

ADDITIONAL FILE 1

Commons *et al*, The haematological consequences of *Plasmodium vivax* malaria after chloroquine treatment with or without primaquine: a WorldWide Antimalarial Resistance Network systematic review and individual patient data meta-analysis

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Checklist S1. PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

| PRISMA-IPD Section/topic | Item No | Checklist item | Reported on page |
|---|---------|---|-------------------|
| Title | | | |
| Title | 1 | Identify the report as a systematic review and meta-analysis of individual participant data. | 1 |
| Abstract | | | |
| Structured summary | 2 | Provide a structured summary including as applicable: | 6 |
| | | Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes. | 6 |
| | | Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias. | 6 |
| | | Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice. | 6 |
| | | Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications. | 7 |
| | | Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis. | 7 |
| Introduction | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 8 |
| Objectives | 4 | Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups. | 8 |
| Methods | | | |
| Protocol and registration | 5 | Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable. | 9 |
| Eligibility criteria | 6 | Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated. | 9-10 |
| Identifying studies - information sources | 7 | Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation. | 9 |
| Identifying studies - search | 8 | Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Additional file 1 |

| | | | |
|--|----|---|-------------------|
| Study selection processes | 9 | State the process for determining which studies were eligible for inclusion. | 9-10 |
| Data collection processes | 10 | Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). | 9; Ref 16 |
| | | If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators. | Additional file 1 |
| Data items | 11 | Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies. | 9-10 |
| IPD integrity | A1 | Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done. | 9; Ref 16 |
| Risk of bias assessment in individual studies. | 12 | Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis. | 11 |
| Specification of outcomes and effect measures | 13 | State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome. | 11-12 |
| Synthesis methods | 14 | Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): <ul style="list-style-type: none"> • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable). | 11-12; Ref 16 |
| Exploration of variation in effects | A2 | If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified. | 11 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables. | 11 |

| | | | |
|----------------------------------|----|---|--------------------------|
| Additional analyses | 16 | Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified. | 11-12 |
| Results | | | |
| Study selection and IPD obtained | 17 | Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram. | 12; Fig 1 |
| Study characteristics | 18 | For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD. | Additional file 1 |
| IPD integrity | A3 | Report any important issues identified in checking IPD or state that there were none. | 12; Fig 1 |
| Risk of bias within studies | 19 | Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions. | 13; Additional file 1 |
| Results of individual studies | 20 | For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot. | Additional file 1 |
| Results of syntheses | 21 | Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based. | 15-18 |
| | | When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials. | |
| | | Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables. | 12-13; Additional file 1 |
| Additional analyses | 23 | Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available. | 15-20; Additional file 1 |
| Discussion | | | |
| Summary of evidence | 24 | Summarise the main findings, including the strength of evidence for each main outcome. | 23-26 |

| | | | |
|---------------------------|----|---|--------|
| Strengths and limitations | 25 | Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available. | 25-26 |
| Conclusions | 26 | Provide a general interpretation of the findings in the context of other evidence. | 26 |
| Implications | A4 | Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research. | 223-26 |
| Funding | | | |
| Funding | 27 | Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support. | 29 |

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Box S1. Search strategy

Search strategy

All prospective *P. vivax* antimalarial clinical trials published between Jan 1, 2000 and March 22, 2017 were identified by the application of the key terms (listed below) through Medline (Pubmed), Web of Science, Embase and the Cochrane Database of Systematic Reviews. 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. Studies on prevention, prophylaxis, reviews, animal studies, patients with severe malaria, where schizontocidal treatment was unsupervised or where data were extracted retrospectively from medical records outside of a planned trial were excluded. The review process is documented in more detail in Commons *et al*, Int J Parasitol Drug Drug Res 2017 [15]. 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.

Key terms

Literature search (conducted March 2017) with the following key terms (version undertaken in Pubmed): (malaria OR plasmod*) AND (amodiaquine OR atovaquone OR artemisinin OR arteether OR artesunate OR artemether OR artemotil OR azithromycin OR artemin 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 piperaquine OR primaquine OR proguanil OR pyrimethamine OR pyronaridine OR proguanil OR quinidine OR quinine OR riamet OR sulphadoxine OR tetracycline OR tafenoquine).

Table S1. Studies included in analysis

| Author-year | Country | Recruitment period | Relapse periodicity* | Study sites | Age range, years | Follow up, days | Treatment arms | Drug supervision | Drug origin | Patients enrolled in initial study | Patient data available | Patients included in current study | G6PD tested at screening | Baseline Hb, g/dL (mean (SD)) | Management of patients with anaemia | PQ dosing | Timing of PQ | Published |
|--------------------|-----------------------|--------------------|----------------------|-------------|------------------|-----------------|--------------------------------|---------------------|--|------------------------------------|------------------------|------------------------------------|---|-------------------------------|--|---|--------------|-----------|
| Taylor-2001 [23] | Indonesia | 1995-1998 | Short | 1 | 16-41 | 28 | CQ, CQ+Doxy, Doxy | Full | CQ: Dumex, Indonesia | 63 | 64 | 23 | No | 13.0 (2.1) | No haematinics given | 14day-High Dose | End of Study | Yes |
| Phan-2002 [24] | Vietnam | 1997-2000 | Short | 1 | 19-51 | 28 | CQ, Art | Full | CQ: Mekophar Company, Vietnam | 226 | 232 | 7 | No | 12.6 (1.1) | Not standardised | 5day-Very Low Dose | End of Study | Yes |
| Leslie-2007 [25] | Afghanistan, Pakistan | 2004-2006 | Long | 2 | 4-63 | 28 | CQ, Chlorproguanil-dapsone, SP | Full | | 767 | 767 | 159 | Yes Quantitative (Spectrophotometry) | 12.6 (1.9) | Not standardised | - | - | Yes |
| Ratcliff-2007 [26] | Indonesia | 2004-2005 | Short | 1 | 1-60 | 28 | CQ | Full | CQ: P.T. Bayer, Indonesia | 40 | 61 | 33 | No | 10.4 (2.3) | Not standardised | 14day-Low Dose | End of Study | Yes |
| Leslie-2008 [27] | Pakistan | 2004-2007 | Long | 3 | 4-50 | 365 | CQ, CQ+PQ, CQ+PQ | Full | | 200 | 210 | 122 | Yes Quantitative (Spectrophotometry) | 12.3 (1.8) | Not standardised | None, 14day-High Dose, weekly over 8 weeks (excluded) | Day0 | Yes |
| Ketema-2009 [28] | Ethiopia | 2007-2008 | Long | 1 | 0-45 | 28 | CQ | Full | CQ: Adigrat Pharmaceutical Factory, Ethiopia | 84 | 84 | 83 | No | 12.1 (2.0) | No haematinics given | - | - | Yes |
| Awab-2010 [29] | Afghanistan | 2007-2009 | Long | 3 | 0-71 | 56 | CQ, DP | Full | CQ: IDA, Netherlands | 536 | 536 | 265 | No | 10.9 (1.5) | Not standardised | - | - | Yes |
| Phyo-2011 [30] | Thailand | 2007-2008 | Short | 1 | 1-63 | 63 | CQ, DP | Full | CQ: Government Pharmaceutical Organization, Thailand | 492 | 498 | 243 | Yes Qualitative (FST) | 12.3 (2.0) | Treated if Hct <30%: >13 years ferrous sulphate + folate Children >10kg ferrous sulphate + folate; Children <10kg ferrous fumerate | 14day-High Dose | End of Study | Yes |
| Poravuth-2011 [31] | Multicentred | 2007-2008 | Variable | 5 | 17-51 | 42 | CQ, AS+Pyr | Full | CQ: Shin Poong Pharmaceutical Co, Ltd, Korea | 456 | 456 | 30 | Yes Qualitative (FST) | 12.2 (2.1) | Not standardised | 14day-Low Dose | Day28 | Yes |
| Barber-2013 [32] | Malaysia | 2010-2011 | Short | 1 | 20-49 | 43 | CQ+PQ, varied | Not stated | | 43 | 86 | 3 | Yes Qualitative (FST) | 12.9 (0.8) | Not standardised | 14day-High Dose | Day0 | Yes |
| Hwang-2013 [33] | Ethiopia | 2009-2010 | Long | 2 | 1-65 | 42 | CQ, AL | Full CQ; Partial AL | CQ: AralenH, Sanofi-Aventis, US | 242 | 242 | 120 | No | 13.0 (2.5) | Treated if Hb <10g/dL: Ferrous sulphate, folate + mebendazole (if >1 year) | - | - | Yes |
| Marques-2014 [34] | Brazil | 2007-2008 | Long | 1 | 13-65 | 28 | CQ+PQ | Full | Farmanguinhos, Brazil | 135 | 154 | 135 | No | 13.9 (1.6) | No haematinics given | 7 day-Low Dose | Day0 | Yes |
| Anez-2015 [35] | Bolivia | 2011 | Long | 1 | 5-61 | 28 | CQ | Full | CQ: Macleods Pharmaceuticals Ltd, India | 100 | 100 | 96 | No | 11.1 (1.8) | Treated with iron tablets | 7 day-Low Dose | Day28 | Yes |
| Getachew-2015 [36] | Ethiopia | 2010-2013 | Long | 4 | 0-65 | 28 | CQ | Full | CQ: Ethiopian Federal Ministry of Health | 288 | 288 | 271 | No | 12.5 (2.2) | No haematinics given | - | - | Yes |
| Gomes-2015 [37] | Brazil | 2011-2012 | Long | 1 | 10-56 | 28 | CQ+PQ | Partial CQ and PQ | Coordination of Pharmaceutical Assistance of Amapá | 103 | 94 | 92 | No | 12.7 (2.1) | No haematinics given | 7day-Low Dose | Day0 | Yes |
| Lidia-2015 [38] | Indonesia | 2013 | Short | 1 | 18-88 | 42 | CQ+PQ, DP+PQ | Full | CQ : Novapharin Pharmaceutical, Indonesia | 51 | 51 | 26 | No | 10.2 (0.8) | No haematinics given | 14day-Low Dose | Day0 | Yes |

