Author's response to reviews

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

Authors:

khadime SYLLA (khadimesylla@yahoo.fr)
Annie Abiola (annie_abiola@yahoo.fr)
Roger Clement Kouly Tine (rogertine@hotmail.com)
Babacar Faye (bfaye67@yahoo.fr)
Doudou Sow (doudsow@yahoo.fr)
Jean Louis Ndiaye (jlndiaye@yahoo.com)
Magatte Ndiaye (magou22000@yahoo.fr)
Amy Cole Lo (amlosn@yahoo.fr)
Kuaku Folly (jkfofo@yahoo.fr)
Oumar Gaye (ogaye@refer.sn)

Version: 5 Date: 13 September 2013

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

On behalf of 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
Reviewer's report

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

Version: 4 Date: 22 June 2013

Reviewer: Rose McGready

Reviewer's report:

This is a timely manuscript. There are a few concerns that need to be addressed….

1. Is the question posed by the authors well defined? yes
2. Are the methods appropriate and well described? Yes
3. Are the data sound? Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? No – needs improvement.
6. Are limitations of the work clearly stated? No
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? No

Major compulsory revisions

1. Please comment on why AL was not given with fat when there are published papers clearly showing the benefit of this: How much fat is necessary to optimize lumefantrine oral bioavailability? Ashley EA et al Trop Med Int Health. 2007 Feb;12(2):195-200.
   Please comment on the cure rate in the discussion especially since fat was not used (in methods it does not say it was used).

   We agree I have added comments on the study limitation

2. How was haemoglobin determined?

   The haemoglobin level was determined using Sysmex XS 1000i automate
3. The sample size calculation needs clarifying. It currently states: “With 150 patients sampled in each arm, the study was powered at 90% to detect a 10% difference between treatment groups, taking into account an expected failure rate at 5% etc.” If the failure rate of 5% is expected and the study is powered to detect a 10% difference it is underpowered from the start. Re-examine the sample size for an open label, randomised, non-inferiority efficacy trial.

*We agree, the sample size was estimated for an open label randomized, non-inferiority efficacy trial. Correction done*

4. Is the age of inclusion into the study similar to previous Senegal studies – nearly young adult age? Has the age of inclusion risen compared to other studies? Would that explain the excellent cure rates? Table 1 could include a breakdown of age groups to make this more clear – how many were < 5 years old?

*Each study had a specific protocol. Subjects were included taking into account the objectives of the study. We haven’t stratified by age*

5. It would be really helpful if the presentation of groups is systematic: use the same order each time in the results (when presenting 3). It gets very hard to read when it keeps changing.

*We agree, correction was done*

6. Figure 2 – change the range on the y axis e.g instead of starting at cumulative failure rate of ‘0%’ start at 90%.

*We agree the curve was done tacking into account the comments*

7. What proportion of patients had fever at enrolment: add this to table 1.

*Correction was done. The proportion of subjects with was added on table 1*
8. For table 4 it would be good to compare the mean/median increase or decrease between groups e.g. is the proportion or values at day 7 different between groups...not just comparing day 0 and day 7. Please check the mean drop in Hb from day 0 to day 7 in each group (control for parasitaemia and age). Likewise for the other haematological and biochemical parameters....

We agree with reviewer, the proportion or values at day 7 were compared between the three treatment groups (Table 4).

9. Why were there late failures with ASAQ and AL but no DHAPQ? Please add this to the discussion.

Some references were added to discuss the high cure rate of DHAPQ.


Minor essential revisions

1. Abstract: 2nd sentence Add the word ‘an’ before essential. Prompt access to effective antimalarial treatment such as Artemisinin based-Combination Therapies (ACT) is an essential tool for malaria control.

Correction done

2. Abstract, Methods. No ‘e’ in artemisinin e.g. dihydro-artemisinine-piperaquine

Correction done
3. Introduction
Last paragraph replace ‘since’ with ‘for’ in the following sentence ‘…established
since several years’.

