SUPPLEMENTAL APPENDIX S1

Yilma et al: Severe hemolysis during primaquine radical cure of *Plasmodium vivax* malaria: two systematic reviews and individual patient data descriptive analyses

Table of Contents

PRIMSA – Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6-7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Appendix pp5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix pp5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Appendix pp5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,9, data file
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8,9, data file
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9,10,12, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Data File
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Data file
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 1,2,3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9,10, data file
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20,21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Box S1 - Search strategy for Review 1 of *P. vivax* Antimalarial Clinical Trials

Search strategy

All prospective *P. vivax* antimalarial clinical trials with a minimum of 28 days follow up, published between Jan 1, 1960 and Aug 23, 2021 were identified by the application of the key terms (listed below) through Medline (Pubmed), Web of Science, Embase and the Cochrane Central Database. Abstracts of all references containing any mention of antimalarial drugs were manually checked to confirm prospective clinical trials, with review of full text when needed.

To be eligible for inclusion in the current review, trials had to have been done since 1990, (after which adverse event detection and reporting was more standardised, include one or more treatment arm(s) in which patients were treated with either partial or fully supervised primaquine therapy, daily dosing for at least 5 days' duration. Primaquine administration had to commence within the first 7 days after starting blood schizontocidal therapy. Data from non-primaquine-containing arms in these studies were also extracted for comparative purposes, but restricted to patients treated with chloroquine, dihydroartemisinin-piperaquine or artemether-lumefantrine. Studies meeting the above criteria, but not reporting the presence or absence of adverse effects of treatment, were excluded.

The year of the study was taken as the year in which the paper was published, although the start and end date of patient enrolment were also recorded.

The review process was undertaken by two independent investigators who also performed data extraction (RJC and RNP), and is documented in more detail in Commons et al, Int J Parasitol Drug Drug Res 2017.

Previously registered at PROSPERO [CRD42016053228].

Key terms:

Literature search (conducted August 23, 2021) with the following key terms (version undertaken in Pubmed):

vivax AND (allopurinol OR amodiaquine OR atovaquone OR artemisinin OR arteether OR artesunate OR artemether OR artemotil OR atovaquone OR azithromycin OR artekin OR chloroquine OR chlorproguanil OR cycloguanil OR clindamycin OR coartem OR dapsone OR dihydroartemisinin OR duo-cotecxin OR doxycycline OR halofantrine OR lumefantrine OR lariam OR malarone OR mefloquine OR naphthoquine OR naphthoquinone OR pafuramidine OR piperaquine OR primaquine OR proguanil OR pyrimethamine OR pyronaridine OR proguanil OR quinidine OR quinine OR riamet OR sulphadoxine OR sulfamethoxazole OR tetracycline OR tafenoquine).

Box S2 - Search strategy for Review 2 of Severe primaquine-associated Hemolysis

A. Review strategy and search terms used

Search strategy

All articles reporting at least one case of severe primaquine-associated hemolysis published between 1 January 1940 and 20 May 2020, were identified by the application of the key terms (listed below), through PubMed, Web of Science, Embase and the Cochrane Central Database.
Title and abstracts of all references were manually checked to confirm papers that reported data attributable to individual patients receiving primaquine for *P. vivax* radical cure or terminal prophylaxis. The review process was undertaken by six independent reviewers (DY, EG, KT, RJC, NMD, RNP), with discrepancies resolved by discussion.

The review was registered at PROSPERO [CRD42020196604].

