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: Jacques Derek Charlwood

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This is obviously a huge amount of work. The authors are to be congratulated for implementing the logistics required for such a study.

Some information on the variability between houses & villages in the two arms of the study might be useful.

Whilst the authors provide a number of possible (but perhaps unlikely) scenarios (such as treated people not sleeping under their nets through some sort of hubris) as a reason for the differences observed in entomological indices between the arms of the study it is also likely that the randomization process included an exceptionally high-density house or village (or two) in one arm and not in the other and that these houses were responsible for the differences between control and intervention arms. Different ethnic groups may also make their houses more or less accessible for mosquitoes they may also spend differing amounts of time outside their houses in the evening. This may also have influenced the result. The take home message being that transmission rates were likely to be similar between both sets of villages, but that in each of them mosquito densities in houses probably followed the 80/20 rule (Woolhouse ME, Dye C, Etard JF, Smith T, Charlwood JD, Garnett GP, Hagan P, Hii,JL, Ndlovu PD, Quinnell RJ, Watts CH, Chandiwana SK, Anderson RM. Heterogeneities in the transmission of infectious agents, implications for the design of control programs. Proceedings of the National Academy of Sciences. 1997 94, 338-342.)
The authors might want to comment on this.

Note M form An. gambiae is now called An. coluzzi and S form retains the name An. gambiae. Table should be amended.

Prospective risk of illness was also higher among people who were parasite negative during mass screening in Sao Tome (and the more clones a person had the lower the risk of future illness). (Müller DA, Charlwood JD, Felger I, Ferreira C, do Rosario VE, Smith T. Prospective risk of morbidity in relation to multiplicity of infection with Plasmodium falciparum in São Tomé. Acta Tropica, 2001 78, 155-162.) There are probably a few other papers out there which would have predicted the observed results – notably by Tom Smith’s group from the Swiss Tropical Institute.

Taken together they raise the ethical question ‘Should such people be treated?’ There is perhaps a good case for asymptomatic people to be treated with anti-gametocidal drugs rather than treatments designed to clear their parasites. Indeed given the already available evidence it is moot whether the study was ethical.

Again the authors might want to comment on this.

During an infection that causes illness parasite densities increase rapidly. One possible reason why parasite densities may have been lower in the intervention arm is that people may have felt worse earlier (because, due to their parasites they had not been ill for some time before) than those in the control group and so reported earlier for treatment.

I congratulate Louisa Reed from PreScript Communications on her preparation of the manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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