Author’s response to reviews

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

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ANSWERS TO REVIEWERS:

Abstract: The authors start the abstract with "The progress of mass, community-directed, treatment with ivermectin (CDTI)" they should state "The progress of mass, community-directed, treatment with ivermectin (CDTI) for onchocerciasis control' the international audience might not be aware why CDTI is used.

Answer: We’ve added the sentence at the beginning of the abstract as suggested: « The progress of mass, community-directed, treatment with ivermectin (CDTI) for onchocerciasis control ».

In the result section of the abstract it should start with the total study population size. '55 deaths related to post-CDTI SAE…..represents 5.8% of all notified cases' notified cases of what…

Answer: In the result section of the abstract, we also modified by starting with the average of the total population treated as follows: « Between the years 2003 and 2017, 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 per year ». 
The 55 deaths related to post CDTI represent 5.8% of all 945 SAE cases recorded in the DRC. We have modified this sentence as follows: « 55 deaths related to post-CDTI SAE were recorded, which represents 5.8% of all cases of SAE ».

'The study also highlighted .....awareness campaigns among the population' there is no mention of this in the method section

Answer: Awareness campaigns among the population were not mentioned in the method section. However, we have stated the weakness of the NOCP in terms of awareness campaigns among the population about ivermectin and its side effects.

We added the need of awareness campaigns among the population in the conclusion as a recommendation in view of our results.

Methods: Study setting: a map would be a nice visual representation of the study area rather than all the details. The authors can integrate this with Figure 1.

Answer: We think that the map as well as a short summary on the DRC are important to describe the study area. For that reason, we integrated "Cf. Figure 1" at the end of the paragraph.

Data collection: who collects the data for SAE and how is it collected, is it collected in the community or from hospital setting?

Answer: The data were collected by medical doctors from various hospitals in the DRC, who were previously trained for this purpose by the Ministry of Public Health. We have included this clarification in the data collection section.

"Adverse drug reaction (ADR) is defined as a noxious and unintended reaction which occurs after ivermectin intake" was there a duration of onset of these noxious phenomenon following intake of ivermectin to be considered as drug related? Same comment for MoSE and SAE.

Answer: Yes, side adverse effects (SAE) appears on average 24 hours after taking ivermectin. (Cf. Table 1) : "Onset of adverse effects (hours) 24 (8-96)"

Minor side effects (MiSE): They appear within the above-mentioned SAE time limit, disappear quickly and do not require treatment.
Moderate side effects (MoSE): They appear within the above-mentioned SAE time limit, do not disappear quickly and may need for care in an outpatient health center (does not require hospitalization for several days) but only observation.

Severe adverse effects (SAE): They appear within the above-mentioned SAE time limit and require hospitalization for several days and may lead to death.

The Medical doctor knows how to diagnose or determine whether an effect is minor, moderate or severe based on clinical examination.

Statistical analyses: What were the Neurological SAEs?

Answer: Neurological SAEs are listed in Table 2. This are Coma, Paralysis, Subconjunctival Palpebral Haemorrhage, Speech disabilities and Motor deficit.

Results: The first three lines of results section…how did the authors come to this conclusion, there was no mention of this in the method section?

Answer: Firstly in the methods section, we mentioned the aim of study was to determine the frequency of SAE post-ivermectin treatment in DRC, as well as factors associated with the occurrence of SAE.

Secondly, we precised as well this retrospective study relied on SAE collection cards, as archived by the Ministry of Health, and compiled for people who benefited from ivermectin treatment then further developed SAE. In such as a total of 945 patients, from 15 out of the 22 CDTI projects implemented in DRC, were included in the study over the 2003-2017 period. (Cf. data collection: The following information was collected: (5) patient’s condition at the last medical examination: hospitalization…

Finally, we analyzed all SAE collection cards which allow us to conclude that the management of CDTI by community distributors, as well as the delivery of Mectizan® according to the recommended dosage, were successful. The existence of an efficient community surveillance of SAE was also noticed through a quick reference of patients to health services (average of 1.5 days after onset of SAE).

What was the annual rate of SAE?

Answer: 6 cases of SAE for 100,000 persons treated per year.
In table 2 it would be more information to first present the profile of the population treated with ivermectin and then the ones who developed SAE in the next column for ease of comparing data.

Answer: Over a 15-year period (2003-2017), the average number of people who have been treated is 15,552,588. These treated people have developed minor, moderate and/or severe adverse effects (SAE). Other people, on the other hand, have not developed any of these adverse effects.

Neither data from people who did not develop adverse effects after taking ivermectin, nor data from people who developed minor and/or moderate adverse effects were collected by the Ministry of Health in DR Congo. In other words, the profile of all the people mentioned above and their characteristics are not known up to now, except for the profile of people who have developed severe adverse effects (SAE). Only a better count was carried out.

Indeed, the Ministry of Health had focused only on collecting data on severe adverse effects (SAE) because their handling is complex and sometimes leads to death if it is not adequate.

The profile of the persons treated is based in particular on the following criteria: any person living in an area considered endemic and over the age of 5 years. Pregnant women and any child under 5 years of age are excluded.

Thus, Table 1 presents the profile of all these people treated with ivermectin and who have developed severe adverse effects (SAE).

Table 2 distinguishes between severe adverse effects (SAE): non-neurological and neurological SAE.

This is the reason that our study aimed to determine the frequency of SAE post-ivermectin treatment in DRC, as well as factors associated with the occurrence of SAE.

Table 3: I think the correct word is Crude OR and not Raw OR.

Answer: We have corrected the table as follows: We deleted "Raw OR" and putted "Crude OR".