Author's response to reviews

Title: monitoring the efficacy and safety of three artemisinin combinations therapies (ACT) in Senegal: results from two years surveillance

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Author's response to reviews: see over
Dear Editor,

On behalf on co-authors, i would like to submit to your attention a revised version of the manuscript entitled: “monitoring the efficacy and safety of three artemisinin combinations therapies (ACT) in Senegal: results from two years surveillance” as well as a point by point responses to the concerns raised by reviewers.

Yours sincerely,

On Behalf of Co-authors:

Dr Khadime SYLLA
1. Throughout the results section:
   a. Proportions require numerator and denominator that defines the proportion. Comments saying there is a difference needs to be supported by p-values.
   b. When comparing the 3 groups the reader needs to see the difference (with respective P-value) between ASAQ; AL and DHAPQ each time the mean or proportions are presented. It means repeating analysis such as ASAQ vs AL, ASAQ vs DHAPQ and AL vs DHAPQ. For an example of comparing 3 drugs in one manuscript look to one of the manuscripts referenced eg ref 22 Ashley EA, et al., JID 2004:190

   \textit{We agree, correction was done}

2. A paired analysis of the mean increase or decrease in HB, Creat and LFT would be more powerful than the way the data is currently presented.

   \textit{We agree, a paired was done (table 5) and results (Safety profil)}

3. The introduction explains that Senegal has commenced a pharmacovigilance system…how does this manuscript relate to this. Does the data get incorporated into the system? Add a short explanation of this to the discussion.

   \textit{We agree, a short explanation was added to the discussion}

4. Incorrect dosage of drugs:
   Please amend: 120mg of Lumefantrine and 20mg of artemether as current sentence is wrong the tablet contains 120 mg of Artemether plus 20 mg of Lumefantrine.
   DHA-PPQ tablet also wrong: One tablet contains 40 mg of dihydroartemisinin and 320 mg of piperaquine. Current sentence is: the tablet contains 320 mg of DHA plus 40 mg of PQ.

   \textit{We agree, all corrections are done}

5. In the methods section for artemether-lumefantrine state that no additional fat was given with each dose.

   \textit{We agree, correction was done}
6. In the discussion it would be more helpful to the reader to say which study the country was done in than who the first author was. If referencing other authors in the discussion replace the ‘and al’ section Makanga and al, with et al. 

We agree, correction was done

7. The following sentence needs amending: A sub-sample of study participants was randomly followed up to day 35 and day 42 to assess the long term protective effect of each drug after curative doses. Is it meant to be a “random” sub-sample of study patients? Randomly followed up to day 35 doesn’t make sense.

We agree, correction was done

8. In biological assessment paragraph 
The addition of ‘the’ incorrect…A blood sample was collected for thick and thin smears for all study patients. Both tests were used to determine the parasite density and the plasmodium species at the day 0, 1, 2, 3, 7, 14, 21, and 28. Both tests were repeated at the day 35, 42 and other days of follow up to evaluate parasite clearance times.

We agree, correction was done

9. Check carefully and replace all occurrences spelling of:
   i.Remove ‘e’ from artemisinin …not artemisinine (including dihydroartemisinine) 
   ii.Check xc in Duocotexcin ….not Duocotexcin 
   iii.Replace ence with ance in Pharmacovigilance …..not pharmacovigilence 
   iv.Check throughout for infection…not infestation 
   v.Spell check has made from into form in multiple places e.g. To distinguish recrudescence form new infection, blood 
   vi.Ae not ea….Haematological not Heamatological also in heamoglobin (should be haemoglobin) 
   vii.Sometimes haemoglobin is spelt hemoglobin. Please be consistent. 
   viii. the words with ï need i.

We agree, all correction are done
10. In the following paragraph *Thick and thin smear*
1st sentence: Finger prick blood was used to collect blood samples (add s to samples).
Last sentence: Thick and thin smears were negative after reading 100 fields microscopics (in this sentence change the ending to “after reading 100 microscopic fields”).

*We agree, correction was done*

11. There is a word missing at ?? Again very ?? cure rates were observed with no significant difference detected between the groups (Table 3).

*We agree, correction was done: a word good was added*

12. Grammar problems
Introduction
3 amendments to the following sentence: ACT can reduce the morbidity and mortality associated with malaria, the transmission of *Plasmodium falciparum* by acting on gametocytes and reducing the chances of development of drug resistance (3, 4, 5).
In Senegal, the National Malaria Control Program (NMCP) has initiated since 2006 a nationwide scaling up of ACT in 2006 (6).
It has thus become relevant to monitor ACT efficacy in Senegal following a nationwide scaling up campaign. Repeat of what already said early in the introduction.

