to “or tuberculosis”
L440. Revise to “treatment duration”
L441, L444. Remove caps from bedaquiline.
L442. Define or replace TB by tuberculosis.
L453. Previous L431 - Reviewer comment – “MDT for PB”. Author answer: Thank you for your suggestion. We added PB MDT instead of MDT.” The authors forgot to made the addition.

Conclusions
L456. Missing final dot
L454-456. Revise to “Further studies evaluating adherence to the treatment, potential development of drug resistance and short treatment regimens are needed to reach the goal of leprosy elimination.”

Answer: The conclusion reads like “None of the evaluated regimes showed any benefit over MDT for patients with PB or MB for relapses. The addition of clofazimine to PB MDT did not show significant improvement.
It is necessary to standardize criteria for diagnosis, cure, and follow-up in the search for more and better evidence to fill existing gaps in information that evaluates the new available antibiotics.
Further studies evaluating adherence to the treatment, potential development of drug resistance and short treatment regimens based on evidence are needed to reach the goal of leprosy elimination.”

Figure legends
Figure 1. Revise to “Flowchart of the study”

Answer: We much appreciated your comments. We added the changes and corrected the mistakes.

I suggest following the suggestion of Reviewer 2 regarding Figure 3a and 3b. Otherwise, they could be combined.

Answer: We decided to leave the figure 3a and 3b because figure 3a only shows studies with outcomes at 6 months, whereas figure 3b includes outcomes with diverse periods of follow-up (between 6 and 36 months). The number of events for the same studies differ from figure 3a to figure 3b in some cases.
Table titles
Revise the words in caps in the middle of table titles.
Table 1. Remove caps from “Paucibacillary Leprosy”. Included also the number of the study as it is in the reference list to enable the identification of the study by the readers. Revise the several words in caps in the middle of the sentences as referred above. RCT is missing from the legend. Table 2 to 4. See comments to table 1.

Answer: Thank you for your corrections, we included all of them in the manuscript.

Additionally, we made an exhaustive review of the article, corrected some typing errors and we have included Rao et al study (reference 43) in table 1. The study does not report the outcomes that we have included in the meta-analysis, but we included a comment in the discussion related to this study. Likewise, in order to increase the trustworthy of the article, we show all the evidence found.