Author’s response to reviews

Title: Prevalence, genetic variants and clinical implications of G-6-PD deficiency in Burkina Faso: a systematic review.

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Answer to reviewer
NB: The different corrections made are highlighted in green in the manuscript.

Technical Comments:

1. Please provide a figure legend.

Legend: The database search according to the search strategy described in the methodology section was clean up to exclude duplicates. Titles and abstract were initially screened to include all relevant studies describing the prevalence and/or genetic variants of the G-6-PD deficiency in Burkina Faso. Review articles, articles without abstract or without full text as well as those that did not meet the inclusion criteria were then excluded during the full-text review. Seven (7) research relevant articles and one (1) conference paper were finally selected for this review of the literature.
1. Rosario Notaro (Reviewer 1): The need for a systematic screening of the G6PD deficiency to prevent iatrogenic adverse events, especially those following the use of antimalarial drugs, in Burkina Faso is well-known. However, this manuscript does not provide additional evidence supporting it.

Answer: Your concerns have been addressed in section 3.2 of the manuscript.

2. The final statement that "Santamaria and Betica Selma variants have relatively high frequencies in the southwest and north of the country", despite likely, is far fetched because it is based on the finding of just one case of each variant reported recently by the same Research Group.

Answer: Despite the ubiquity of the 202A/376G G-6-PD A- variant in all regions of the country, it will be necessary to consider the Santamaria and Betica Selma variants whose frequencies remain to be specified in the different areas of the country.

3. The manuscript is lengthy and wordy: most of the discussion and of conclusion should be summarized.

Answer: The discussion has been significantly reduced and some parts of the conclusion has been modified.

4. Lucio Luzzatto (Reviewer 2): My main criticism is that no picture emerges as to the frequencies in different parts of the country which seemed, from the title of the paper, to be a main purpose of the work.

Answer: Figure 2 shows the map of Burkina Faso with the different frequencies of the G6PD deficiency in the different regions of the country.

5. Line 55. It is not correct that G6PD A- , having two mutations in cis, is a combination of a class III and a class IV G6PD. The classification referred to was meant to classify variants, not mutations. G6PD A is class IV, whereas G6PD A- is class III.

Answer: The most common deficient haplotype or G-6-PD A- in sub-Saharan Africa has two mutations in cis. These are G202A (rs1050828) and A376G (rs1050829) mutations with a high linkage disequilibrium [8]. Other alleles responsible for the G-6-PD deficiency with frequencies that are over 1% have also been reported in West Africa. The latter is represented respectively by T968C (rs76723693) and A542T (rs5030872) substitutions.

6. Line 76. The majority of antimalarials currently in use, except primaquine, are not a risk for G6PD deficient persons.

Answer: The use of certain antimalarials such as primaquine,

7. Line 77. Only fava beans are dangerous for G6PD deficient persons: not the other beans.
Table I. Enzymatic tests cannot distinguish between G6PD A- and other variants. In addition, it is not clear whether the frequencies in this Table are for males or females. If the two genders are mixed, the frequency data are uninterpretable.

Answer: …consumption of certain foods (fava beans), induce hemolytic anemia in G-6-PD deficient individuals.

Answer: Table I: “G6PD A-” has been replaced by “G6PD deficiency”. The data represents the overall prevalence of G6PD deficiency in the two genders for each study.

8. Section 2.2. It is confusing that in the first part of this section alleles are identified by point mutations; in the second part by variant names. It would be desirable to state which mutations correspond to which named variants.

Answer: In this section, we made an effort to specify the names of the variants corresponding to the different mutations: Santamaria (376G/542T) and Betica Selma (376G/968C).

9. Lines 125-127. The meaning of this paragraph is not clear to me.

Answer: I mean that in Burkina Faso, self-medication in the treatment of malaria is a reality as indicated in the references [31-33]. These antimalarials used without medical prescription can therefore lead to fatal attacks in people who are deficient in G6PD and thus increase the morbidity and mortality rate due to iatrogenic effects. It should be noted that very few published studies have addressed the prevalence and genetics variants of G-6-PD deficiency in Burkina Faso

10. Line 129. 17% is almost double of 9.2. The Authors should tell us how they explain this considerable discrepancy: is it because different surveys come from different parts of the country, or because of different methodologies?

Answer: These disparities in the prevalence could be explained by the fact that the different surveys were carried out in different parts of the country and by methodologies, which differ from one study to another.

11. In the discussion the point above is addressed, but no effort is made to map the frequency of G6PD deficiency in various parts of the country, as I would have expected from the title of the manuscript. It is all too easy to say that a new national study should be carried out: in the meantime, the best should be made out of the data already available.

Answer: Figure 2 shows the map of Burkina Faso with the different frequencies of the G6PD deficiency in the different regions of the country.
12. It is also not clear whether the data being summed in Table III are from the same population, how Table III relates to the other two tables, and whether the data were tested for whether or not the population is in Hardy-Weinberg equilibrium.

The data in this table come from these three references [14, 27 and 28] with information allowing the calculation of the different haplotypes. The populations a, b and c from Ouagadougou with symptomatic or asymptomatic malaria as shown in Tables 1 and/or 2, were conform to Hardy-Weinberg Equilibrium.

13. The discussion re clinical expression of G6PD deficiency does not seem relevant to the rest of the paper. The clinical implications of G6PD deficiency - covered in numerous existing reviews, some of them quoted in the reference list - are almost certainly no different in Burkina Faso compared to those in other countries. The only specific point I found of interest is that about the safety of a methylene blue-containing antimalarial in G6PD deficient subjects. YH

Answer: The discussion has been significantly reduced and most of the clinical expression of G6PD deficiency has been removed.