Author’s response to reviews

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

Authors:

Abdoul Karim OUATTARA (ak_ouattara@yahoo.fr)
Pouiré YAMEOGO (pouireyameogo@gmail.com)
Lassina TRAORE (ttl.lass@yahoo.fr)
Birama DIARRA (diarra.birama679@gmail.com)
Maléki ASSIH (assihmalki@yahoo.fr)
Tegwindé COMPAORE (rebecca23fr@yahoo.fr)
Dorcas OBIRI-YEBOAH (castella.oy@gmail.com)
Serge SOUBEIGA (s.soubeiga@yahoo.fr)
Florence DJIGMA (florence.djigma@gmail.com)
Jacques SIMPORE (jacques.simpore@yahoo.fr)

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Answer to reviewer

NB: The different corrections made are highlighted in yellow in the manuscript

Lucio Luzzatto (Reviewer 2):

1. The map is a great addition, but it risks backfiring since most of it is blank. The Authors know very well that there must be G6PD deficiency throughout Burkina Faso, especially since all surrounding countries also have relatively high frequencies. There are many - more or less sophisticated (see ref. 3) - methods to use available info in order to obtain, by interpolation, an estimate of what may be the frequencies in areas not yet tested or insufficiently tested (they could use grey shadings instead of colour for estimates as opposed to data, and explain details in the figure legend). It is
understandable that the Authors wish to cover themselves; but as it stands now the map risks becoming seriously misleading for readers.

Answer: Data from three studies were used for Inverse Distance weighted interpolation of the allelic frequency of G-6-PD deficiency in Burkina Faso using QGIS 2.18.14 software (Figure 2).

2. The confusion between genders has not been eliminated. For an X-linked trait there is no such thing as an overall frequency: in every table and figure, and wherever a statement about frequency is made - including the abstract - it must be clear whether it is in males or in females; or each one should be given.

Answer: Tables 1 and 2 have been grouped into a single table with frequencies by gender except the study carried out by Modiano et al. (2001).

3. Mentions of anti-malarials, self-medication etc are repetitious and vague. In Burkina Faso probably the only drug potentially hemolytic for G6PD deficient persons is primaquine; and the only indication for this in Burkina Faso is as gametocytocidal agent after treatment of an acute P falciparum malaria attack. However, the dose recommended for this use has been decreased to a single dose of 0.25 mg/Kg, regarded as safe for G6PD deficient persons (Malaria J 11: 418, 2012).

The sweeping warnings in this paper risk being involuntarily a deterrent to prompt treatment of a malaria attack, which almost without exception will be more life-threatening than G6PD deficiency.

Answer: Indeed, self-medication involves risks such as maladjustment between medication and pathology, wrong dosage or drug interaction that can lead to an increase in oxidative stress. Although when given at a single low dose of 0.25 mg base/kg body weight, primaquine is well tolerated regardless of the patient’s G6PD status, a wrong dosage through self-medication could be dangerous for G-6-PD deficient individuals [45]. Self-medication against malaria remains a reality for a large part of the population

4. Personally I believe there are good reasons to challenge (as has been done in ref. 11) some aspects of the conventional (WHO) classification of G6PD variants: therefore in my view the Authors are at liberty to accept it or to reject it. They can also point out - correctly - that the clinical manifestations of one and the same variant will depend to some extent on the environment; what they cannot say is that the classification may change from one place to another, because for a classification of genetic variants that would make no sense. Incidentally, G6PD Santamaria is not in class III, but in class II: its activity in red cells has been found to be 2-3% of normal (see Ann Hum Genet. 61:229, 1997).

Answer: Among the three deficient variants identified in Burkina Faso, the G-6-PD A-(202A/376G) and Betica Selma (376G/968C) variants have class III phenotype, while the Santamaria (376G/542T) variant has WHO class II phenotype.