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 Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?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).

2. How was haemoglobin determined?

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.
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 break down of age groups to make this more clear – how many were <5 years old?

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.

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

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

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

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.

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

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

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.

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?

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

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."

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

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

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

12. Check spelling of ‘haem’ throughout the manuscript e.g. Haematological and biochemical assessment should be Haematological etc. Sometimes spelt hemoglobin.

13. Replace ‘Merozoït’ with ‘Merozoite’

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

15. Results
Trial profile
Withdraw should be withdrawal of consent

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

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.

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

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).

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

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?

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).

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
Day 1
Day 2

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

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.

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

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.