Reviewer's report

Title: Possible increased malaria transmission and susceptibility to clinical malaria episodes following treatment of Plasmodium falciparum asymptomatic carriers: Results of a cluster-randomized study of community-wide screening and treatment

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Reviewer: Lucy Okell

Reviewer's report:

This paper describes detailed malaria indicators from a cluster-randomized trial testing the impact of mass screening & treatment (MSAT) of asymptomatic carriers during the dry season on incidence of disease during the rainy season. This article is a follow up to the earlier publication of the primary outcome of the trial. The authors are to be congratulated for an extremely well-designed trial on an important question – MSAT is increasingly being considered as a control intervention and there are very few previous cluster-randomized trials.

The results of the trial are extremely puzzling in that MSAT appeared not only to have no impact but to actually have a negative impact. As far as I'm aware no previous study of mass treatment has shown this, although lack of impact has certainly been seen before. The authors’ main explanation for this is the ‘rebound effect’ i.e. a decrease in immunity after treating existing infections. I agree this was a possible contributor to what happened. However I don’t think the authors' have given nearly enough discussion to another explanation, which was that for an unknown reason (and despite randomization) the mosquito biting rate and rate of infectious bites (EIR) were ~1.5-2 fold higher in the intervention arm. It’s very fortunate the authors collected these data so thoroughly and to me they could well be the most important factor explaining the results. I would recommend adding a lot more discussion of this.

Otherwise my main suggestion is that the authors add a few more details on their results – suggestions given below.

Major revisions

1. Discussion p14 & Table 1. The average EIR is exactly 2-fold higher in the intervention arms at 7.8 versus 3.9. I understand that there was not a significant difference in any one month until October. However, as you say, the difference is consistent over time and I would guess that the annual average (or total) figures are significantly different, so I don’t think this can be dismissed as an explanation for the apparently negative effect of the intervention. The mosquito biting rate is also approx 1.6 times higher in the intervention arm. I would guess that if you tested the difference in the mosquito biting rate, it would be significantly higher over much of the year, because if say 5% of mosquitoes were sporozoite-positive, the mosquito biting rate gives you 20-fold higher power to detect a significant difference compared with the EIR (although the
fold-difference is smaller).

I would suggest adding the following:

a) Statistical tests for differences in the annual average (or total EIR), and both the monthly and annual average mosquito biting rates between control and intervention arms.

b) If there is space, a table with monthly entomological data which shows numbers of mosquitoes collected, proportion fed on humans and proportion sporozoite-positive. I think knowing the sample size in different months is key to understanding the results.

c) Please can the authors double check the monthly EIR is not significantly different until October. In particular the measure at the end of July, since the difference is quite big and the number of mosquitoes collected at this time is larger than October.

I would then suggest rephrasing the discussion along the lines of there being a number of possible explanations for the unexpected results of the trial, one of which is a chance difference in mosquito biting rates and EIR in the intervention arm, and another of which is a rebound effect (it could be a combination of the two). Can the authors comment whether a rebound effect has ever been seen that was sufficiently large to explain the negative MSAT effect?

It is very puzzling that the mosquito density was not at all different between the trial arms while other entomological indicators are. The authors’ thorough data rules out species differences and vector resistance. I think the authors’ explanation about use of LLIN being lower in the intervention arm is plausible. Whatever the reason, it seems likely that some very unlucky chance has led to the control and intervention arms being non-comparable in terms of mosquito biting rate and EIR. I would conclude that this is a limiting factor in being able to understand MSAT effect from the trial. However, because the authors have very good monthly biting rate and EIR data, they could do a nice future analysis in which they estimate what the difference in clinical incidence should have been given the EIR differences, and then estimate MSAT impact, perhaps based on a model or other published relationship.

2. The authors suggest in the discussion p144 “The difference in EIR could be due to treated asymptomatic carriers being more infectious to mosquitoes than untreated individuals when they become reinfected.” I don’t see that there is evidence for this given the statement in the previous paragraph that there was no difference in gametocyte carriage and even a higher gametocyte density in the control arm. It seems more likely to just be chance, to which measures at the cluster level are more susceptible - there are only 9 EIR measures per trial arm.

Minor revisions

3. Please could the authors remind the reader of the prevalence measures taken at each screening round by microscopy. I appreciate these were published in your last paper but a brief mention (or an extra series on one of your figures) is
very useful to understanding the results.

4. The abstract and text says there is no effect of the intervention until week 11-12. It’s a bit non-intuitive why AL would have an effect 11 weeks later – perhaps it could be more clearly written along the lines of there being an impact on prevalence immediately but there was no distinguishable difference in clinical incidence until the transmission season started (as you’d expect).

5. Methods, p7-8 – please can the authors add the calendar dates or months of the screening rounds and treatment campaigns here. The EIR data are given by calendar month but the intervention timings are not – therefore I cannot tell in which months of the dry season the intervention was done relative to the EIR pattern.

6. Results: what was the concordance between microscopy and RDT results? Did RDT miss any carriers that were later identified by microscopy? Or vice versa.

7. Table 1: check EIR units. The EIR is per year in the table but per month in graph. I think the table may show the average values per month, not per year?

8. Abstract, results and conclusion. Can the authors more clearly highlight that the intervention had a negative impact. When reading quickly it’s easy to miss this because of not expecting the results to go in this direction. E.g. in discussion 1st paragraph say “Community screening and targeted treatment of asymptomatic carriers had a negative impact on the incidence....”

9. p13 discussion: “clearance of subpatent infections” – subpatent normally means below the detection limit of microscopy or RDT, but in this study, only positive carriers were treated – do you mean “patent infections”?

10. I don’t follow this statement in the discussion p13: “As shown in Figures 2–4, the probability of developing a symptomatic malaria episode with a parasite density >5,000/µL after the three screening campaigns was similar in children <5 years of age, in individuals of at least 5 years of age and in the total population”. To me the under-fives and over-fives look very different – approx 50% of <5’s are infected by day 200 versus 11% of over fives.

11. Discussion p13 paragraph 3. Lower density among cases in the intervention arm. A third explanation could be lingering prophylaxis by lumefantrine in the early part of the study, reducing the overall average.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests