Author’s response to reviews

Title: Analysis of severe adverse effects following community-based ivermectin treatment in the Democratic Republic of Congo

Authors:

Jean-Claude MAKENGA BOF (jcmakebof@yahoo.fr)
Daniel Muteba (danielmuteba2002@yahoo.fr)
Paul Mansiangi (pmansiangi@gmail.com)
Félicien Ilunga-Ilunga (feilunga@yahoo.fr)
Yves Coppieters (yves.coppieters@ulb.ac.be)

Version: 2 Date: 20 Mar 2019

Author’s response to reviews:

Technical Comments:

Editor Comments:

BMC Pharmacology and Toxicology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Comments: We thank BMC for this policy of open peer review.

Reviewer reports:

Mark Naunton (Reviewer 1): This is an interesting study and worthy of publication. I am unable to see any of the tables as they were not included in my files. The paper is well written.

Answer: The tables were sent in a separate file. Please find here attached again the tables for your appreciation.

My comments which I think the authors need to address are:
Background

1) line 78, sighted guide. -->>> what does this mean?

Answer: « sighted guides » was meant « a guide of a blind person ». So we replaced « sighted guides » by « blind guides ».

Results

1) Numbers are represented without much details if they are mean/median (without mean/median) and if an odds ratio is presented then the 95%CI is not presented. Perhaps these are in the tables which I cant see??

Answer: Please find details in different tables attached. Numbers are represented in: Mean (Me) ± Standard Deviation (SD) ; Number = N ; Interquartile Range = IQR ; Odds Ratio = OR; Confidence Interval = CI.

Discussion

1) My major criticism is the fact that some key things are not discussed e.g. why might there have been a peak in adverse effects in 2005-07?

Answer: As u recommended we discussed and added in our study the peak of SAE seen from 2006-2008 in the following way: « There was an interruption of the CDTI between 2004 and 2005 because of the occurrence of SAE in coendemic areas. Although a recovery of the CDTI after this interruption, a peak of SAE occurred in 2006, 2007 and 2008. The most important peak of SAE were observed in 2006 following the occurrence of many cases of death. Our observation is different from those of Kamgno et al. who argue that despite over 350 million people being safely treated with ivermectin in endemic or co-endemic areas, there have been rare cases of death post-CDTI; these cases are most often associated with high Loa loa microfilaremia ».

2) There is no real attempt (except line 273-4 page 10) to discuss any limitations to this study. e.g. alcohol intake, hemp use

Answer: We discussed the limitations of our study and we focused about alcohol and hemp’s (cannabis) influences in the following way: « Our study was retrospective and did not consider the effect of dose-response for the quantity of alcohol and/or hemp (cannabis) according to SAE occurred. Based on WHO’s publication on the settling of alcohol-related problems, it has been
pointed out that alcohol interacts with many drugs according to the quantity consumed. Therefore alcohol may change or alter the reaction of a drug.

On the other hand, our study is limited to demonstrate the association between hemp (cannabis) and SAE occurred. Our study did not consider as well the harmful effects of hemp (cannabis), which can also have an influence on the occurrence of the SAE. Indeed, Grotenhermen and Kirsten Müller showed that the most common cannabinoids side’s effects are tiredness, dizziness, psychological effects and a dry mouth, all of these side effects are similar to those that occurred after taking ivermectin; so they may skew determination of the SAE.

Our study focused only on the factors associated with NSAE. Indeed the occurrence of these effects reduced community adherence to treatment as demonstrated by Makenga et al. in their study related on untreated villages and factors associated with the absence of CDTI in DRC.

A prospective study should have highlight the relationship between the quantity of alcohol consumed and or hemp (cannabis) used with the occurrence of the SAE.

Rebecca Ellen Chandler (Reviewer 2): The authors report a study with the aim to determine the frequency of severe adverse events (SAE) after post-community directed treatment with ivermectin with a retrospective study design using SAE collection cards, over a time period from 2003 to 2017.

An important piece of information which is missing (but likely very hard to find) is the total number of persons which received ivermectin treatment during these programs in the stated time period.

Answer : The total average number of persons who received treatment with ivermectin during APOC’s activities concerning 22 CDTI projects in DR Congo is available in the National Program for Onchorcerciasis Control.

In this study with the aim to determine the frequency of severe adverse events (SAE) after post-community directed treatment with ivermectin, we consider the total average number specifically within 15 CDTI projects implemented in DR Congo which faced the occurrence of SAE after ivermectin treatment. These projects are located in Bas Congo, Beni Butembo, Equateur kiri, Ituri nord, Ituri Sud, Kasongo, Lubutu, Masisi Walikale, Mongala, Nord Ubangi, Sankuru, Sud Ubangi, Tshuapa, Tshopo and Uélés.

These informations has been added in the part of results of our study in the following way: « Between 2003 and 2017, the total average population at risk was estimated around 18,514,987 and
the total average population treated was around 15,552,588 among which 945 cases of SAE were registered in DR Congo, i.e. 6 cases of SAE for 100,000 persons treated.

This description and analysis of risk factors for SAE after ivermectin in Congo pairs nicely with the report published from Nzolo et al. "Central and Peripheral Nervous System Disorders Following Ivermectin Mass Administration: A Descriptive Study Based on the Democratic Republic of Congo Pharmacovigilance System."

The findings appear to be consistent with those which have been documented previously in Congo as well as other countries with similar community treatment programs.

More specific comments:

Background: Very informative, but it could be shortened. For example, from line 115-129, much of this information is repeated in the Results and Discussion sections.

Answer: Indeed, we removed lines 115 to 124 of the initial text because the same information are included in the results section. However, for a better understanding for the reader, we maintained the lines 215-229 those information will be addressed during the discussion.


Answer: We added in the discussion part, the potential of using the LoaScope as follows: « The potential of using the LoaScope-based test-and-not-treat strategy in DR Congo in areas where deaths have disturbed the CDTI is essential in order to be able to quickly identify persons at risk of SAE and to treat them effectively as well. In their study, Kamgno and al confirm that the LoaScope-based test-and-not-treat strategy enabled the reimplementation of community-wide ivermectin distribution in a heretofore "off limits" health district in Cameroon and is a potentially practical approach to larger-scale ivermectin treatment for lymphatic filariasis and onchocerciasis in areas where L. loa infection is endemic. ».