Cory Hayes Review

This study was an in vivo exploration of how murine animal models treated with Artesunate or melfloquine are able to clear Plasmodium in comparison to mice not on antimalarials. I would recommend a provisional acceptance of the paper with a few minor recommended edits.

There were numerous strengths in this paper:

- An extensive and thorough methods section
- Clear motivation was provided for why each experiment was conducted
- Two different Plasmodium species and two different antimalarials were utilized to prove that observations were truly representative.
- The discussion section touched on everything I expected it to; the performance of MQ compared to artesunate and why, the difference between murine and human models in this specific context, future experiments with a longer period of observation, and potentially why there wasn't complete parasite killing.

The following are suggested edits in order to further strengthen the paper:

1. In the introduction, you mention the growing parasitic resistance to artesunate and the search for alternative treatments, and then proceed with this detailed study of artesunate, failing to mention resistance again until the discussion. In the current state of the paper it's a confusing section to the reader, that's not connected with the study itself. I think it's wise to either remove this section from the introduction entirely, or to add more speculation in the results/discussion sections involving possible resistance in this experiment.
2. I. In the methods section under the heading "parasites and infections", there are two different titers of infection. Is there any specific reason?

   II.Was this why there was a mention of possible sub-optimal dosing at the end of the 3.1 results section? If so, it might be sensible to add a quick discussion of the titers to the end of the 3.1 results section?
3. In the preliminary infection experiment shown in Figure 1 A, there is a large spike in the Artesunate group around 11 days (6 days into treatment) that isn't analyzed as much as it should be. Is this resistance forming or something else? At least a sentence or two should be added to the results section about this spike.
4. In figure 5A, MQ doses of 200 uG are interesting. In 5Aa, MQ at 200uG appears to be lower than the negative control for % of initial donor parasites at 24 hours. In 5Ab, MQ at 200uG appears to show equal or slightly increased fold growth from the negative control. Though it's mentioned later in the section, a sentence at the end of the first paragraph in results section 3.4 discussing this specific suboptimal dose, and potentially why, would be helpful to the reader.