Correction done

4. Methods
First sentence needs some rewording as shown below
Delete ‘in’; Delete double use of health post; Witch can be deleted; Which direction is
Keur Soce from Dakar? The study was carried out in during two malaria transmission
seasons (2011 and 2012) in two Health posts: (i) Deggo, health post witch is located at 20
km from form Dakar, the capital city and (ii) Keur Soce health post located at 200 km
north/south/east/west? from Dakar.

Correction done

5. Next sentence – please clarify
Not sure what is intended by the following sentence: In theses health posts, malaria is
highly seasonal during the rainy season (July to October) with a peak of transmission
from September to December. Is this what is intended?: In the areas around the health
posts malaria is highly seasonal… Then the months are confusing rainy season is July to
October and the peak is after the rains peaking from September to December?

Correction done

6. Study design: Randomization was done by permuted block of 10. Can change
to: Randomization was done by permuted in blocks of 10.

Correction done

7. Study population: 1st sentence: Add with …..and they presented with uncomplicated
Plasmodium etc
2nd sentence: Change inform to informed i.e. written informed consent
Add ‘the’ after ‘of’ i.e. as part of the inclusion criteria.
3rd sentence: Add with before mono-infection
Replace infestation with infection
Add ‘a’ for:….women with a positive pregnancy test…
And the last part of the sentence should say …”or did not give informed consent were excluded from the study.”

Correction done

8. Antimalarial treatment
Top of page 5 “received quinine”; does this mean intravenous quinine?

We agree, quinine was given by intravenous

9. When explaining each of the three dosing regimens add the word ‘to’ after according: i.e
adjusted according to the weight: or according to the age

Correction done

10. Biological assessment
Add ‘A’ at the beginning of the first sentence e.g. A blood sample was collected for…
Add ‘the’ before day and change parasitaemia to parasite in the following sentence: … at the day of parasite reappearance.

Correction done

11. Thick and thin smears
Explain how many fields were read before a slide was declared negative.

Thick and thin smears were negative after reading 100 fields microscopics.
12. Check spelling of ‘haem’ throughout the manuscript e.g. Haematological and biochemical assessment should be Haematological etc. Sometimes spelt hemoglobin.

Correction done

13. Replace ‘Merozoït’ with ‘Merozoite’
Correction done

14. Statistical analysis
The word ‘tree’ should be ‘three’
Correction done

15. Results
Trial profile
Withdrawal should be withdrawal of consent
Correction done

16. Baseline characteristics of subjects at inclusion in the three treatment groups
First sentence should say ‘At inclusion…’ not ‘At the inclusion…’
Correction done

17. For example this sentence can be written to be consistent with the rest of the paragraph:
The mean weight in each group was 43.6±18 kg, 42.3±20 kg and 46.7±19 kg for ASAQ, AL and DHAPQ, significantly higher in the later group.
Correction done

18. Spelling of creatinin is with an ‘e’ i.e creatinine.
Correction done

19. In the section on Baseline characteristics of subjects at inclusion in the three treatment groups the paragraph could be considerably shortened by including table 1 rather than having it as supplementary e.g.
At the inclusion, the three groups were comparable in term of age, weight, sex
ratio, temperature and parasitemia (Table 1). Note the higher weight in the DHAPQ group (Table 1).

Remarks are taken into account

20. Table 4 seems to come before table 2 in the text.
Correction done

21. Please take another look at table 2 the formatting shifts NA onto the next row and it not clear what the row starting with NA refers to?
Remarks are taken into account

22. In the section on “Therapeutic efficacy” the text can be shortened and table 2 is very informative, better in the main manuscript than as a supplementary file. It could be reworded as follows:
There were no early treatment failures and cure rates, both PCR uncorrected and corrected, for all three treatment groups were higher than 95% by ITT and PP analysis, with no significant differences observed between the groups (Table 2). The Kaplan Meier survival analysis resulted in a very similar cumulative incidence failure rate at day 28 in all three groups (log rank test, p=0.83) (Figure 2). A very low rate of late parasitological failures were detected (Table 2). There were 88% (n=470) and 77% (n=411) of all patients seen at day 35 and day 42 respectively. Again very cure rates were observed with no significant difference detected between the groups (Table 3).

