Reviewer's report

Title: Increased deposition of C3b on red cells with low CR1 and CD55 in a malaria endemic region of western Kenya: Implications for the development of severe anemia

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Reviewer: Jørgen Kurtzhals

Reviewer's report:

The manuscript demonstrates a convincing association between C3b deposition on RBC and Hb-levels in individuals without detectable parasitaemia at the time of investigation living in an area where malaria is holoendemic. The amount of C3b correlates inversely with complement regulatory proteins CD35 and CD55. Most interestingly, both Hb levels and C3b deposition appears to be independently correlated with age. The conclusion is that age-dependent maturation or other factors important for complement regulation may independently of malaria infection play an important role in pathogenesis of severe malarial anaemia.

This is a cross-sectional study, and asymptomatic malaria may be difficult to detect with a single blood smear. In addition, even in the absence of malaria parasites at the time of investigation, the participants are so heavily exposed to malaria that recent infections may still be important, independently of the present findings. On the other hand, the authors have used appropriate statistical methods to allow their relatively cautious conclusions. The use of statistics is so important for the conclusions of the study that I think this should be evaluated by an expert statistician.

Minor essential revisions:
1. P. 7, l. 8-9: Please provide details on the criteria for selection of study subjects. (e.g. random selection from a census?)
2. P. 7, l. 13-15: The paper relies heavily on the fact that patients were parasite free. Please indicate the detection level of the microscopy (i.e. were 1000 WBC counted in thick smears?) Who did the microscopy and how were results quality controlled?
3. P. 11, l. 10-12 plus Figure 1 appear irrelevant and could simply be mentioned briefly in the introduction.
4. P. 13, l. 3-7: This paragraph is not easily comprehensible to me. What does it mean? I cannot see the described pattern in Figure 4b-c, and why suddenly an interpretation in the results section? Should probably just be omitted.
5. P. 16, first paragraph: Please refer to comment 2 above: C3b deposition could be caused by previous infection but in this area one could expect higher than
50% asymptomatic carriers (as reported in Table 1), and it is very likely that some study subjects were actually harbouring parasites below the detection limit. In fact, the treated subjects are probably more likely to be parasite free at the time of blood collection than the untreated subjects. This should be discussed.

6. P. 16, last paragraph: I agree with proposed reasons for low parasitaemia in the very young. However, it could also be due to selection bias. Thus, the very young children are non-immune and any high parasitaemia would be clinically important and either exclude the child from enrolment or lead to treatment.

Discretionary revisions:
1. There is too much use of non-standard abbreviations. E.g. p. 9, l. 1: antibody binding capacities (ABC) and l. 4 ICs (meaning immune complexes)
2. P. 12, last line-P. 13, l. 2: The authors should not overinterpret single observations on only 6 individuals.
3. There are some typing errors, including missing words that sometimes disturb the reading (e.g. p. 13, 2nd line from bottom, add 'change' before the last word). However several other places, please go through this.

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

What next?: Accept for publication in BMC Medicine after minor essential revisions

Quality of written English: Acceptable

Statistical review: Yes

Declaration of competing interests:
I declare that I have no competing interests