**South African National Essential Medicine List**
**Primary Health Care Medication Review Process**
**Rapid Review report**
**Component: Infections – malaria *(P. falciparum infection)***

# TITLE: SINGLE, LOW-DOSE PRIMAQUINE WITH AN ARTEMISININ-BASED TREATMENT TO REDUCE *P. FALCIPARUM* MALARIA TRANSMISSION: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

**Date:** 25 January 2021

**Research question:** Does the addition of single low-dose primaquine to artemisinin-based treatment for *P. falciparum* malaria reduce disease transmission?

## Key findings

- We conducted a rapid review of available clinical evidence on the efficacy and safety of single low-dose primaquine (SLD PQ) with an artemisinin-combination treatment (ACT) to reduce *P.falciparum* malaria transmission.
- We found an Individual Participant Data (IPD) meta-analysis (n=2574 subjects; 14 RCTs up to and including 30 June 2018) that assessed the effect of SLD PQ + ACT on gametocyte carriage, and a Cochrane systematic review (24 RCTS and one quasi-RCT; up to 21 July 2017) that assessed the effect of SLD PQ + ACT on infectiousness and the risk of haemolysis. We also included an RCT published after the systematic reviews, that assessed the safety and tolerability of SLD PQ + ACT for *P. falciparum* in terms of the risk of haemolysis in patients with G6PD deficiency.
- IPD meta-analysis showed that SLD (0.25 mg/kg) PQ has the potential to block transmission in combination with ACT. The effectiveness of the combination on gametocyte persistence and infectivity is dependent on the type of ACT (artemether-lumefantrine produced better results compared to dihydroartemisinin-piperaquine).
    - SLD PQ reduced PCR-determined gametocyte carriage compared to those not treated with PQ on days 7 (23.4% (258/1101) vs 57.4% (316/551)) and 14 (11.4% (106/931) vs. 42.9% (202/471)) in patients presenting with gametocytemia on day 0.
- The Cochrane review showed that SLD PQ reduced infectiousness on day 3 or 4 from 14% to 2% and on day 8 from 4% to 1% when compared to no PQ in combination with ACT.
- The RCT reviewed showed that SLD PQ is well tolerated and appears safe in G6PD deficient (G6PDd) patients.
- The evidence suggests that SLD PQ safely reduces malaria transmission with no evidence of severe haemolysis, even in G6PDd patients.

**PHC/ADULT HOSPITAL LEVEL ERC AND NEMLC RECOMMENDATION:**

| Type of recommendation | We recommend against the option and for the alternative **(strong)** | We suggest not to use the option or to use the alternative **(conditional)** | We suggest using either the option or the alternative **(conditional)** | We suggest using the option **(conditional)** | We recommend the option **(strong)** |
|---|---|---|---|---|---|
| | | X | | | |

**Recommendation:** The PHC/Adult Hospital Level Committee recommends that single low-dose primaquine (0.25mg/kg), be added to artemisinin-based treatment for *P. falciparum* malaria, to reduce transmission. Pre-testing for G6PD deficiency is not required unless there is a clinical indication.
*Rationale:* Evidence of efficacy and safety for SLD primaquine for reducing gametocyte carriage.
**Level of Evidence: II Moderate certainty evidence**
**Review indicator: Evidence of reduced community transmission**

***However, the NEMLC reviewed the evidence presented by the PHC/Adult Hospital Level Committee and recommended the following (see below):***

**NEMLC MEETING 25 FEBRUARY 2021:**

**NEMLC Recommendation:** NEMLC acknowledges that there is reasonable evidence showing that primaquine, single dose (SLD), reduces gametocyte carriage. However, there is uncertainty regarding the actual effect on reduction of transmission and malaria eradication *(South African Malaria Elimination Committee was engaged, but no further evidence was forthcoming).* As SAHPRA registration of this product is currently underway, NEMLC recommends that including primaquine SLD on the national EML is premature for use from primary level of care. However, this will be revisited once the product is SAHPRA registered.