| PQ: Phapros, Indonesia | | | | | | | | | | | | | | | | | | |
|------------------------|------------|-----------|-------|---|--------|-----|----------------------------|---------------------------------|---|-----|-----|-----|-----|------------|--|--|--------------|-------------------------|
| Rishikesh-2015 [39] | India | 2012-2014 | Long | 1 | 18-76 | 28 | CQ+PQ | Full CQ; Partial PQ | CQ: Bayer Pharmaceuticals, India PQ: IPCA Laboratories, India | 125 | 125 | 124 | Yes | 13·7 (2·2) | Not standardised | 14day-Low Dose, weekly over 8 weeks (excluded) | Day0 | Yes |
| Thanh-2015 [40] | Vietnam | 2009-2011 | Short | 1 | 3-60 | 28 | CQ+PQ | Full | National malaria control Program, Vietnam | 260 | 260 | 260 | No† | 11·5 (2·2) | Treated if Hb ≤8g/dL; Ferrous sulphate + multivitamins | 10day-High Dose | Day0 | Yes |
| Grigg-2016 [41] | Malaysia | 2012-2014 | Short | 3 | 9-35 | 42 | AS+MQ+PQ, CQ+PQ | Full CQ and ASMQ Partial PQ | CQ: Kotra Pharma, Malaysia PQ: Pharmaniaga, Malaysia | 103 | 103 | 8 | Yes | 11·1 (1·5) | Not standardised | 14day-High Dose | Day28 | Yes |
| Ley-2016 [42] | Bangladesh | 2014-2015 | Short | 1 | 6-30 | 30 | AL+PQ, CQ+PQ | Partial AL; Full CQ; Partial PQ | CQ: Jayson Pharmaceuticals, Bangladesh PQ: Globe Pharmaceuticals, Bangladesh | 55 | 66 | 12 | Yes | 11·9 (2·6) | No haematinics given | 14day-Low Dose | Day2 | Yes |
| Pereira-2016 [43] | Brazil | 2013-2015 | Long | 1 | 19-68 | 28 | CQ+PQ | Partial CQ and PQ | Farmanguinhos—Fiocruz, Brazil | 88 | 88 | 86 | No | 13·5 (1·5) | Not standardised | 7-9day-Low Dose | Day0 | Yes |
| Saravu-2016 [44] | India | 2012-2015 | Long | 1 | 18-75 | 28 | CQ+PQ, CQ+PQ(weekly) | Partial CQ and PQ | National Vector Borne Disease Control Programme, India | 161 | 161 | 135 | Yes | 13·2 (1·9) | Not standardised | 14day-Low Dose, weekly over 8 weeks (excluded) | Day0 | Yes |
| Thuan-2016 [45] | Vietnam | 2013-2014 | Short | 2 | 7-67 | 63 | CQ, DP | Full | CQ: National Malaria Program, Vietnam | 128 | 128 | 44 | Yes | 13·5 (1·7) | No haematinics given. | 14day-Low Dose | End of Study | Yes |
| Wangchuk-2016 [46] | Bhutan | 2013-2015 | Short | 5 | 25-53 | 365 | CQ+PQ | Full | | 24 | 28 | 4 | No | 12·8 (0·6) | Not standardised | 14day-Low Dose | Day28 | Yes |
| Abreha-2017 [47] | Ethiopia | 2012-2016 | Long | 2 | 1-67 | 365 | AL, AL+PQ, CQ, CQ+PQ | Partial AL; Full CQ; Partial PQ | CQ: Micro Labs Limited, India PQ: Sanofi-Aventis, US | 398 | 398 | 102 | Yes | 13·6 (1·7) | Not standardised | 14day-Low Dose | Day2 | After literature search |
| Chu-2018a [51] | Thailand | 2012-2014 | Short | 1 | 1-61 | 365 | DP+PQ, DP+PQ, CQ+PQ, CQ+PQ | Full | DP: Guilin Pharmaceutical, China PQ: Government Pharmaceutical Org, Thailand | 680 | 680 | 337 | Yes | 13·0 (2·0) | Treated if Hct <30%. | 7day-High dose, 14day-High dose | Day0 | After literature search |
| Grigg-2018 [50] | Malaysia | 2013-2016 | Short | 1 | 11-29 | 42 | CQ+PQ, variable | Full CQ; Partial PQ | | 57 | 57 | 3 | Yes | 12·5 (0·4) | Not standardised | 14day-High Dose | Day0 | After literature search |
| Siqueira-2017 [48] | Brazil | 2012-2013 | Long | 1 | 1-74 | 42 | AS+AQ, CQ | Full | CQ: Farmanguinhos, Brazil | 380 | 380 | 189 | No | 13·2 (1·7) | No haematinics given | - | - | Yes |
| Chu-2018b [49] | Thailand | 2010 | Short | 1 | 1·5-63 | 365 | CQ, CQ+PQ, AS | Full | CQ: Maneesh Pharmaceuticals & Medopharm, India PQ: Maneesh Pharmaceuticals, India & Government Pharmaceutical Organization, Thailand | 645 | 645 | 409 | Yes | 11·8 (1·7) | Treated if Hct <30% | None, 14day-High Dose | Day0 | After literature search |

Art – artemisinin; AS – artesunate; AL – artemether-lumefantrine; CQ – chloroquine; Doxy – doxycycline; DP – dihydroartemisinin-piperaquine; FST – fluorescent spot test; Hb – haemoglobin; Hct – haematocrit; PQ – primaquine; Pyr – pyronaridine; RDT – rapid diagnostic test; SD – standard deviation; SP – Sulfadoxine-pyrimethamine; * Short relapse periodicity ≤47 days; † One patient tested *post hoc*.

Table S2. Reasons for studies not being included in analysis

| Reason | Number of studies | Studies* |
|---|--------------------------|-----------------|
| No chloroquine treatment arm | 28 | 58-85 |
| Adjunctive drug(s) used | 4 | 86-89 |
| Study of pregnant women | 2 | 90,91 |
| No record of collecting haematological measurements in manuscript | 70 | 92-161 |
| Patient data available but no haematology results | 8 | 162-169 |
| Data not available | 2 | 170,171 |
| Investigators unable to be contacted | 3 | 172-174 |
| Missing minimum data for inclusion | 3 | 175-177 |
| Initial investigator response but no data provided | 2 | 178,179 |
| No response from investigators | 21 | 55,180-199 |

* References of studies not included are provided in Additional File 1: References S1