We agree with the reviewer,

23. Fever and parasite clearance
This paragraph could also be improved. Firstly we do not know what proportion of patients had fever on admission. Please present the median days [range] to fever and parasite clearance in each group.
The proportion with fever on each day would also be easy to present e.g.
ASAQ DHAPQ Al
Day 0
We agree, the proportion of subject with fever was given at day 0, 1 and 2 in the three treatment arms.

24. Discussion – when comparing to other studies the year of the study would be helpful to add.

We agree, the year of the study was added.

25. When referring to DHAPQ in Thailand it is important to note how old the study is. The DHAPPQ study was done prior to the downturn in resistance observed on the Thai-Burmese border.

The year of the study was added

26. Add limitations to the discussion. E.g no fat with AL

Study limitation was added in the discussion

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.
Reviewer's report

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

Version: 4 Date: 24 June 2013

Reviewer: Verena I. Carrara

Reviewer's report:

1. Is the question posed by the authors well defined? yes
2. Are the methods appropriate and well described? yes
3. Are the data sound? yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? yes
6. Are limitations of the work clearly stated? no
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? no

This is an important paper in the context of emergence of artemisinin-resistance. Although primary endpoint was D28 PCR-adjusted parasitological response, patients were followed up to D42, a very important endpoint for one using such drug-combinations. The manuscript however needs some revisions.

Major compulsory revisions

Sample size: none of the drug combinations used was expected to be inferior to another (all contained an artemisinin-based derivative and the authors state that the failure rate is expected to be 5%); could the authors justify their sample size with more clarity? Have they accounted for some lost to follow-up? How do they explain the differences in number of patients enrolled in each group? Why did they choose a block of 10 in their randomization?

We agree, the sample size was re-estimated tacking into account the remarks of the reviewer. We choose a block of 10 because we wanted to keep the comparability of the three groups.

Antimalarial treatment: the authors state that ASAQ and DHAPQ treatments were given once a day, but for how many days? Were all the doses supervised or only the first one? AL treatment was provided twice a day: were the tablets given with fat to increase absorption? Was the treatment totally supervised, and for how many days? Quinine was given if vomiting: oral treatment or iv treatment?

All drugs were given for three days; all doses were given under direct supervision of medical staff. AL was given twice a day and quinine was given by iv treatment

Presentation of the drug groups throughout the paper: it would be easier for the reader if the description of each drug group would always be in the same order (ie Fig 1 order is ASAQ, AL, DHAPQ, drug group order in all the tables is DHAPQ, AL, ASAQ, order in the abstract and the text if shifting)
Figure 1 / trial profile: It is not quite clear what happened to some of the patients between enrolment and D28 follow-up; for the ASAQ group, there is no mention of Lost to follow-up, however there are 7 patients “absent” at D28; 4 are “missing” at D28 in the AL group and 8 in the DHAPQ group. Could the authors explain what happened to those patients if they were not lost?

We agree with the reviewer; data was completed (Figure 1)

Baseline characteristics: the authors state that the patients in the 3 groups are similar in all general characteristics; however there is a difference in sex ratio, mean weight, and mean parasitaemia (was it the geometric mean?); were those differences significant? What was the proportion of patients afebrile on admission? The mean age is quite high; what was the proportion of children in each group?

The difference between the three groups was not significative. The proportion of subjects with fever was represented on table 1. The mean age was quite high because the study population was essentially represented by subject age more than 10 years.

Figure 2: the scale of the figure should be improved so the reader can see the 3 survival curves a bit better (i.e. by reducing the y-axis scale and starting it at 0.5 or 0.75). The y-axis has no description and the days in the x-axis could end at D28 rather than D30.

