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:**

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 Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?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

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?

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?

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?

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.

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?
Statistical methods: “qualitative outcomes” and “quantitative outcomes” might be changed for categorical and continuous variables
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)
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 parasite clearance time should also be as the proportion of patients remaining parasitaemic at D1, D2 etc in each group.
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?).
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.
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