Table S3. Studies targeted for the analysis but not included

| Author-Year | Treatment arms | Sites | Country | Follow up, days | Randomised | Recruitment period | Treatment arms* | Patients treated with CQ+/-PQ | Haematology collected or reported in publication | Female (%) | Age | | Haemoglobin | | Haematocrit | | G6PD status |
|----------------------------|----------------|-------|-------------------|-----------------|------------|--------------------|--|-------------------------------|--|------------|---------------------|----------------|----------------------|------------|-----------------------|------------|-----------------------------------|
| | | | | | | | | | | | Mean (SD) | Median (range) | Mean (SD) | Median | Mean (SD) | Median | |
| Pukrittayakamee-2000 [180] | 9 | 1 | Thailand | 28 | Yes | 1992-1998 | CQ2+PQ14; CQ2; PQ14; Qu; Mfq; Halo; AS; Am; SP | 60 | Hct | 0 | 25 (9) | Not stated | Not stated | Not stated | 37 (-) [†] | Not stated | Not reported |
| Buchachart-2001 [181] | 1 | 1 | Thailand | 28 | No | 1992-1997 | CQ3+PQ14 | 593 | Hct | 37.1 | 25 (-) [†] | Not stated | Not stated | Not stated | 36.2 (-) | Not stated | 34 deficient 559 normal |
| Fryauff-2002 [182] | 1 | 1 | Indonesia | 28 | No | 1998 | CQ3 | 36 | Hb | 38.9 | 14 (-) | Not stated | 9.5 (-) | Not stated | Not stated | Not stated | Not reported |
| Maguire-2002 [183] | 2 | 1 | Indonesia | 28 | No | Not stated | CQ3 | 73 | Hb | 62.5 | 32 (-) | Not stated | Not stated | Not stated | Not stated | Not stated | Not reported |
| Mohapatra-2002 [174] | 1 | 1 | India | 365 | No | 1998-2000 | CQ3+PQ14 | 110 | Hb | 36.4 | Not stated | Not stated | 8.6 (-) [†] | Not stated | Not stated | Not stated | 4 deficient 106 normal |
| Tjitra-2002 [184] | 3 | 1 | Indonesia | 28 | Yes | 1999 | CQ3; CQ3+SP; AS+SP | 9 | Hb | 33 | 8.8 (-) | Not stated | 10.7 (-) | Not stated | Not stated | Not stated | Not reported |
| Krudsood-2006 [173] | 2 | 1 | Thailand | 28 | Yes | 2004-2005 | CQ3+PQ7; CQ3+EQ | 141 | Hb and Hct | 74.6 | 25.0 (6.7) | Not stated | Not stated | Not stated | 36.6 (-) [†] | Not stated | 7 deficient 134 normal |
| Tasanor-2006 [185] | 2 | 1 | Thailand | 28 | Yes | 2002-2004 | CQ3+PQ14; Qu+PQ14 | 31 | Type not stated | 41.9 | Not stated | 22 | Not stated | Not stated | Not stated | Not stated | 31 normal |
| Kolaczinski-2007 [178] | 2 | 1 | Afghanistan | 42 | Yes | 2004 | CQ3; SP+AS | 96 | Hct | 43 | Not stated | 8.5 | Not stated | Not stated | 35.3 (-) | Not stated | Not reported |
| Krudsood-2007 [186] | 2 | 1 | Thailand | 28 | Yes | 2004-2005 | CQ3; AL | 51 | Hct | 31.4 | 24.3 (6.3) | Not stated | Not stated | Not stated | 37.4 (6.1) | Not stated | Not reported |
| Barnadas-2008 [179] | 1 | 3 | Madagascar | 28 | No | 2006 | CQ3 | 105 | Hb | 53 | 11.2 (-) | Not stated | 10.2 (-) | Not stated | Not stated | Not stated | Not reported |
| Carmona-Fonseca-2008 [176] | 1 | 2 | Colombia | 30 | Yes | 2004 | CQ3; CQ3 | 82 | Hb and Hct | 62 | Not stated | Not stated | 10.3 (2.9) | Not stated | 31.3 (4.8) | Not stated | Not reported |
| Lee-2009 [172] | 1 | 1 | Republic of Korea | 28 | No | 2007 | CQ3+PQ14 | 142 | Hb | 0 | Not stated | 21 (19-50) | 13.6 (1.4) | Not stated | Not stated | Not stated | Not reported |
| Daneshvar-2010 [177] | 1 | 1 | Malaysia | 28 | No | 2006-2007 | CQ3+PQ14 | 23 | Type not stated | 0 | 38.5 (7.6) | Not stated | Not stated | Not stated | Not stated | Not stated | 23 normal |
| Kinzer-2010 [187] | 1 | 1 | Vanuatu | 28 | No | 2005 | CQ3 | 21 | Hb | 66.7 | Not stated | 11 (5-53) | Not stated | Not stated | Not stated | Not stated | Not reported |
| Asih-2011 [188] | 1 | 1 | Indonesia | 28 | No | 2007 | CQ3 | 73 | Hb | 50.7 | Not stated | 13.2 (2-60) | Not stated | 11.8 | Not stated | Not stated | Not reported |
| Maneeboonyang-2011 [189] | 2 | 1 | Thailand | 90 | Yes | 2005-2006 | CQ3+PQ14; CQ3+PQ14 | 92 | Hct | 40 | Not stated | Not stated | Not stated | Not stated | 38.1 (-) [†] | Not stated | Not reported |
| Saravu-2012 [170] | 1 | 1 | India | 28 | No | 2007-2009 | CQ3+PQ14 | 110 | Hb | 26.3 | Not stated | 28.5 | Not stated | Not stated | Not stated | Not stated | All tested – results not reported |

| | | | | | | | | | | | | | | | | | | |
|--------------------------|---|---|----------|-----|-----|------------|---------------------------------------|------|-----------------|------------|-------------|---------------|------------|------------|------------|------------|--------------|-----------------------------------|
| Ganguly-2013 [190] | 2 | 1 | India | 42 | Yes | 2011-2012 | CQ3; CQ3+PQ14 | 250 | Hb | 10.8 | 25.2 (-) | Not stated | 12.6 (-) | Not stated | Not stated | Not stated | Not stated | 250 normal |
| Liu-2013 [191] | 2 | 1 | China | 365 | Yes | 2009-2010 | CQ3+PQ8; ART+NQ | 132 | Hb | 14 | Not stated | Not stated | 14.6 (1.7) | Not stated | Not stated | Not stated | Not stated | Not reported |
| Macareo-2013 [192] | 2 | 1 | Thailand | 90 | Yes | Not stated | CQ5+PQ14; CQ5+TND | 6 | Type not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | 6 normal |
| Amaratunga-2014 [193] | 1 | 1 | Cambodia | 28 | No | 2012-2013 | CQ3 | 87 | Hct | 20.7 | Not stated | 26 (4-68) | Not stated | Not stated | Not stated | 39 | Not reported | |
| Llanos-Cuentas-2014 [55] | 6 | 4 | Brazil | 180 | Yes | 2011-2013 | CQ3; CQ3+PQ14; CQ3+TQ; CQ3+TQ; CQ3+TQ | 104 | Hb | 28.8 | 34.8 (-) | Not stated | 12.5 (-) | Not stated | Not stated | Not stated | Not stated | 104 normal |
| Rajgor-2014 [194] | | 1 | India | 180 | Yes | Not stated | CQ3; CQ3+PQ7; CQ3+PQ14; CQ3+PQ14 | 1556 | Hb | 4.8 | 31.2 (-) | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | All tested – results not reported |
| Shalini-2014 [175] | 1 | 1 | India | 28 | No | 2010 | CQ3 | 125 | Hb | 5 | 25.9 (10.5) | Not stated | 14.4 (1) | Not stated | Not stated | Not stated | Not stated | Not reported |
| Assefa-2015 [195] | 1 | 1 | Ethiopia | 28 | No | 2014 | CQ3 | 63 | Hb | 41.7 | Not stated | 23 (4-59) | 11.5 (-) | Not stated | Not stated | Not stated | Not stated | Not reported |
| Pareek-2015 [196] | 3 | 8 | India | 180 | Yes | Not stated | CQ3+PQ7; CQ3+PQ14; CQ3+PQ14 | 358 | Hb | 17.3 | Not stated | 20 | Not stated | Not stated | Not stated | Not stated | Not stated | 358 normal |
| Beyene-2016 [197] | 1 | 1 | Ethiopia | 28 | No | 2014 | CQ3 | 76 | Hb | 32 | Not stated | 19 (3-54) | 12.2 (-) | Not stated | Not stated | Not stated | Not stated | Not reported |
| Negreiros-2016 [198] | 1 | 1 | Brazil | 168 | No | 2014 | CQ3+PQ7 | 119 | Hb | 45.4 | Not stated | 23.4 (5-67.3) | Not stated | 14.3 | Not stated | Not stated | Not stated | 119 normal |
| Valecha-2016 [171] | 2 | 9 | India | 42 | Yes | 2011-2013 | CQ3+PQ14; ATM+PIP+PQ14 | 158 | Hct | 8.2 | 33.7 (13.5) | Not stated | Not stated | Not stated | 37.8 (5.3) | 37.75 | 158 normal | |
| Seifu-2017 [199] | 1 | 1 | Ethiopia | 28 | No | 2013 | CQ3 | 87 | Hct | 29.7 | Not stated | 20 (1-65) | Not stated | Not stated | 35.5 (-) | Not stated | Not reported | |

AL – artemether-lumefantrine; Am - artemether; ART - artemisinin; AS – artesunate; ATM – arterolane maleate; Az – azithromycin; BQ – bulaquine; CQ – chloroquine; EQ – elubaquine; Halo – halofantrine; Hb – haemoglobin; Hct – haematocrit; Mfq – mefloquine; NQ - naphthoquine; PIP – piperaquine; PQ – primaquine; Qu – Quinine; SD – standard deviation; SP – sulfadoxine-pyrimethamine; TND – tinidazole; TQ – tafenoquine; * Treatment arms in study described as drug and number of days given if CQ+/-PQ; † Recalculated from subgroups within study.