*Rationale:* Routine section 21 access at primary level of care, specifically by nurse prescribers, of an essential medicine is problematic in terms of continuous availability and consistency of price.

**Review indicator: Availability of SAHPRA registered primaquine products.**

## BACKGROUND

Current World Health Organization (WHO) Malaria Treatment Guidelines recommend treatment of children and adults with uncomplicated *P. falciparum* malaria (excluding pregnant women in their first trimester) with an artemisinin-based combination therapy (ACT). In low transmission areas, as part of malaria elimination or pre-elimination strategies and to limit transmission, WHO advises the addition of a single dose of 0.25mg/kg primaquine, except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months.[1]

However, primaquine is not currently registered in South Africa. Accessing primaquine for this indication therefore requires approval from the South African Health Products Regulatory Authority (SAPHRA) in terms of section 21 of the Medicines and Related Substances Act. The National Malaria Programme (NMP) currently holds section 21 approval for the use of single low-dose primaquine in low-transmission districts approaching malaria elimination.

The objective of the review is to review evidence for safety and efficacy of single low-dose primaquine when given with artemisinin-based combination therapy (ACT) in reducing the transmission of malaria. A particular safety concern is the risk of haemolysis in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency, when treated with single, low-dose primaquine.

### Introduction

Malaria is caused by one of five species of *Plasmodium* parasites, transmitted by the bites of infected female *Anopheles* mosquitoes. *P. falciparum*, one of the plasmodium species, poses the greatest threat to humans. In 2018 the WHO reported that, *P. falciparum* accounted for 99.7% of estimated malaria cases in the WHO African Region.[2]

Gametocytes represent the sexual reproductive phase of the malaria parasite that facilitate the transmission of the parasite from humans to the *Anopheles* mosquito. ACT is efficacious at eliminating asexual parasites and early gametocytes but not very effective against mature stage *P. falciparum* gametocytes. Mature gametocytes can remain infectious for up to 2 weeks, supporting the transmission of malaria from humans to mosquitoes. By clearing the mature gametocytes, primaquine reduces the transmission of malaria.[3] (Figure 1)[4]

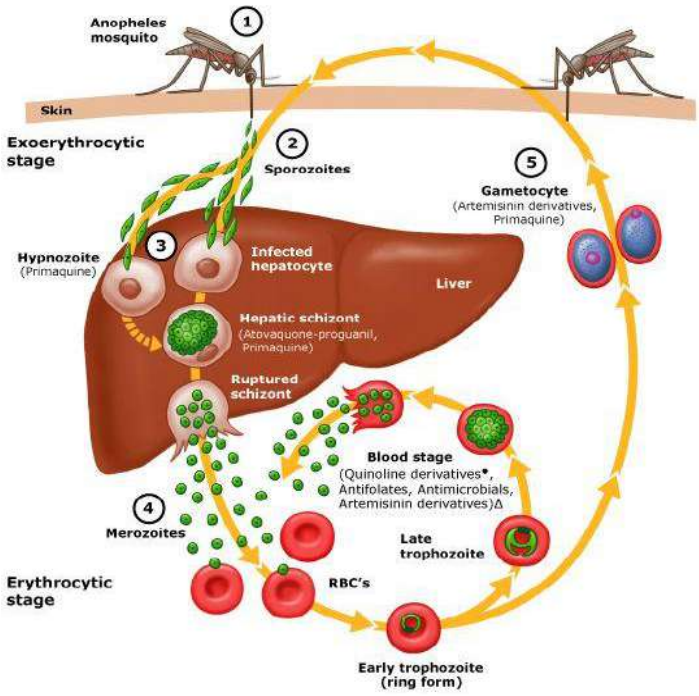


**Figure 1: Lifecycle of the Malaria Paracyte Showing the Gametocyte Stage, the Point at Which Antimalarials (Artemisinin-Based Combination Therapy and Primaquine) Work**

*Sourced from:* Hill AV. Vaccines against malaria. Philos Trans R Soc Lond B Biol Sci. 2011 Oct 12;366(1579):2806-14.[4]