Key terms:
Literature search (conducted May 2020) with the following key terms (version undertaken in Pubmed):

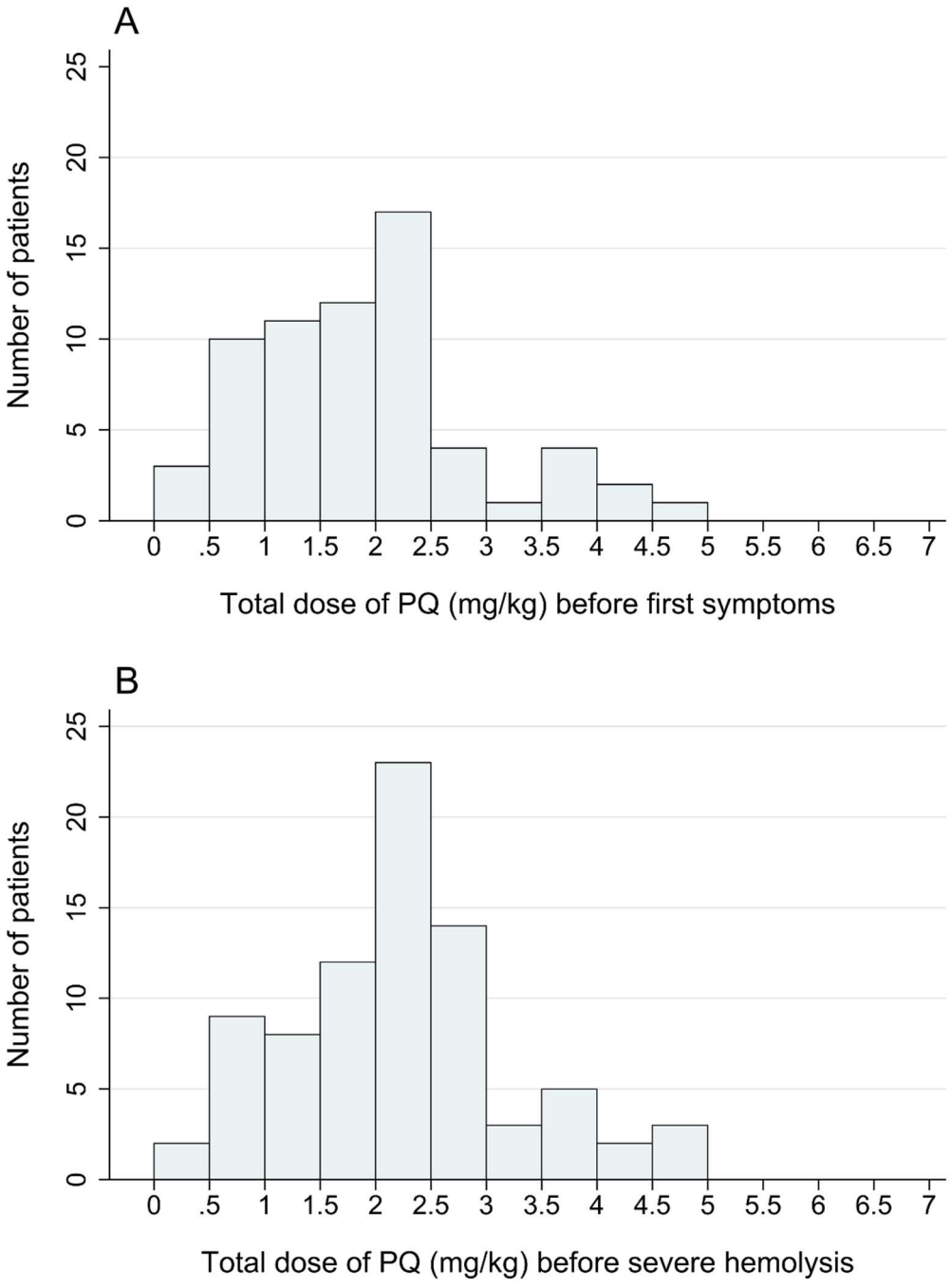
vivax and (hospital* or renal or dialysis or transfusion or severe or serious or haemolysis or hemolysis or fatal or death or died or methemoglobin* or methaemoglobin* Or 'cerebral complicat*' or convuls* or unconscious* or prostrat* or 'kidney injury' or 'renal failure' or 'renal impairment' or haemoglobinuria or hemoglobinuria or 'circulatory collapse' or shock or jaundice or hyperbilirubinemia or hyperbilirubinaemia or 'hepatic dysfunction' or 'liver dysfunction' or bleeding or hemorrhage or haemorrhage or thrombocytopenia or thrombocytopaenia or 'disseminated intravascular coagulation' or DIC or 'acute respiratory distress syndrome' or ARDS or 'pulmonary edema' or 'pulmonary oedema' or 'metabolic acidosis' or hyperlactat* or 'severe anaemia' or 'severe anemia' or hypoglycemia or hypoglycaemia or complicat*)

