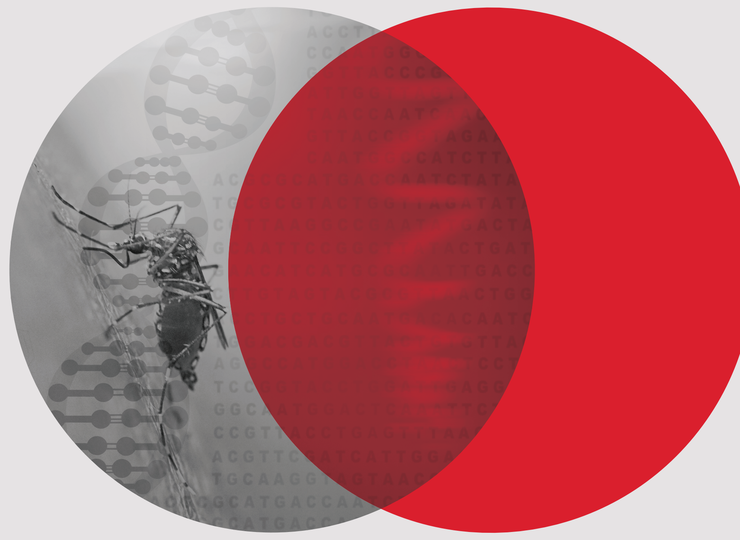
Highlighting the need for harmonisation of G6PD reporting following the introduction of new antimalarials



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Introduction

The recent introduction of new antimalarial drugs (e.g. Tafenoquine) [1] come with a recommendation to ascertain G6PD deficiency in order to avoid drug induced haemolysis.

A recent review of RCPAQAP G6PD survey results revealed a degree of variation in the interpretation of assay results in the deficient/borderline range of 2.0 – 9.0 U/g Hb.

Aim

To assess the current status of G6PD testing and reporting with a view to providing additional information to laboratories and clinicians when assessing patients prior to prescribing antimalarial drugs.

Methods

An online survey was forwarded to laboratories participating in the 2019 RCPAQAP Haematology G6PD program seeking further information about their testing, interpretation and reporting of G6PD results. 76 of the 144 participating labs (53%) responded.

Results and Discussion

Of the 144 enrolees of the G6PD program, 76 responses to this questionnaire were received. The key findings were as follows:

- The wide variation of reference intervals for G6PD activity used by respondents who perform G6PD assays (see Figure 1).
- The reference intervals submitted varied from age-related breakdowns (e.g. adult/child/neonate) to a general interval encompassing all age groups (See Figure 1).
- The lower limit of normal for adults ranged from 4.6 U/g Hb to 10.1 U/g Hb.
- The majority of respondents (69%) do not have their G6PD results reviewed by a haematologist even when the result is abnormal/decreased (see Figure 2).
- The vast majority of respondents (93%) do not specify a cut-off level and/or interpretive comment below which it is not advisable to administer antimalarial drugs (See Figure 3).
- Given the lack of harmonisation on reference intervals and potential problems with interpretation of results, we noted 2 labs using interpretative comments which may assist with informing clinicians on the risk of prescribing the new antimalarials for their patients:
  - One lab reported G6PD activity as a percentage of the adjusted male median (%AMM) in addition to the quantitative result with an interpretive comment "Males with less than 30% of the AMM are at risk of haemolysis from exposure to the anti-malarial drug tafenoquine. Female carriers with 30–70% AMM also at risk with long term use of tafenoquine."
  - One lab included a comprehensive guide on the risk of haemolysis which may occur if the subject is exposed to certain drugs based on the G6PD activity (U/g Hb) and the patient's Hb level (See Figure 4)

Figure 1. Reference intervals for G6PD activity submitted by respondents

Lab	Reference Interval	Source
A	7 – 20.5 U/g Hb (mixed population)	Manufacturer of the kit/reagents
B	Adult: 6.4 – 12.9 U/g Hb, Child: 8.8 – 18.4 U/g Hb, Neonate: 12.5 – 21.6 U/g Hb	Preventive Medicine Foundation of Taiwan
C	11 – 18 U/g Hb	Manufacturer of the kit/reagents and verified by lab
D	Deficient: < 2.0 U/g Hb, Intermediate: 2.0 – 10.0 U/g Hb, Normal: 10.1 – 14.19 U/g Hb	The Journal of Pediatrics
E	All age groups: 5.0 – 13.0 U/g Hb	Established "in-house" by lab
F	Age <3 months: Deficient: <3.86 Borderline: 3.86 – 9.61 Normal: ≥9.62 Age >3 months: Deficient: <2.41 Borderline: 2.41 – 6.10 Normal: ≥6.11	Established "in-house" by lab
G	Neonate to ≤3 months: Normal: ≥9.0 U/g Hb; Borderline Normal: ≥3.5 – 8.9 U/g Hb; Deficient: <3.5 U/g Hb Healthy males and females >3 months: Normal: ≥4.6 U/g Hb	Manufacturer of the kit/reagents and verified by lab
H	Newborns: (up to 1 month): 10.8 – 19.9 U/g Hb; Adults: 4.6 – 13.5 U/g Hb (30°C)*	Established "in-house" by lab
I	>6.9 U g/Hb	Not indicated
J	0 – 8 weeks: 9 – 39 U/g Hb; > 8 weeks: 9 – 22 U/g Hb	Established "in-house" by lab
K	146 – 376 U/10^{12} RBC	Manufacturer of the kit/reagents and verified by lab
L	>3 months: Normal >6.1 U/g Hb, Intermediate 2.41 – 6.1 U/g Hb, Deficient <2.41 U/g Hb. <3 months: Normal >9.61 U/g Hb, Intermediate 3.86 – 9.61 U/g Hb, Deficient <3.86 U/g Hb	Established "in-house" by lab
M	4.6 – 13.5 U/g Hb (30°C)*	Established "in-house" by lab
N	M/F 0 – 1 year: 7 – 17 U/g Hb; M/F 1 year – Adult: 6 – 12 U/g Hb	Not indicated
O	Male 0 – 2 days: 9 – 39 units/g/Hb; Male >2 days: 9 – 22 units/g/Hb	Established "in-house" by lab

* Assays performed at 30°C. All other laboratories listed perform their assays at 37°C.