We agree with the reviewer, correction was done (Figure 2)

Minor essential revisions

Thick and thin smear: the authors describe only the calculation of the parasite density using the thick smear; do we have to assume that none of the patients had a parasite count that was calculated using the thin smear?

All parasite density was calculated using the thick smear.

Statistical methods: “qualitative outcomes” and “quantitative outcomes” might be changed for categorical and continuous variables

Correction done

Therapeutic efficacy: the definition of early and late parasitological failure should be mentioned somewhere in the text. From the tables 2 and 3 data, it seems that all PCR-confirmed failures were prior to Day28. Is this correct? It would be maybe easier for the reader if there was a sentence summarizing the failures (ie. xx failures occurred, xx prior to Day28, xx between D28 and D35 etc)
Definition of early and late parasitological failure was mentioned. The therapeutic efficacy results were summarized.

Fever and parasite clearance time: the paragraph as it is is rather unfriendly to read; it would be clearer if there was a sentence mentioning the number of patients with fever on admission and of those, the median time to clear the fever in each group.

The number of patients with fever on admission was represented on table 1

The parasite clearance time should also be as the proportion of patients remaining parasitaemic at D1, D2 etc in each group.

We agree with the reviewer; Correction done

Table 4: its order in the text comes prior to table 2. Bilirubin needs a measurement value; what is “normality” for bilirubin level and creatinin level? The table could be probably dropped and summarized in the text as the only major negative issue is the drop in haemoglobin between D0 and D7 (was there a difference in the fraction of haemoglobin change per patient in each group?).

The normal value of bilirubin and creatinine was added on table 1 and 4

Discussion: add to the discussion the limitations of your study, discuss about the use of AL (as twice a day, with fat); the dates of the different trials described in the discussion should be added as some were conducted prior to the time of emergence of artemisinin-resistance. Discuss also on the level of immunity of the population and its potential effect on drug-efficacy.

The use of AL twice a day with was discussed on the study limitation.

We agree with the reviewed the level of immunity must be discuss

General: please review the grammar throughout the text.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests
Reviewer's report

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

Version: 4 Date: 8 July 2013

Reviewer: Issaka Sagara

Reviewer's report:

Minor Essential Revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests

This is a relevant paper a clearly written paper. Whoever the authors needs to address the below queries

1. Under Method section, Study period and area subsection:
   a. at the second line, “Center” needs to be added after “health” word.
   b. at the fith line Plasmodium Falciparum needs to be replaced by *Plasmodium falciparum*

*Correction done*
2. Under Method section, subsection Data collection at the first line: the author needs to provide the reason why? And the number only the sub-sample of study participants was followed up to day 35 and day 42.

This should be specify in the abstract section as well in case if only the sub-sample of study participants was followed up to day 35 and day 42.

Correction done

3. Under Statistical methods, at the fifth line, should be “Data collected were entered into Excel…” instead of “Data collected were computed into Excel software…”

Correction done

4. Under the Acknowledgment section, the author needs to specify the financial support of the study

We agree with the reviewer, the financial support of the was specified

5. Under Result section, Fever and parasite clearance subsection:

a) at the fifth line, “The” should be added before “Three treatments showed…”

b) at the seventh line, The author should specify the specific day of parasite decrease when saying that: “It decreased to 1936 trophozoites/µl in ASAQ group, 2164 trophozoites/µl in AL group and 882 trophozoites/µl in DHAPQ group”

We agree, all correction were done

6. Under Result section, Clinical and biological tolerance subsection: the author needs to provide the frequency of vomiting in each treatment group as this is an important sign for drug tolerability and also it was cited by the author.

We agree, the frequency of vomiting was given in each group
7. Figure 1 is showing a randomization profile of 1:1:1. However, the author said in the Study Design section that “Randomization was done by permuted block of 10” which is unlike to be with 3 arms study with equal sample size in each arm. Could the author can check that or explain?

*We choose a block of 10 because we wanted to keep the comparability of the three groups.*