*We agree, all grammar problems in the introduction are revised*

13. Methods, Study period and area
The study was carried out during two malaria transmission seasons (2011 and 2012) in two health centers: (i) Deggo which is located at 20 km (add direction here) from form Dakar, the capital city and (ii) Keur Soce located at 200 km of South from Dakar.
In the same paragraph it states the same thing twice. We only need it once…could delete it from the above sentence or delete the last sentence of the paragraph.

*We agree, correction was done*
14. Methods, Study design

The English in the following sentence needs repairing: Randomization was done by permuted in blocks of 10. There is a problem with the blocks of 10 because there are 3 drugs. In one block of 10 there will be 3 of each drug and then one other drug which may not result in equal sample size. So one would normally randomize in blocks of 9 or 18?

Amend: The study was conducted as part of a national surveillance program aiming at monitoring ACTs efficacy under routine conditions.

*We agree, correction was done*

15. Study population

Subjects were enrolled if their age was above 6 months and they presented with uncomplicated *Plasmodium falciparum* malaria with a parasite density ranged from 1,000 to 100,000 trophozoites/µl

We only do pregnancy tests in women so can delete…...a women with positive pregnancy test

Antimalarial treatment: Participants who vomited a second time were excluded to from the study In the following sentence is 25mg/kg/day correct? Is quinine given 3 times daily. Please add BID or TID?

Participants who vomited a second time were excluded from to the study and received intravenous quinine treatment in accordance with the national malaria control program guidelines (25 mg/kg/day for seven days).

*We agree, all corrections are done*

16. Which method exactly for the nested PCR methodology, needs supporting reference?

Nested PCR was conducted to compare the genetic polymorphism of *P falciparum* genes (Merozoïte Surface Protein): *MSP1* and *MSP2*.

17. Statistical methods
In this sentence include needs a d i.e. included: The intention to treat include all randomized subjects who took at least one full dose and had one post-baseline efficacy without major protocol deviation.
In the above sentence what is the meaning of “One post-baseline efficacy”?
In this sentence include needs a d i.e. included: The per protocol analysis include all subjects who received the three dose and had no major protocol deviation.
The sample size calculation does not appear to be correct (See addition at the end from statistician review).

We agree, all corrections are done

18. Results
Add of after withdrawal i.e. Withdrawal of consent was noted in 2 patients in the ASAQ arm, 1 patient in the AL arm and 3 patients in the DHAPQ arm.
Add s to violation: Protocol violations were observed in 2 subjects in ASAQ group, 4 patients in AL group and 3 subjects in DHAPQ group
Add s to term: At inclusion, the three groups were comparable in term of mean age..etc
In the following sentence it is a proportion and should say, ...“The proportion of patients with fever at inclusion was…” not “At inclusion, the number of with fever was 75%, 75.8% and 76.14% respectively in ASAQ, AL and DHAPQ group”.
Is the proportion of fever in the AL group higher than the other groups – needs a P-value in the following sentence: “After first dose administration, 3.8% patients in ASAQ group and 3.4% patients in DHAPQ group were found with fever. The proportion of patients with fever was more important in the AL group (8.4%).”
This sentence is missing a word see ??: Again very ?? cure rates were observed with no significant difference detected between the groups (Table 3).

This sentence (and others) need the numbers (numerator and denominator) that represents the proportions and P-values: Abdominal pains were more frequent in ASAQ group 16.66% versus 10.79% in DHAPQ group and 7.86% in AL group. Vomiting were more frequent in DHAPQ group (5.68%) compared to AL group (2.45%) and ASAQ group (1.66%). Labial herpes was more frequent in AL group (3.37%).
The herpes is most likely to be unrelated to study drug that is why the number of cases is important not just the proportion. Was this more than one case in one family? Was this from the drinking cup used to administer the drug?

*We agree, all corrections are done*

19. Discussion
All cure rates are over the WHO recommended 95% cure rate (see the 2010 treatment guidelines). With such high cure rates the 2nd sentence where is says “still effective” could be amended to “remain highly effective”.

*We agree, the sentence still amended is substituted by remain highly effective*

20. Tables
Table 1:
This is a proportion: Patients with normal level of bilirubin (0.23 -1 mg/dl)

*yes it is a proportion of subjects with normal level*

Table 2 and Table 3: the upper limit of the reported 95%CI cannot be higher than 100%

*We agree, the upper limit of confidence interval is 100*

Table 4: Need to report the units for ALAT and ASAT.
Patients with ALAT < 40 (%)  
Patients with ASAT < 40 (%)  

*We agree, a normal value was added*

20. Statistician review

*We agree, some comments were taken into account*