B. Secondary searches:

1. Review all articles included in the WWARN *P. vivax* clinical trial database from the first systematic review of serious adverse events

2. Identify additional studies, conference abstracts and unpublished works from reference lists of identified articles and documents

Figure S1 - Total dose of PQ (mg/kg) administered (A) before first symptoms of hemolysis and (B) manifestation of severe hemolysis



Footnote: Data restricted to the 101 cases with probable or possible severe PQ-associated hemolysis

Example of Form for reporting drug-induced hemolysis following treatment of malaria

REPORTER DETAILS

Name of reporter:_____	**Date of assessment**: __ / __ / ___
Role / Function: _____	Report type:
Tel:_____	☐ Initial ☐ Follow-up FU #: ____
Email:_____	

PATIENT DETAILS

Patient initials: _____ Medical ID number: _____

Sex: ☐ M ☐ F **Age**: _____ Date of Birth: __ /__ /___

Weight: _____ kg

Country: _____ **Site:** _____

MALARIA DETAILS

Treatment Indication: ☐ Acute malaria ☐ Terminal prophylaxis ☐ Other:_____

Date of Malaria Diagnosis: __ / __ / ___ **Method:** ☐ Microscopy ☐ RDT ☐ Other___

Malaria Species: ☐ Pf ☐ Pv ☐ Pm ☐ Po ☐ Pk ☐ Unknown

Baseline parasitaemia: _____ per ul ++++ +++ ++ + ☐ Unknown

TREATMENT DETAILS

Schizontocidal Treatment: ☐ CQ ☐ AL ☐ DP ☐ Quinine ☐ None ☐ Other:_____

Hypnozoitocidal drug: ☐ PQ ☐ Tfq

Date Commenced: ___ /___ /____ **Time Commenced**: __ __ :__ __

Daily Dose of PQ or Tfq: _____.__ mg Calculated mg/kg dose:_____

Planned duration of PQ: _____ days

Target total dose of PQ: ___.__ mg/kg

Number of doses taken before adverse event detected: _____

Did the patient take their PQ / TQ tablets with food? ☐ Yes ☐ No ☐ Unsure

CONCOMITANT MEDICATION

Medication	Indication	Start date dd/mm/yyyy	Stop date dd/mm/yyyy	Dose	Frequency

CLINICAL PRESENTATION

Date adverse event detected: __ / __ / __

Temperature:____.___ C | Pulse: _____ per min | Resp rate: ____ per min

Symptom	Severity (see criteria table)	If present, date of onset
Abdominal pain	None 1 2 3 4	___/___/20___
Nausea	None 1 2 3 4	___/___/20___
Unable to eat	None 1 2 3 4	___/___/20___
Vomiting	None 1 2 3 4	___/___/20___
Back pain	None 1 2 3 4	___/___/20___
Breathlessness	None 1 2 3 4	___/___/20___
Dizziness	None 1 2 3 4	___/___/20___
Fatigue	None 1 2 3 4	___/___/20___
Severe Conjunctival Pallor	Yes / No	___/___/20___
Fever	Yes / No	___/___/20___
Jaundice	Yes / No	___/___/20___
Tachycardia	Yes / No	___/___/20___
Cyanosis	Yes / No	___/___/20___
Dark (red or black) urine	Colour:_____ (See Hillman chart)	___/___/20___
Other: _____	None 1 2 3 4	___/___/20___