WHO recommends single low-dose primaquine (SLD PQ) to reduce malaria transmission in low-transmission areas.[Error! Bookmark not defined.] The National Malaria Programme in South Africa is committed to eliminating malaria by 2023, as outlined in the Elimination Strategic Plan for South Africa 2019-2023.[5] Despite high coverage (>85%) of indoor residual spraying (IRS), additional efforts are needed to achieve malaria elimination in South Africa. One of those additional efforts is the provision of SLD PQ. To be practical, primaquine needs to be effective after a single dose administration, linked to ACT administration, and safe in all patients (including those with glucose 6 phosphate dehydrogenase (G6PD) deficiency). Based on available research evidence, the WHO currently recommends that G6PD testing is not required before administration of SLD PQ. [6, 7]

Preliminary results from a pilot study conducted in two malaria endemic provinces in South Africa showed promising results for the addition of SLD PQ. In the pilot study, 2783 patients were treated with SLD PQ (2097 in Nkomazi sub-district, Mpumalanga, & 686 in uMkhanyakude District, KwaZulu-Natal). In addition, 42 patients (9 in Bushbuckridge, Mpumalanga, and 33 in Greater Giyani, Limpopo) were treated with SLD PQ in the joint COVID-19-malaria screen, test and treat programmes between 20 April and 16 July 2020. A total of 1577 patients were traced for case investigation (1388 in Mpumalanga, 146 in KwaZulu-Natal and all 42 in the joint COVID-19 malaria screen, test and treat programme in Greater Giyani, Limpopo and Bushbuckridge, Mpumalanga). In Nkomazi, Mpumalanga, 17 (1.2%) of patients reported that they were "still ill", with a wide range of symptoms described, most of which could be malaria related. Symptoms reported were fever (n=2), body pain (6), sweating (1), shivering / "hot and cold" (4), "poor appearance" (1), loss of appetite (1), diarrhoea (1), and a nose bleed (1). Seven of these 17 patients were followed-up while they were still taking their 3-day artemether-lumefantrine treatment course. In uMkhanyakude, KwaZulu-Natal, 6 patients reported that they were "still ill"; 2 complained of "body pains", 1 complained of loss of appetite, 1 complained of fever and the remaining 2 patients did not specify their complaints. Five of these 6 patients were followed-up while they were still taking their 3-day artemether-lumefantrine treatment course. In the joint COVID-19-malaria campaign in Bushbuckridge, Mpumalanga and Greater Giyani, Limpopo, all 42 patients reported that they were fully recovered. The researchers report that although most adverse events were mild and considered malaria-related, the gastrointestinal adverse effects were considered possibly related to primaquine.[8]

Raman *et al*. (2019) studied the addition of SLD PQ on day 3 to standard AL treatment for uncomplicated *P. falciparum* malaria in South Africa. Efficacy, safety, and tolerability were assessed on days 3, 7, 14, 28 and 42. The study results showed that no gametocytes were detected by either microscopy or PCR in any of the follow-up samples collected after randomization on day 3, preventing assessment of primaquine efficacy. In terms of safety, one third of the sample had a haemoglobin drop > 2 g/dL but this drop was not associated with PQ treatment. The drop was associated with G6PD genotype (52.9% (9/17)) with A− genotype vs. other genotypes (31% (36/116); p = 0.075). This study included a

small sample and study population, which might have been skewed toward nourished individuals who sought care by day 3. However, the RCT showed that from a safety perceptive SLD PQ can be implemented without G6PD testing to advance malaria elimination in South Africa.[9]

The following review summarises the evidence for the use and effect on outcomes of interest of SLD PQ in combination with ACT compared to malaria treatment with an ACT alone in adults and children with uncomplicated *P. falciparum* malaria.

## Eligibility criteria for review

Population: Adults or children with uncomplicated *P. falciparum* malaria, diagnosed by either microscopy or rapid diagnostic tests (except pregnant women, infants aged <6 months and women breastfeeding infants aged <6 months)

Intervention: Single low dose primaquine (0.75mg/kg or less) in combination with artemisinin-based regimens

Comparators: Treatment with an artemisinin-based regimen alone

Outcomes:
Efficacy: Transmission potential, assessed by weekly gametocyte carriage using molecular methods and/or by membrane feeding assay conducted on day 0 and any day post treatment (measures of community transmission - mosquito infectivity); incidence of *P. falciparum malaria* at community level
Safety: serious adverse events, particularly incidence of severe haemolysis in treated patients

Study designs: Systematic reviews of randomised controlled trials (RCTS) and individual RCTs

## METHODS

We conducted a rapid review of the evidence by systematically searching three electronic databases (Cochrane library, PubMed and Epistemonikos) on 8 December 2020. We included systematic reviews, where possible with meta-analyses of randomised controlled trials (RCTs), and individual RCTs (for studies not included in the relevant systematic reviews). We excluded observational studies, case reports, case series and narrative reviews. Publications were restricted to those published in English. The search strategy is shown in Appendix 1. Two reviewers screened records and extracted data (TL & MR). Screening of records was done independently and in duplicate (TL, MR), with disagreement resolved through discussion. Excluded studies with the rationale for exclusion are summarised in Table 1; whilst relevant study data were extracted in a narrative table of results (TL, MR), with results reviewed and checked by the third reviewer (AG). AG reviewed the overall report.

The quality of evidence was assessed independently using the AMSTAR 2 tool[10] for systematic reviews (MR, TL) and GRADE assessment[11] for RCTs (MR, TL), as required.

## RESULTS

***Results of search***
After the removal of 3 duplicates, two reviewers (TL, MR) screened 21 records and identified a Cochrane review (Graves et al, 2018[12]), an individual participant data (IPD) meta-analysis (Stepniewska *et al*, 2020[13]) and an RCT (Dysoley *et al*, 2019[14]). The RCT was published after the date of the last search performed for the systematic review by Stepniewska *et al.* (30 June 2018). Some of the RCTs included in the Cochrane review were also included in the IPD meta-analysis.

***Description of the studies***

*Individual participant analysis:*[13]
Stepniewska et al., 2020 conducted an individual patient meta-analysis (n=2574; 14 studies) to evaluate the gametocytocidal and transmission-blocking efficacy of PQ in combination with different ACTs. i.e., to quantify PQ effect on (1) gametocyte carriage in the first 2 weeks post treatment; and (2) the probability of infecting at least 1 mosquito or of a mosquito becoming infected.

- *Study Results*:
  - **Gametocyte carriage**: PQ treatment reduced PCR-determined gametocyte carriage compared to those not treated with PQ on days 7 (23.4% (258/1101) vs 57.4% (316/551)) and 14 (11.4% (106/931) vs. 42.9% (202/471)) in patients presenting with gametocytemia on day 0 (odds ratio [OR], 0.22; 95% confidence interval [CI]: 0 .17 to 0.28 & OR 0.12; 95% CI: 0.08 to 0.16, respectively). The rate of decrease of gametocyte carriage was faster when PQ was combined with artemether lumefantrine (AL) compared to dihydroartemisinin-piperaquine (DP) (P = .010 at day 7).
  - **Transmission to mosquitoes:** in 3 of 14 studies mosquito infections were rarely observed 1 week after administration of 0.25 mg/kg PQ (irrespective of other drugs) – as a surrogate marker for community transmission.

- *Quality of evidence:*
  - Risk of observer bias was low because laboratory personnel performing molecular assays for dissecting mosquitoes were blinded in all studies related to gametocyte carriage, only one of the 14 studies was sequential in design, and for all but one study the randomization method was computer generated or envelope drawn.
  - Only 3 studies of 14 reviewed transmission to mosquitoes, limiting the conclusion that mosquito infections were rarely observed 1 week after administration of 0.25 mg/kg PQ.

The IPD showed that 0.25 mg/kg PQ has the potential to block transmission in combination with ACT. The effectiveness of the combination on gametocyte persistence and infectivity is dependent on the type of ACT (AL producing better results compared to DP) used in combination with PQ.

*Cochrane review[12]:*

This systematic review of 24 RCTS and one quasi-RCT (up to 21 July 2017) assessed whether single dose PQ added to artemisinin-based combination treatment (ACT) for falciparum malaria reduced disease transmission. The investigators found no cluster-randomised studies measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate), which would give direct evidence for malaria transmission. Therefore, indirect evidence from feeding studies or measurement of reduced *P. falciparum* gametocytaemia was considered to determine infectiousness (people infectious and mosquitoes infected) amongst those assigned to PQ compared with those who were not. Trials were stratified according to PQ dose (low, 0.2 to 0.25 mg/kg; moderate, 0.4 to 0.5 mg/kg; and high dose, 0.75 mg/kg).

- *Study results:*
  - **Infectiousness,** with low dose PQ was reduced on day 3 or 4 from 14% to 2% and on day 8 from 4% to 1% when compared to no PQ, in combination with ACT (low certainty evidence) – with waning infectiousness in the control group by day 8. Infectiousness was similarly reduced with moderate dose PQ on day 3 or 4 from 14% to 2% and on day 8 from 4% to 1% when compared to no PQ, in combination with ACT (low certainty evidence). Infectiousness was reduced with high-dose PQ on day 3 and 4 from 10% to 2% and on day 8 from 5% to 1% (low certainty evidence). Low dose (SLD) PQ appeared to be as effective as higher doses (moderate and high dose PQ).– see Table 1.
  - **Gametocytes detected by PCR**, low dose PQ had little or no effect at day 3 or 4 (moderate certainty evidence); with a reduction at day 8 (RR 0.52, 95% CI: 0.41 to 0.65; high certainty evidence). Moderate- and high-dose PQ had a similar effect to low-dose PQ on gametocyte prevalence – see Table 1.
  - **Severe haemolysis** associated with low-dose PQ was infrequent (12.3% vs 13.2% in the control group; RR 0.98, 95% CI: 0.69 to 1.39; moderate certainty evidence), although small numbers of patients with G6PD deficiency were included. Moderate dose PQ was probably associated with severe haemolysis (2% in no PQ vs 4% with moderate dose PQ); whilst there were no reports for severe haemolysis in the high-dose PQ studies reviewed.

- *Quality of evidence:*
  - An AMSTAR 2 review of the Cochrane Review confirmed that the methodological quality of the review was of high quality.
  - For the meta-analyses, where there was heterogeneity between trials, so the random-effect model (rather than the fixed-effects model) was used to estimate the risk ratios.

- Evidence was graded as low certainty for comparisons on infectiousness mostly due to imprecision and small sample sizes.
- Risk of bias for individual RCTs was assessed as low to moderate, with more than half of the RCTs assessed as low risk, and 20% assessed as high risk; whilst the remainder of the RCTs (mostly older RCTs) did not report sufficient information for assessment. The highest risk of bias was inadequate blinding of study participants and personnel. There were also insufficient trials to conduct a sensitivity analysis of the quality of the RCTs.
- Publication bias was not assessed due to insufficient trials within each comparison.

The Cochrane review concluded that low-dose PQ reduced infectiousness with no evidence of harm, but whether this reduction translates to reduced malaria transmission needs to be verified in community-level studies.

*Randomised controlled study:*

One RCT was reviewed, that studied low-dose PQ in combination with ACT vs no addition of PQ. Dysoley et al., 2019[14] evaluated the tolerability of single low dose PQ in Cambodia (n=109). The primary outcome of interest was day 7 hemoglobin (Hb) concentration. Secondary outcomes of interest included D7-D0 absolute and fractional falls in Hb, modelled Hb changes over time, total malaria attributable fall (MAFt), D28Hb-nadir Hb, Hb recovery (D28 Hb > D0 Hb concentration), G6PD geno- and phenotype, thalassemia type, D28 cure rate, gametocyte carriage, and PQ, carboxy PQ, and PP concentrations.

- *Study results:*
  - **Severe haemolysis - Day 7 Hb concentration:** Mean nadir Hb occurred on D7 [11.6 (range 6.4 to 15.6) g/dL] and was significantly lower (p = 0.040) but not clinically significant in terms of acute haemolytic anaemia in glucose-6-phosphate dehydrogenase deficiency (G6PDd) (n = 9) vs. G6PDn (normal G6PD) (n = 46) DHAPP+SLDPQ recipients: 10.9 vs. 12.05 g/dL, Δ = -1.15 (95% CI: -2.24 to -0.05) g/dL.
- *Quality of evidence:*
  - The main study limitation was the very small number of G6PDd patients.

Single dose PQ is tolerated and may be safe in G6PDd patients.

## CONCLUSION

The Cochrane review showed that SLD PQ may reduce infectiousness and is safe with no evidence of severe haemolysis. The subsequent IPD meta-analysis quantified the ability of SLD PQ, given in combination with ACT, to clear gametocytes and to potentially reduce malaria transmission. Studies measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate) would further verify SLD PQ's effectiveness in reducing malaria transmission.

**Reviewer(s):** Dr M Reddy, Ms TD Leong, Mr A Gray, Dr T Kredo

**Declaration of interests:** MR (Better Health Programme, South Africa), TDL (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme) and TK (Cochrane South Africa, South African Medical Research Council) have no interests to declare in respect of primaquine for malaria. AG (Division of Pharmacology, University of KwaZulu-Natal) is a member of the South African Malaria Elimination Committee.

**Acknowledgement:** Prof Karen Barnes (South African Malaria Elimination Committee) for providing the preliminary data from pilot study conducted in two malaria endemic provinces in South Africa[8].