Table S4. Country of origin and background prevalence of G6PD deficiency in patients with unknown G6PD status (n=1,701)

| Country | Number of included patients with unknown G6PD status | Background prevalence of G6PD deficiency (%)* |
|----------------|---|--|
| Afghanistan | 265 | 13 |
| Bhutan | 4 | 10 |
| Bolivia | 96 | 0 |
| Brazil | 502 | 8 |
| Ethiopia | 474 | 2 |
| India | 11 | 14 |
| Indonesia | 82 | 12 |
| Thailand | 1 | 24 |
| Vietnam | 266 | 15 |

* Percentage with G6PD deficiency was based upon data from Howes *et al*, PLoS Med 2012; 9(11):e100139.

In total 136 (8.0%) of the 1,701 patients would be expected to have G6PD deficiency, assuming equivalent prevalence in patients with *P. vivax* to the background population.

Table S5. Planned primaquine regimens

| Total planned dose (mg/kg) | Regimen | Country | Number (%) n=1,446 |
|---------------------------------------|------------------------|----------------|-------------------------------|
| 3·5 | 0·25 mg/kg/d x 14 days | Indonesia | 259 (19·7%) |
| 3·5 | 0·25 mg/kg/d x 14 days | India | 26 (19·7%) |
| 3·5-4·5 | 0·5 mg/kg/d x 7-9 days | Brazil | 313 (28·9%) |
| 5·0 | 0·5 mg/kg/d x 10 days | Vietnam | 260 (18·0%) |
| 7·0 | 1 mg/kg/d x 7 days | Thailand | 170 (11·8%) |
| 7·0 | 0·5 mg/kg/d x 14 days | Thailand | 359 (28·9%) |
| 7·0 | 0·5 mg/kg/d x 14 days | Pakistan | 55 (28·9%) |
| 7·0 | 0·5 mg/kg/d x 14 days | Malaysia | 4 (28·9%) |



Figure S1. Study sites for clinical trials

Green – included; Orange – targeted but not included.

Table S6. Demographics, baseline characteristics and baseline haemoglobin measurements of G6PD normal patients

| | Chloroquine alone | | | Chloroquine plus primaquine | | | Overall | | |
|--|--------------------|--------------|--------------|-----------------------------|--------------|--------------|--------------------|--------------|--------------|
| | Number (%)* | Mean Hb (SD) | Range | Number (%)* | Mean Hb (SD) | Range | Number (%)* | Mean Hb (SD) | Range |
| Overall | 856 (100) | 12.4 (1.9) | 6.5 to 18.1 | 836 (100) | 12.8 (2.0) | 5.4 to 19.0 | 1692 (100) | 12.6 (2.0) | 5.4 to 19.0 |
| Parasitaemia, parasites per uL; median (IQR) | 5280 (1793, 12434) | | | 2688 (945, 8792) | | | 3880 (1280, 10360) | | |
| <i>Gender</i> | | | | | | | | | |
| Female | 344 (40.2) | 11.9 (1.7) | 6.5 to 17.3 | 233 (27.9) | 11.7 (1.6) | 7.3 to 17.4 | 577 (34.1) | 11.8 (1.7) | 6.5 to 17.4 |
| Male | 512 (59.8) | 12.8 (2.0) | 7.0 to 18.1 | 603 (72.1) | 13.3 (2.0) | 5.4 to 19.0 | 1115 (65.9) | 13.0 (2.0) | 5.4 to 19.0 |
| <i>Age category, years</i> | | | | | | | | | |
| <5 | 56 (6.5) | 10.4 (1.5) | 7.0 to 14.0 | 29 (3.5) | 10.5 (1.5) | 7.3 to 14.1 | 85 (5.0) | 10.4 (1.5) | 7.0 to 14.1 |
| 5 to <15 | 331 (38.7) | 11.7 (1.6) | 7.5 to 16.0 | 194 (23.2) | 11.6 (1.5) | 7.5 to 16.3 | 525 (31.0) | 11.7 (1.6) | 7.5 to 16.3 |
| ≥15 | 469 (54.8) | 13.1 (1.9) | 6.5 to 18.1 | 613 (73.3) | 13.3 (1.9) | 5.4 to 19.0 | 1082 (63.9) | 13.2 (1.9) | 5.4 to 19.0 |
| <i>Weight category, kg</i> | | | | | | | | | |
| 5 to <15 | 63 (7.4) | 10.4 (1.7) | 7.0 to 14.8 | 31 (3.7) | 10.4 (1.3) | 7.3 to 13.2 | 94 (5.6) | 10.4 (1.5) | 7.0 to 14.8 |
| 15 to <25 | 192 (22.4) | 11.5 (1.5) | 7.5 to 16.0 | 97 (11.6) | 11.3 (1.4) | 8.2 to 15.9 | 289 (17.1) | 11.4 (1.5) | 7.5 to 16.0 |
| 25 to <35 | 84 (9.8) | 12.1 (1.4) | 9.0 to 15.1 | 62 (7.4) | 11.8 (1.5) | 7.5 to 15.1 | 146 (8.6) | 12.0 (1.4) | 7.5 to 15.1 |
| 35 to <45 | 116 (13.6) | 12.2 (1.8) | 7.1 to 17.1 | 90 (10.8) | 12.4 (1.8) | 6.4 to 17.1 | 206 (12.2) | 12.3 (1.8) | 6.4 to 17.1 |
| 45 to <55 | 236 (27.6) | 13.1 (1.7) | 6.5 to 17.8 | 244 (29.2) | 13.0 (1.9) | 5.4 to 17.8 | 480 (28.4) | 13.1 (1.8) | 5.4 to 17.8 |
| 55 to <80 | 162 (18.9) | 13.6 (1.8) | 7.1 to 18.1 | 285 (34.1) | 13.6 (1.9) | 5.8 to 19.0 | 447 (26.4) | 13.6 (1.9) | 5.8 to 19.0 |
| ≥80 | 3 (0.4) | 14.3 (0.2) | 14.1 to 14.5 | 27 (3.2) | 14.2 (1.5) | 10.5 to 16.8 | 30 (1.8) | 14.2 (1.4) | 10.5 to 16.8 |
| <i>Relapse Periodicity</i> | | | | | | | | | |
| Long | 332 (38.8) | 12.7 (1.9) | 7.1 to 18.1 | 303 (36.2) | 13.3 (2.0) | 5.4 to 18.2 | 635 (37.5) | 13.0 (2.0) | 5.4 to 18.2 |
| Short | 524 (61.2) | 12.2 (1.9) | 6.5 to 17.8 | 533 (63.8) | 12.6 (1.9) | 7.3 to 19.0 | 1057 (62.5) | 12.4 (1.9) | 6.5 to 19.0 |
| <i>Geographical region</i> | | | | | | | | | |
| Asia-Pacific | 757 (88.4) | 12.2 (1.9) | 6.5 to 17.8 | 836 (100) | 12.8 (2.0) | 5.4 to 19.0 | 1593 (94.1) | 12.5 (2.0) | 5.4 to 19.0 |
| The Americas | 0 (0) | - | - | 0 (0) | - | - | 0 (0) | - | - |
| Africa | 99 (11.6) | 13.6 (1.7) | 10.2 to 18.1 | 0 (0) | - | - | 99 (5.9) | 13.6 (1.7) | 10.2 to 18.1 |

Hb – haemoglobin; SD – standard deviation; IQR – interquartile range; * Number of patients (percentage of total patients in group) unless otherwise specified.

Table S7. Demographics, baseline characteristics and baseline haemoglobin measurements of patients with unknown G6PD status

| | Chloroquine alone | | | Chloroquine plus primaquine | | | Overall | | |
|--|-------------------|--------------|-------------|-----------------------------|--------------|-------------|-------------------|--------------|-------------|
| | Number (%)* | Mean Hb (SD) | Range | Number (%)* | Mean Hb (SD) | Range | Number (%)* | Mean Hb (SD) | Range |
| Overall | 1092 (100) | 12.1 (2.2) | 6.0 to 18.7 | 609 (100) | 12.5 (2.2) | 4.0 to 18.9 | 1701 (100) | 12.2 (2.2) | 4.0 to 18.9 |
| Parasitaemia, parasites per uL; median (IQR) | 2696 (1118, 6302) | | | 2720 (870, 5720) | | | 2698 (1026, 6120) | | |
| <i>Gender</i> | | | | | | | | | |
| Female | 422 (38.6) | 11.7 (2.0) | 6.0 to 17.4 | 205 (33.7) | 11.6 (1.9) | 4.0 to 17.2 | 627 (36.9) | 11.7 (2.0) | 4.0 to 17.4 |
| Male | 670 (61.4) | 12.3 (2.2) | 6.6 to 18.7 | 404 (66.3) | 12.9 (2.3) | 4.9 to 18.9 | 1074 (63.1) | 12.6 (2.2) | 4.9 to 18.9 |
| <i>Age category, years</i> | | | | | | | | | |
| <5 | 169 (15.5) | 10.8 (2.2) | 6.0 to 16.6 | 43 (7.1) | 10.1 (2.0) | 4.9 to 13.4 | 212 (12.5) | 10.7 (2.1) | 4.9 to 16.6 |
| 5 to <15 | 355 (32.5) | 11.5 (2.0) | 6.6 to 17.4 | 132 (21.7) | 11.3 (1.8) | 5.5 to 14.5 | 487 (28.6) | 11.5 (2.0) | 5.5 to 17.4 |
| ≥15 | 568 (52.0) | 12.8 (2.0) | 6.2 to 18.7 | 434 (71.3) | 13.1 (2.1) | 4.0 to 18.9 | 1002 (58.9) | 12.9 (2.0) | 4.0 to 18.9 |
| <i>Weight category, kg</i> | | | | | | | | | |
| 5 to <15 | 132 (12.1) | 10.4 (2.0) | 6.0 to 16.3 | 52 (8.5) | 10.2 (1.8) | 5.2 to 13.4 | 184 (10.8) | 10.4 (1.9) | 5.2 to 16.3 |
| 15 to <25 | 244 (22.3) | 11.6 (2.1) | 6.9 to 16.6 | 75 (12.3) | 10.9 (1.9) | 4.9 to 14.5 | 319 (18.8) | 11.4 (2.1) | 4.9 to 16.6 |
| 25 to <35 | 98 (9.0) | 11.4 (1.8) | 6.6 to 16.2 | 32 (5.3) | 11.4 (1.9) | 7.8 to 14.6 | 130 (7.6) | 11.4 (1.8) | 6.6 to 16.2 |
| 35 to <45 | 79 (7.2) | 11.8 (1.9) | 6.5 to 17.4 | 63 (10.3) | 11.7 (2.1) | 5.8 to 15.3 | 142 (8.3) | 11.8 (2.0) | 5.8 to 17.4 |
| 45 to <55 | 157 (14.4) | 12.5 (2.2) | 6.2 to 18.7 | 93 (15.3) | 12.6 (2.1) | 6.0 to 18.1 | 250 (14.7) | 12.6 (2.1) | 6.0 to 18.7 |
| 55 to <80 | 311 (28.5) | 12.9 (1.9) | 7.0 to 18.0 | 223 (36.6) | 13.5 (1.8) | 4.0 to 18.9 | 534 (31.4) | 13.1 (1.9) | 4.0 to 18.9 |
| ≥80 | 71 (6.5) | 13.8 (1.4) | 9.9 to 16.5 | 71 (11.7) | 13.9 (1.7) | 8.2 to 17.9 | 142 (8.3) | 13.8 (1.6) | 8.2 to 17.9 |
| <i>Relapse Periodicity</i> | | | | | | | | | |
| Long | 1024 (93.8) | 12.1 (2.1) | 6.0 to 18.0 | 324 (53.2) | 13.5 (1.8) | 4.0 to 18.9 | 1348 (79.2) | 12.4 (2.2) | 4.0 to 18.9 |
| Short | 68 (6.2) | 11.7 (2.4) | 6.2 to 18.7 | 285 (46.8) | 11.4 (2.2) | 4.9 to 18.1 | 353 (20.8) | 11.5 (2.2) | 4.9 to 18.7 |
| <i>Geographical region</i> | | | | | | | | | |
| Asia-Pacific | 333 (30.5) | 11.1 (1.7) | 6.2 to 18.7 | 296 (48.6) | 11.5 (2.2) | 4.9 to 18.1 | 629 (37.0) | 11.3 (2.0) | 4.9 to 18.7 |
| The Americas | 285 (26.1) | 12.5 (2.0) | 7.0 to 17.4 | 313 (51.4) | 13.5 (1.8) | 4.0 to 18.9 | 598 (35.2) | 13.0 (2.0) | 4.0 to 18.9 |
| Africa | 474 (43.4) | 12.6 (2.3) | 6.0 to 18.0 | 0 (0) | - | - | 474 (27.9) | 12.6 (2.3) | 6.0 to 18.0 |

Hb – haemoglobin; SD – standard deviation; IQR – interquartile range; * Number of patients (percentage of total patients in group) unless otherwise specified.

Table S8. Comparison of baseline characteristics between included and targeted studies

| Characteristic | Included studies (n=29) | Targeted studies* (n=31) |
|----------------------------------|----------------------------|-----------------------------|
| Region | | |
| Asia-Pacific, studies (%) | 20 (69.0%) | 24 (77.4%) |
| Africa, studies (%) | 4 (13.8%) | 4 (12.9%) |
| The Americas, studies (%) | 5 (17.2%) | 3 (9.7%) |
| Year of enrolment [†] | | |
| Pre-2009, studies (%) | 9 (31.0%) | 16 (59.3%) [‡] |
| 2009-2017, studies (%) | 20 (69.0%) | 11 (40.7%) [‡] |
| Age, mean (SD) | 22.1 (15.1) | 28.3 (4.9) [§] |
| Female, % of patients, mean (SD) | 35.4% | 22.2 (19.5) [¶] |
| Baseline Hb, mean (SD) | 12.4 (2.1) | 12.0 (1.3) |

SD – standard deviation; Hb – haemoglobin; * Age, female percentage and baseline haemoglobin of targeted studies calculated using frequency weighted mean according to number of patients treated with chloroquine alone or chloroquine and primaquine; † Year of enrolment defined as the year study enrolment completed; ‡ Year of enrolment not available from four studies; § Mean age not available from 17 studies; ¶ Percentage not available from one study; || Percentage not available from 11 studies and haemoglobin recalculated from haematocrit for eight studies.

Table S9. Risk factors for baseline anaemia (Hb < 10 g/dL)

| | Number with anaemia (%) n=3,421 | Unadjusted Odds Ratio (95% CI) | p value | Adjusted Odds Ratio (95% CI) | p value |
|--|------------------------------------|-----------------------------------|---------|---------------------------------|---------|
| <i>Gender</i> | | | | | |
| Male | 205/2211 (9.3%) | Reference | - | Reference | - |
| Female | 180/1210 (14.9%) | 1.71 (1.27, 2.29) | 0.0003 | 1.34 (1.05, 1.71) | 0.0188 |
| <i>Age category, years</i> | | | | | |
| ≥15 | 118/2107 (5.6%) | Reference | - | Reference | - |
| <5 | 114/297 (38.4%) | 10.50 (5.86, 18.82) | <0.0001 | 10.37 (6.09, 17.67) | <0.0001 |
| 5 to <15 | 153/1017 (15.0%) | 2.98 (2.07, 4.31) | <0.0001 | 3.07 (2.07, 4.54) | <0.0001 |
| <i>G6PD status</i> | | | | | |
| Normal | 149/1692 (8.8%) | Reference | - | Reference | - |
| Borderline | 0/3 (0.0%) | - | - | - | - |
| Deficient | 4/25 (16.0%) | 1.97 (0.79, 4.94) | 0.1466 | 2.88 (1.14, 7.32) | 0.0259 |
| Not known | 232/1701 (13.6%) | 1.64 (0.88, 3.03) | 0.1174 | 1.59 (0.93, 2.73) | 0.0897 |
| <i>Relapse periodicity</i> | | | | | |
| Long | 199/1987 (10.0%) | Reference | - | Reference | - |
| Short | 186/1434 (13.0%) | 1.34 (0.69, 2.60) | 0.3889 | 1.94 (1.01, 3.71) | 0.0470 |
| <i>Geographical region</i> | | | | | |
| Asia-Pacific | 275/2247 (12.2%) | Reference | - | - | - |
| Africa | 65/598 (11.3%) | 0.91 (0.37, 2.25) | 0.8416 | - | - |
| The Americas | 45/576 (7.5%) | 0.58 (0.16, 2.19) | 0.4247 | - | - |
| <i>Parasitaemia, parasites per uL every ten times increase</i> | | | | | |
| | - | 1.20 (0.84, 1.70) | 0.3244 | 0.96 (0.72, 1.28) | 0.7738 |
| <i>Temperature >37.5°C at baseline*</i> | | | | | |
| Absent | 179/1808 (9.9%) | Reference | - | Reference | - |
| Present | 150/1280 (11.7%) | 1.21 (0.83, 1.75) | 0.3166 | 1.10 (0.76, 1.61) | 0.6100 |

Covariates to include in the model were decided *a priori*. Geographical region was not included in the multivariable model due to collinearity with relapse periodicity. * Data on baseline temperature was only available for 3,088 patients.

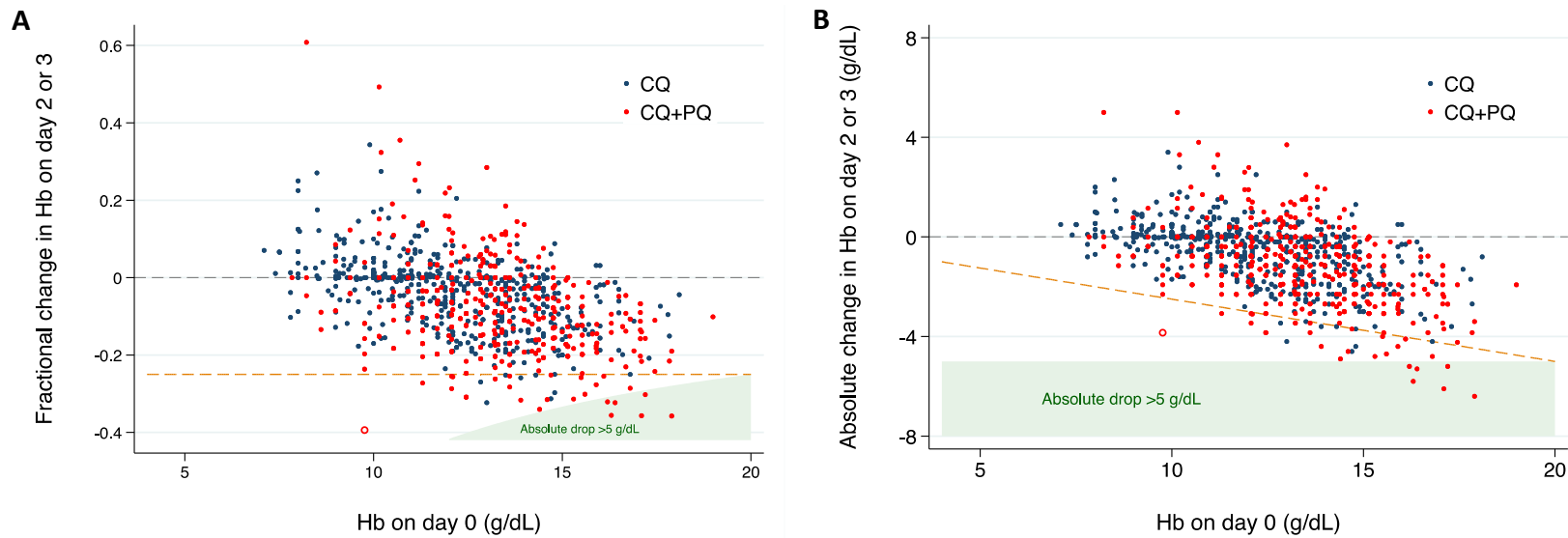


Figure S2. Relationship between day 0 haemoglobin and haemoglobin on day 2/3 in patients treated with chloroquine alone (n=610) and chloroquine plus primaquine (n=471) as (A) fractional change or (B) absolute change.

Open circle represents the single patient with a clinically significant fall >25% to <7 g/dL at day 2/3 (male patient with normal G6PD status). Dashed orange line represents a fractional fall of 25%. The fitted linear regression model estimated the relationship in patients with CQ alone to be: Absolute change in Hb on day 2/3 = (Day 0 Hb - 11.55)/-1.04. The baseline Hb correlates negatively with the fractional change in Hb at day 2/3 ($r=-0.463$ [95%CI -0.509 to -0.415], $p<0.0001$).

Table S10. Sensitivity analysis for estimated mean change in haemoglobin for patients treated with chloroquine and primaquine compared to chloroquine (reference group)

| Timepoint | Range of estimated mean Hb change g/dL | Coefficient of Variation (%)* |
|------------------|---|--------------------------------------|
| Day of nadir | -0.23 to 0 [†] | 23.53 |
| Day 7 | -0.45 to -0.26 | 7.44 |
| Day 42 | 0.33 to 0.65 | 9.19 |

Sensitivity analysis was generated by removing each study site one at a time

There were a total of 47 sites; * The coefficient of variation calculated as standard deviation divided by the mean of the estimates; † Removal of 45 of the 47 study sites had an estimated mean haemoglobin (Hb) change of -0.19 to -0.08 g/dL at nadir. Removal of patients from Jalalabad from Awab *et al* [29] led to an estimated mean Hb change of 0 g/dL at nadir and removal of Thanh *et al* [40] led to estimated change of -0.23 g/dL.

Table S11. Factors associated with change in haemoglobin between day 0 and day 2/3 in G6PD normal patients

| | Number of patients n=672 | Crude change in haemoglobin*, g/dL (95% CI) | p value | Adjusted change in haemoglobin, g/dL (95% CI) | p value |
|--|-----------------------------|--|---------|--|---------|
| Baseline haemoglobin, g/dL every gram increase | 672 | -0.28 (-0.32, -0.24) | <0.0001 | -0.37 (-0.42, -0.32) | <0.0001 |
| <i>Gender</i> | | | | | |
| Male | 417 | Reference | - | Reference | - |
| Female | 255 | -0.34 (-0.52, -0.16) | 0.0002 | -0.37 (-0.54, -0.19) | <0.0001 |
| <i>Age category, years</i> | | | | | |
| ≥15 | 19 | Reference | - | Reference | - |
| <5 | 251 | -0.96 (-1.47, -0.44) | 0.0003 | -0.93 (-1.43, -0.42) | 0.0003 |
| 5 to <15 | 402 | -0.52 (-0.72, -0.32) | <0.0001 | -0.58 (-0.78, -0.38) | <0.0001 |
| <i>Primaquine use</i> | | | | | |
| No | 338 | Reference | - | Reference | - |
| Yes | 334 | -0.18 (-0.59, 0.22) | 0.3773 | -0.14 (-0.41, 0.14) | 0.3296 |
| <i>Relapse periodicity</i> | | | | | |
| Long | 260 | Reference | - | Reference | - |
| Short | 412 | -0.12 (-0.44, 0.21) | 0.4808 | -0.33 (-0.62, -0.04) | 0.0259 |
| Chloroquine dose, mg/kg, every mg/kg increase | 672 | -0.04 (-0.07, -0.004) | 0.0276 | -0.02 (-0.06, 0.01) | 0.1838 |
| Parasitaemia, parasites per uL every ten times increase | 672 | -0.31 (-0.44, -0.17) | <0.0001 | -0.33 (-0.46, -0.20) | <0.0001 |

Analysis undertaken in 672 patients with haemoglobin data available for day 2/3; * Adjusted for baseline haemoglobin

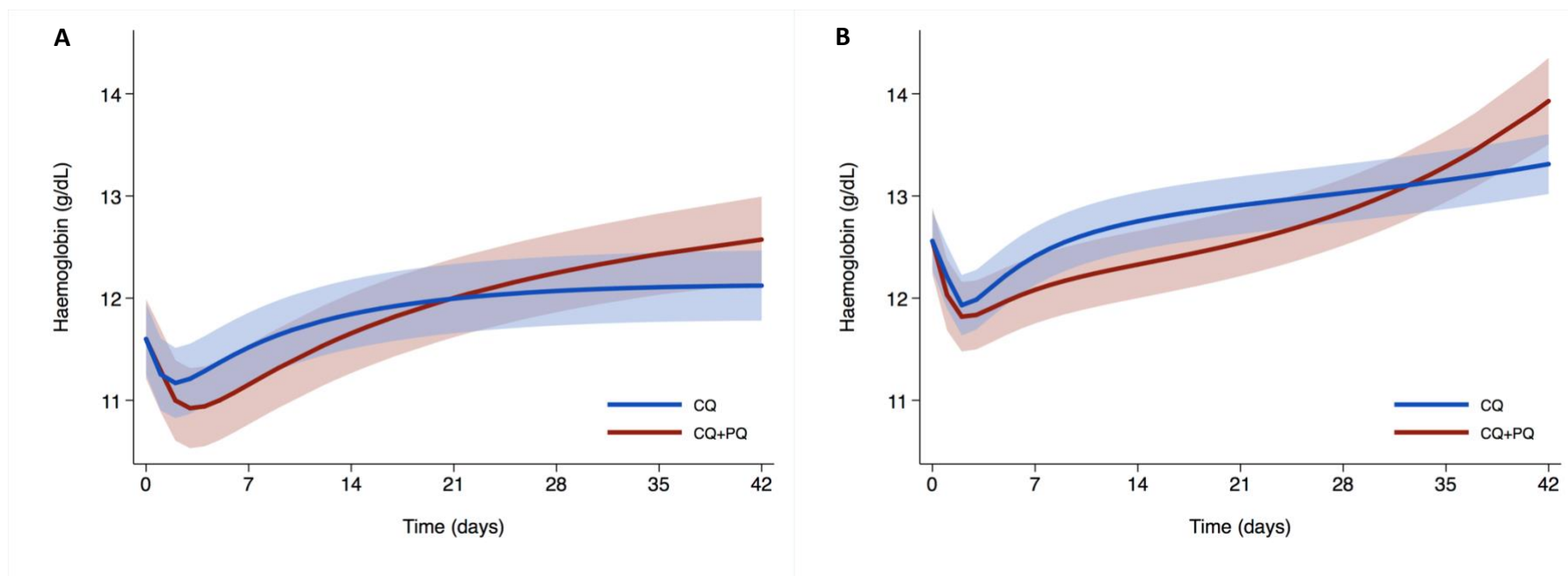


Figure S3. Mean haemoglobin versus time profiles for (a) female patients treated with chloroquine with (n=438) or without (n=772) primaquine and (b) male patients treated with chloroquine with (n=1,008) or without (n=1,203) primaquine.

CQ – chloroquine; PQ – primaquine. Profiles for chloroquine alone and chloroquine plus primaquine adjusted to the same baseline haemoglobin. Figures derived from linear mixed effect models with fractional polynomial terms for time. Shaded regions show 95% confidence intervals.

Table S12: Patients with a Hb fall >25% leading to development of severe anaemia (Hb <7 g/dL) during the first 42 days

| | Age (yrs) | Gender | Study | Country | Periodicity | CQ total dose (mg/kg) | G6PD status | Primaquine | PQ total dose (mg/kg) | PQ regimen | Recurrence | Day0 Hb (g/dL) | Minimum Hb (g/dL) | Absolute Hb drop (g/dL) | Percentage Hb drop | Day of minimum |
|---|-----------|--------|---------------|----------|-------------|-----------------------|-------------|------------|-----------------------|--------------------|------------|----------------|-------------------|-------------------------|--------------------|----------------|
| 1 | 1.5 | M | Getachew-2015 | Ethiopia | Long | 44.12 | Unknown | No | - | None | No | 11.0 | 6.6 | 4.4 | 40.0% | 28 |
| 2 | 3 | F | Thanh-2015 | Vietnam | Short | 22.50 | Unknown | Yes | 3.75 | 10 days from day 0 | No | 10.5 | 6.6 | 3.9 | 37.1% | 28 |
| 3 | 5 | F | Thanh-2015 | Vietnam | Short | 30.00 | Unknown | Yes | 5.00 | 10 days from day 0 | No | 13.3 | 6.5 | 6.8 | 51.1% | 28 |
| 4 | 5 | M | Chu-2018a | Thailand | Short | 29.87 | Normal | Yes | 7.11 | 7 days from day 0 | No | 9.8 | 5.9 | 3.8 | 39.4% | 3 |
| 5 | 8 | M | Thanh-2015 | Vietnam | Short | 26.47 | Unknown | Yes | 4.41 | 10 days from day 0 | No | 11.0 | 4.6 | 6.4 | 58.2% | 14 |
| 6 | 9 | M | Thanh-2015 | Vietnam | Short | 27.27 | Unknown | Yes | 5.11 | 10 days from day 0 | No | 13.1 | 5.9 | 7.2 | 55.0% | 14 |
| 7 | 26 | M | Thanh-2015 | Vietnam | Short | 28.30 | Deficient | Yes | 4.60 | 10 days from day 0 | No | 14.0 | 6.6 | 7.4 | 52.9% | 14 |
| 8 | 30 | F | Chu-2018a | Thailand | Short | 23.67 | Normal | Yes | 7.68 | 7 days from day 0 | No | 13.2 | 5.9 | 7.3 | 55.3% | 7 |
| 9 | 40 | F | Thanh-2015 | Vietnam | Short | 29.27 | Unknown | Yes | 5.03 | 10 days from day 0 | No | 8.3 | 5.0 | 3.3 | 39.8% | 14 |

Table S13. Patients with haemoglobin falling >5 g/dL during the first 42 days

| | Age (yrs) | Gender | Study | Country | Periodicity | CQ total dose (mg/kg) | G6PD status | PQ | PQ total dose (mg/kg) | PQ regimen | Recurrence | Day0 Hb (g/dL) | Minimum Hb (g/dL) | Absolute Hb drop (g/dL) | Percentage Hb drop | Day of minimum |
|----|-----------|--------|---------------|-----------|-------------|-----------------------|-------------|-----|-----------------------|--------------------|------------|----------------|-------------------|-------------------------|--------------------|----------------|
| 1 | 25 | F | Leslie-2007 | Pakistan | Long | 26-16 | Normal | No | - | None | No | 16.5 | 11.1 | 5.4 | 32.7% | 1 |
| 2 | 28 | M | Getachew-2015 | Ethiopia | Long | 29-59 | Unknown | No | - | None | No | 14.9 | 8.0 | 6.9 | 46.3% | 28 |
| 3 | 38 | M | Phyo-2011 | Thailand | Short | 23-86 | Normal | No | - | None | No | 16.3 | 9.8 | 6.5 | 40.1% | 23 |
| 4 | 41.3 | M | Taylor-2001 | Indonesia | Short | 34-62 | Unknown | No | - | None | Yes | 13.8 | 8.2 | 5.6 | 40.6% | 7 |
| 5 | 5 | F | Thanh-2015 | Vietnam | Short | 30-00 | Unknown | Yes | 5.00 | 10 days | No | 13.3 | 6.5 | 6.8 | 51.1% | 28 |
| 6 | 8 | M | Thanh-2015 | Vietnam | Short | 26-47 | Unknown | Yes | 4.41 | 10 days | No | 11.0 | 4.6 | 6.4 | 58.2% | 14 |
| 7 | 9 | M | Thanh-2015 | Vietnam | Short | 27-27 | Unknown | Yes | 5.11 | 10 days | No | 13.1 | 5.9 | 7.2 | 55.0% | 14 |
| 8 | 10 | F | Chu-2018a | Thailand | Short | 26-78 | Normal | Yes | 7.24 | 7 days from day 0 | No | 13.2 | 7.5 | 5.8 | 43.6% | 5 |
| 9 | 14 | M | Chu-2018a | Thailand | Short | 25-36 | Normal | Yes | 7.50 | 14 days from day 0 | No | 16.3 | 9.4 | 6.9 | 42.5% | 8 |
| 10 | 15 | M | Chu-2018a | Thailand | Short | 25-36 | Normal | Yes | 7.50 | 14 days from day 0 | No | 14.4 | 8.6 | 5.8 | 40.1% | 6 |
| 11 | 17 | M | Marques-2014 | Brazil | Long | 23-08 | Unknown | Yes | 3.23 | 7 to 9 days | No | 16.3 | 10.5 | 5.8 | 35.6% | 3 |
| 12 | 18 | M | Marques-2014 | Brazil | Long | 24-19 | Unknown | Yes | 3.39 | 7 to 9 days | No | 16.2 | 11.0 | 5.2 | 32.1% | 3 |
| 13 | 21 | M | Thanh-2015 | Vietnam | Short | 25-00 | Unknown | Yes | 4.69 | 10 days | No | 16.8 | 11.1 | 5.7 | 33.9% | 28 |
| 14 | 22 | M | Thanh-2015 | Vietnam | Short | 27-27 | Unknown | Yes | 4.69 | 10 days | No | 15.3 | 10.0 | 5.3 | 34.6% | 14 |
| 15 | 23 | F | Marques-2014 | Brazil | Long | 29-41 | Unknown | Yes | 4.12 | 7 to 9 days | No | 17.2 | 12.0 | 5.2 | 30.2% | 3 |
| 16 | 25 | M | Marques-2014 | Brazil | Long | 21-74 | Unknown | Yes | 3.04 | 7 to 9 days | No | 17.1 | 11.0 | 6.1 | 35.7% | 3 |
| 17 | 25 | F | Chu-2018a | Thailand | Short | 24-40 | Normal | Yes | 7.50 | 14 days from day 0 | No | 12.8 | 7.8 | 5.0 | 38.9% | 4 |
| 18 | 26 | M | Thanh-2015 | Vietnam | Short | 28-30 | Deficient | Yes | 4.60 | 10 days | No | 14.0 | 6.6 | 7.4 | 52.9% | 14 |
| 19 | 26 | M | Thanh-2015 | Vietnam | Short | 25-00 | Unknown | Yes | 4.69 | 10 days | No | 15.7 | 8.8 | 6.9 | 43.9% | 14 |
| 20 | 28 | M | Chu-2018a | Thailand | Short | 24-85 | Normal | Yes | 7.35 | 7 days from day 0 | No | 14.4 | 7.1 | 7.3 | 50.8% | 4 |
| 21 | 30 | M | Marques-2014 | Brazil | Long | 19-74 | Unknown | Yes | 2.96 | 7 to 9 days | No | 17.9 | 11.5 | 6.4 | 35.8% | 3 |
| 22 | 30 | F | Chu-2018a | Thailand | Short | 23-67 | Normal | Yes | 7.68 | 7 days from day 0 | No | 13.2 | 5.9 | 7.3 | 55.3% | 7 |
| 23 | 40 | M | Marques-2014 | Brazil | Long | 23-44 | Unknown | Yes | 3.28 | 7 to 9 days | Yes | 16.4 | 11.1 | 5.3 | 32.3% | 3 |