Figure 2. Haematologist review of results

Are G6PD reports reviewed and commented on by a Haematologist in conjunction with other related results?

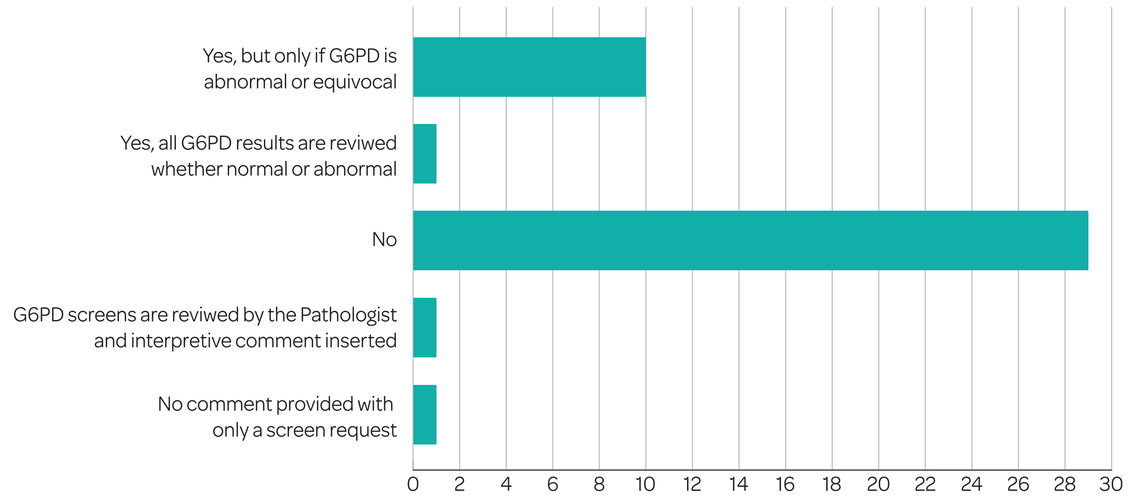

Figure 3. Cut-off level for G6PD deficiency

Does your report specify a cutoff level of G6PD and/or interpretive comment below which it is not advisable to administer antimalarial drugs?

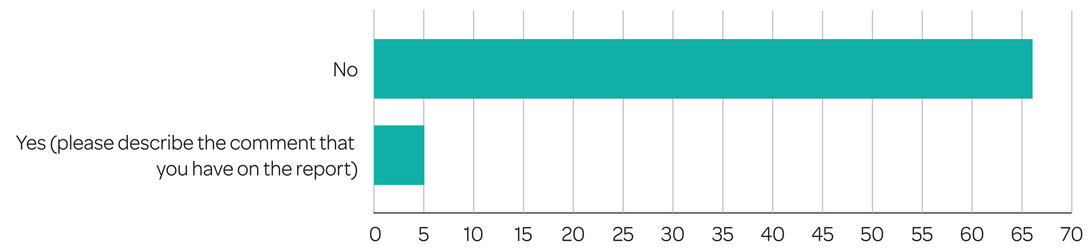

Figure 4. Table of interpretive comments used by a respondent

G6PD level (7.0 – 20.5 U/g Hb)	Hb Level	Interpretive Variant Class	Code on Report*
< 1 U/g Hb	Anaemic	Probable Class 1 (< 1%)	G61
< 2 U/g Hb	Normal	Probable Class 2 (<10%	G62
1 – 2 U/g Hb	Anaemic	Probable Class 2 (<10%)	G62
2 – 7 U/g Hb	Normal/Anaemic	Probable Class 3 (10-60%)	G63
7 – 12 U/g Hb	Anaemic	Possible Class 3 (10-60%)	G63
7 – 12	Male Normal	Equivocal Class 4	GLNM
7 – 12	Female Normal	Equivocal Class 4	GLNF
12 – 20.5	NORMAL	NORMAL	GLNF
>20.5		Elevated Class 5	

*On data entry, each code expands to an explanatory statement, e.g code **G61** expands to:
Class I variant G6PD deficiency. This is associated with very low levels of G6PD and usually leads to a state of chronic oxidative haemolysis. An acute severe exacerbation may be triggered by exposure to certain drugs such as "Sulpha" type compounds.

Conclusion

The feedback from this survey confirms the lack of standardisation of reference intervals and reporting of G6PD assay results. There is a need for the harmonisation of methods and cut-off levels for G6PD deficiency given anti-malarial drug manufacturers quote specific values in their product information. A possible first step to mitigate potential patient harm would be to consider interpretive comments along the lines of the two examples provided here.

We acknowledge the RCPA and AACB are also looking to raise the awareness of the need to harmonise G6PD quantitative assays and reporting of results to assist clinicians when prescribing the new anti-malarial drugs.

References

1. The past, present and future of anti-malarial medicines, Tse, E et al, *Malaria Journal*, 2019

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