NARRATIVE

_____

_____

_____

_____

_____

_____

RELEVANT MEDICAL HISTORY

Medical condition	Start date dd/mmm/yyyy	Stop date dd/mmm/yyyy	Ongoing
			☐
			☐
			☐
			☐

RELEVANT INVESTIGATIONS

Hemoglobin	Date	Result
Pre-treatment	__ / __ / 202__	Hb: __ . __ g/dL
At time of event	__ / __ / 202__	Hb: __ . __ g/dL
Current	__ / __ / 202__	Hb: __ . __ g/dL
Nadir	__ / __ / 202__	Hb: __ . __ g/dL
	Max fall in Hb:	Hb: __ . __ g/dL
	Max fractional fall in Hb	____.__ %

G6PD STATUS

G6PD test: □ Quantitative □ Qualitative □ Unknown □ Not Done

Name of test: _____

Date of testing: __ / __ / __ **Time of testing**: __ __:__ __

Quantitative result: ____ . __ U/g Hb □ Deficient □ Intermediate □ Normal

Qualitative result: □ Deficient □ Normal □ Indeterminant

Genotyping: □ NA □ Normal □ Variant _____

OTHER LABORATORY TESTS

Test	Pre-treatment	At time of event	Follow-up	Not Available
	__ / __ / ___	__ / __ / ___	__ / __ / ___	
WBC:	_____ x10^9	_____ x10^9	_____ x10^9	□
Plt:	_____	_____	_____	□
Na:	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
K:	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
Urea:	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
Total Bili:	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
Unconj Bili:	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
ALP	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
ALT	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
LDH:	_____ µmol/L	_____ µmol/L	_____ µmol/L	□
Met Hb:	____.____ %	____.____ %	____.____ %	□

Other Investigations:

ADVERSE EVENT CLASSIFICATION		
Severity Maximum Graded Symptom	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4	
AESI **Hemolysis** ☐ Yes ☐ No	Any of the following: ☐ Grade 3 or 4: fatigue, dizziness, breathlessness (onset after starting PQ) ☐ Severe pallor or jaundice ☐ Dark urine: Hillman >7 ☐ Fall in Hb > 3 g/dL ☐ Hb <7g/dl	
SAE Meets "serious" criteria ☐ Yes ☐ No	☐ Death	
	☐ Life threatening	
	☐ Hospitalisation or prolongation of hospitalisation	Admission date: __ / ___ / 202__ Discharge date: __ / ___ / 202__
	☐ Persistent or significant disability	
	☐ Is a congenital abnormality / birth defect	
	☐ Is an important and significant medical event	
Relationship (causality) to PQ	☐ Not related ☐ Unlikely related ☐ Possibly related ☐ Probably related ☐ Definitely related	

CLINICAL MANAGEMENT		
IV Fluids	☐ Yes ☐ No	
Blood transfusion	☐ Yes ☐ No	Number of units: _____ Date: __/__/202_
Dialysis	☐ No	☐ Peritoneal dialysis ☐ Haemodialysis
Changes to PQ	☐ No change ☐ Withhold ☐ Cease ☐ Restart	
	If Restarted: Date Restarted: __/__/202_ ☐ Same dose ☐ Modified dose Dose: ___.__ mg ☐ 1x Day ☐ 2x day Duration: ___ Days	

NARRATIVE:

_____

_____

_____

_____

_____

_____

OUTCOME

□ Recovered / Resolved

□ Recovering / Resolving

□ Not recovered / Not resolved

□ Recovered / Resolved with sequelae Specify:_____

□ Fatal: Date of death: ___ / ___ / 202__
Cause of death: _____

□ Unknown

CLINICIAN RESPONSIBLE FOR THE REVIEW

Name : Date: __ / __ / 202__

Role :

Address :

Mobile: _____

Email : _____

Signature: _____