Reviewer’s report

Title: Comparison of simultaneous capillary and venous parasite density and genotyping results from children and adults with uncomplicated malaria: A prospective observational study in Uganda

Version: 0 Date: 11 Feb 2019

Reviewer: Sean Murphy

Reviewer's report:

This paper compared a large number of capillary (fingerstick) and venous blood samples by blood smear microscopy and DBS-based genotyping to determine if there were any meaningful differences between blood sampled from these two different sites. The study utilized clinical trial samples from Uganda and add a good deal of data toward answering this question. There is some scientific rationale for capillary blood behaving different perhaps due to parasite sequestration, although it is well known that only ring-stage Pf parasites are usually seen in blood smears regardless capillary vs. venous source. This question has been studied by a few different groups, with varying conclusions..but also with varying results. The paper is well written, but has some method omissions that need to be corrected as well as some analyses that could be repeated using a log10 scale more appropriate for parasite density data.

Major:

- Line 98-99: although this sentence introduces the other studies on this question and although these are explored more in the discussion, perhaps you can add a little foreshadowing here? The way the current Intro reads it makes it sound like the prior literature on this topic is minimal. This was also recently explored for molecular diagnostics (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4350552/), which could also be commented on. Because the patients in this report were all positive, there's no need to compare the "sensitivity" of molecular diagnostics for venous vs. capillary blood in this dataset unless a quantitative endpoint was available and could be systematically compared for same volume samples applied to blood spot cards (additional molecular testing is not necessary to move this manuscript forward).

- Replace parasitemia with "parasite density" for any parasite/volume results

- I suggest changing Table 1, Figure 2-3 and Supplemental Table 1 comparisons to log10 para/μL-based data rather than linear scale data unless you have a good rationale for why 2- or 4-fold changes are meaningful
- I would suggest using the same terminology or abbreviations for Tables 2-3 (i.e., CC, VV, VC, etc or spelled out)

- There seems to be an error in the last line of Supplemental Table 1 (p=0.09??). Please adjust to use a consistent number of significant digits

- Figures 2-4 need clearly labeled X and Y axis labels and figures need to be higher quality.

- There is an error in Figure 4 as presented since panels A and B appear identical.

- The Results section is a little difficult to read as is. Some of the results section currently magnifies differences in opposite directions without contextualizing the meaning or impact of such differences. After re-analysis on log10 scale, I would suspect that some of the differences would be less significant and the Results (no difference) could become easier to present.

- This statement (Each compartment frequently detects strains that are not seen in other compartment) seems like the data should be shown, as this is one important outcome in the manuscript. Is this a function of volume of blood sampled?

- Line 231-233: it's not clear to me that a 19% vs. 30% difference is significant, especially since the data not shown comment seems to indicate considerable variability upon additional testing

- The comparison of the outcome of this study to prior reports needs to take into consideration whether the data in prior reports was evaluated on a log10 or linear scale for quantitative comparisons between venous and capillary blood. Ref 21 = linear; Ref 22 at least partially log scale; I didn't find quantitative parasite density comparisons in the 1991 French-language manuscript in Ref 23 (though my French is rather elementary so please double-check). There's likely considerable variability in the methods of microscopy between the sites that generated these prior papers.

- Line 261-271: this is an excellent takeaway paragraph. Some other results sections could be simplified to adopt clear style. There's some sections of the Results that read as if these differences ARE significant AND important in the final analysis.

- Suggest adding a summary Table to the Discussion that integrates the results of prior studies and this data (not really a meta analysis but at least a one-stop authoritative listing).
Minor:

Line 40: spell out 3rd as third in the abstract

Line 91: Would probably be good to cite comparable DBS vs. venous blood literature in HIV (https://jcm.asm.org/content/52/5/1343; https://www.sciencedirect.com/science/article/pii/S1386653217301282)

Line 103: the placement of Ref 3 here is misleading. Suggest keeping sentence as is but deleting Ref.

Lines 116, 125, 236, etc. Be sure to consistently use P. falciparum after first use of Plasmodium falciparum.

Line 119-121: number of enrolled participants should be moved to "Results"

Line 125: anticoagulant for venous blood

Line 125: how was blood spotted onto DBS for capillary vs. venous blood? Microhematocrit tubes? Pipettes?

Line 132: Should be titled "Parasite densities"

Line 142: list volume of blood spotted onto on DBS

Line 143: list diameter of spots and number of spots need to be listed as input for QiaAMP extraction

Line 176: delete "of" in range of …

Line 178-179: Suggest change all instances of "parasitemia" to "parasite density" since para/volume is parasite density

Line 187 and 189: use consistent P or p in "p value" presentations (possible other instances elsewhere too)

Line 198: spell out 'doesn't'

Fig 1: fix the spell check red underlining for drug name

Line 330: delete UCSF abbreviation unless reusing this abbreviation

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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