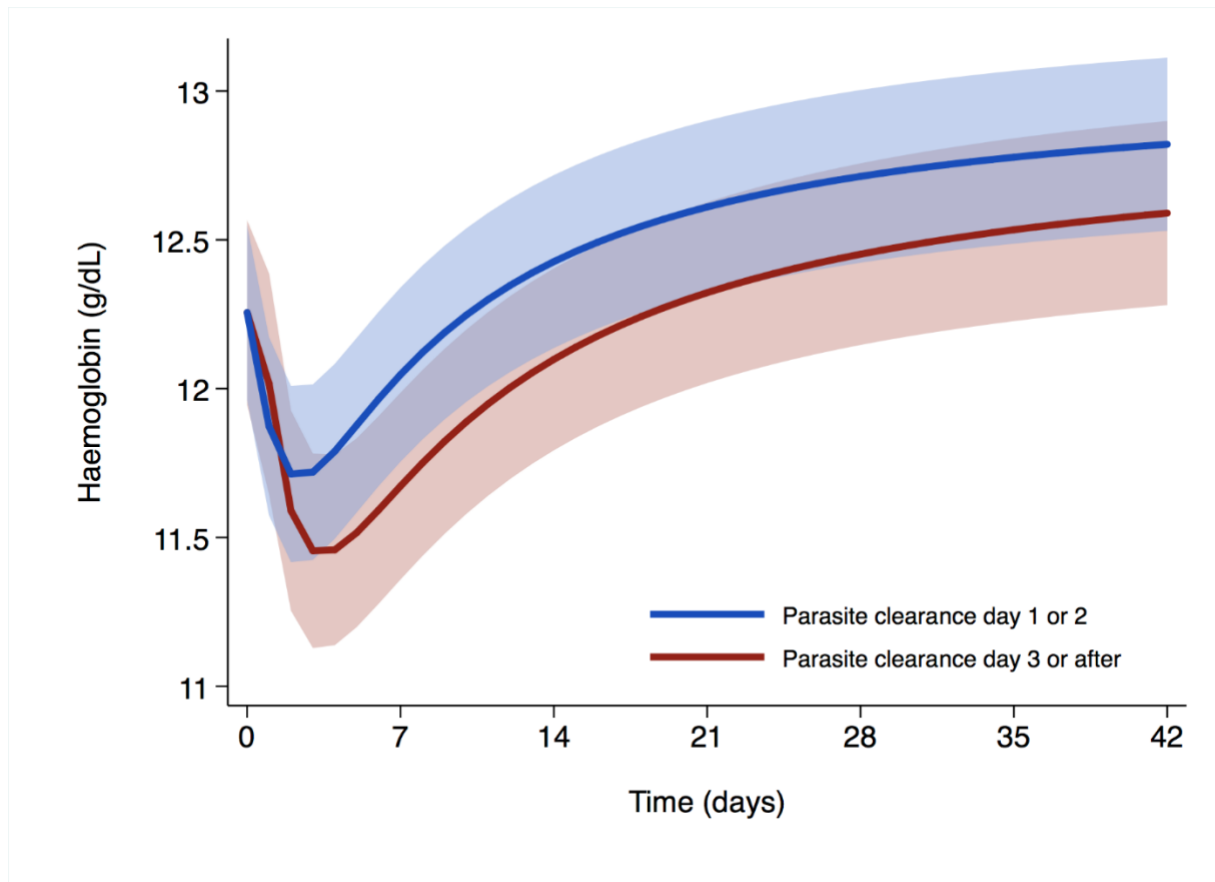


Figure S4. Mean haemoglobin versus time profile for patients with (n=622) or without (n=2,076) delayed parasite clearance.

Profiles adjusted to the same baseline haemoglobin. Figures derived from linear mixed effect models with fractional polynomial terms for time. Shaded regions show 95% confidence intervals.

Table S14. Unadjusted absolute and percentage change in haemoglobin and risk of anaemia if G6PD deficient

| Day and metric | Chloroquine alone | Chloroquine plus primaquine |
|---|--------------------------------|-----------------------------|
| <i>Day 2/3 (number of patients)</i> | 14 | 0 |
| Absolute change*, mean (SD) [range]; g/dL | -0.7 (1.1) [-2.3 to 1.2] | - |
| Percentage change*, mean (SD) [range]; % | -5.5 (8.1) [-17.6 to 10.7] | - |
| Percentage fall >25% | 0/14 (0%) | - |
| >25% fall associated with severe anaemia (%) [†] | 0/14 (0%) | - |
| Absolute fall >5 g/dL [‡] | 0/14 (0%) | - |
| <i>Day 7 ± 2</i> | 26 | 0 |
| Absolute change*, mean (SD) [range]; g/dL | -0.3 (1.3) [-2.7 to 1.9] | - |
| Percentage change*, mean (SD) [range]; % | -1.8 (10.2) [-18.6 to 16.4] | - |
| Percentage fall >25% | 0/26 (0%) | - |
| >25% fall associated with severe anaemia (%) [†] | 0/26 (0%) | - |
| Absolute fall >5 g/dL [‡] | 0/26 (0%) | - |
| <i>Day 28 ± 3</i> | 22 | 1 |
| Absolute change*, mean (SD) [range]; g/dL | 0.4 (1.1) [-2.5 to 2.7] | -0.4 (-) |
| Percentage change*, mean (SD) [range]; % | 4.1 (9.7) [-17.2 to 31.3] | -2.9 (-) |
| Percentage fall >25% | 0/22 (0%) | 0/1 (0%) |
| >25% fall associated with severe anaemia (%) [†] | 0/22 (0%) | 0/1 (0%) |
| Absolute fall >5 g/dL [‡] | 0/22 (0%) | 0/1 (0%) |

SD – standard deviation; * Results are reported as a change in haemoglobin (Hb), with positive results reflecting a rise in Hb and negative results reflecting a fall in Hb; † Patients were considered to develop severe anaemia if their baseline Hb was ≥ 7 g/dL and their follow up Hb was < 7 g/dL, with the denominator the number of people with a Hb recorded for that day who had a baseline ≥ 7 g/dL. All patients that developed severe anaemia had a Hb fall $> 25\%$. Table S12 provides additional patient details; ‡ Table S13 provides additional patient details.

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