**Table 1: Excluded studies**

| Citation | Type of Record | Reason for Exclusion |
|---|---|---|
| Abba K et al. Rapid diagnostic tests for diagnosing uncomplicated non-falciparum or Plasmodium vivax malaria in endemic countries. Cochrane Database of Systematic Reviews. 2014 | Cochrane review | Review on diagnostic tests |
| Sinclair D et al. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database of Systematic Reviews. 2009 | Cochrane review | Did not meet PICO criteria. Only 1 RCT reviewed Primaquine |
| Gogtay N et al. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. Cochrane Database of Systematic Reviews. 2013 | Cochrane review | Did not meet PICO criteria |
| Osei-Akoto A. Atovaquone-proguanil for treating uncomplicated malaria. Cochrane Database of Systematic Reviews. 2005 | Cochrane review | Did not meet PICO criteria |
| Poirot E et al. Mass drug administration for malaria. Cochrane Database of Systematic Reviews. 2013 | Cochrane review | Did not meet PICO criteria |
| Bradley et al. Clin Infect Dis. 2019 Sep 27;69(8):1436-1439. doi: 10.1093/cid/ciz134. Transmission-blocking Effects of Primaquine and Methylene Blue Suggest Plasmodium falciparum Gametocyte Sterilization Rather Than Effects on Sex Ratio. | RCT (Pubmed) | Report |
| Mendes Jorge M et al. PLoS One. 2019 Oct 10;14(10):e0222993. doi: 10.1371/journal.pone.0222993. eCollection 2019. Safety and efficacy of artesunate-amodiaquine combined with either methylene blue or primaquine in children with falciparum malaria in Burkina Faso: A randomized controlled trial. | RCT (Pubmed) | Did not meet PICO criteria |
| Raman J, et al. Safety and tolerability of single low-dose primaquine in a low-intensity transmission area in South Africa: an open-label, randomized controlled trial. Malar J. 2019 Jun 24;18(1):209. doi: 10.1186/s12936-019-2841-8. | RCT (Pubmed) | RCT data pooled in the IPD by Stepniewska *et al* (2020). |
| Phommasone K et al. PLoS One. 2020 Feb 5;15(2):e0228190. doi: 10.1371/journal.pone.0228190. eCollection 2020. Mass drug administrations with dihydroartemisinin-piperaquine and single low dose primaquine to eliminate Plasmodium falciparum have only a transient impact on Plasmodium vivax: Findings from randomised controlled trials. | RCT (Pubmed) | Did not meet PICO criteria |
| Sutanto I et al. Clin Infect Dis. 2018 Oct 15;67(9):1364-1372. doi: 10.1093/cid/ciy231. Negligible Impact of Mass Screening and Treatment on Mesoendemic Malaria Transmission at West Timor in Eastern Indonesia: A Cluster-Randomized Trial. | RCT (Pubmed) | Did not meet PICO criteria |
| von Seidlein L. PLoS Med. 2019 Feb 15;16(2):e1002745. doi: 10.1371/journal.pmed.1002745. eCollection 2019 Feb. The impact of targeted malaria elimination with mass drug administrations on falciparum malaria in Southeast Asia: A cluster randomised trial. | RCT (Pubmed) | Did not meet PICO criteria |
| Phommasone K et al. Malar J. 2020 Jan 3;19(1):4. doi: 10.1186/s12936-019-3091-5. The use of ultrasensitive quantitative-PCR to assess the impact of primaquine on asymptomatic relapse of Plasmodium vivax infections: a randomized, controlled trial in Lao PDR. | RCT (Pubmed) | Did not meet PICO criteria |
| Hsiang MS. Lancet. 2020 Apr 25;395(10233):1361-1373. doi: 10.1016/S0140-6736(20)30470-0. Effectiveness of reactive focal mass drug administration and reactive focal vector control to reduce malaria transmission in the low malaria-endemic setting of Namibia: a cluster-randomised controlled, open-label, two-by-two factorial design trial. | RCT (Pubmed) | Did not meet PICO criteria |
| Pongvongsa T, et al. The dynamic of asymptomatic Plasmodium falciparum infections following mass drug administrations with dihydroarteminisin-piperaquine plus a single low dose of primaquine in Savannakhet Province, Laos. Malar J. 2018 Nov 3;17(1):405. | RCT (Pubmed) | Did not meet PICO criteria |
| Shekalaghe S et al. Optimal timing of primaquine to reduce Plasmodium falciparum gametocyte carriage when co-administered with artemether-lumefantrine. Malar J. 2020 Jan 21;19(1):34. doi: 10.1186/s12936-020-3121-3. | RCT (Pubmed) | RCT data pooled in the IPD by Stepniewska *et al.* (2020). |
| Commons RJ et al. Risk of Plasmodium vivax parasitaemia after Plasmodium falciparum infection: a systematic review and meta-analysis. Lancet Infect Dis. 2019 Jan;19(1):91-101. | Systematic review (Epistemonikos) | Risk of Plasmodium vivax parasitaemia |
| Graves PM, et al. Primaquine or other 8-aminoquinolines for reducing Plasmodium falciparum transmission. Cochrane Database Syst Rev. 2018 Feb 2;2(2):CD008152. | Systematic review (Epistemonikos) | Duplicate, record also retrieved in Cochrane database search |
| Haeusler IL, et al. The arrhythmogenic cardiotoxicity of the quinoline and structurally related antimalarial drugs: a systematic review. BMC Med. 2018 Nov 7;16(1):200. | Systematic review (Epistemonikos) | Did not meet PICO criteria |

RCT = Randomized Control Trial

## Table 2: Characteristics of reviewed studies

*i) Individual participant data (IPD) analysis*

| Citation | Study design | Population (n) | Treatment | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|
| Stepniewska et al., 2020 | Systematic Review and IPD | n=2574<br><br>14 studies<br><br>Studies mainly from Africa | Single dose primaquine (PQ) + Artemether-lumefantrine (AL) **or** dihydroartemisinin-piperaquine (DP), artesunate-sulfadoxine-pyrimethamine (ASSP) and (sulfadoxine-pyrimethamine-amodiaquine | Gaemtocytemia | ***PQ vs no PQ***<br><u>Gametocytaemia in non-detectable gametocytes at baseline:</u><br>• 12.9% (39/302) vs 19.6% (35/179) (OR 0.55; 95% CI, 0.32 to 0.96; P = 0.035)<br>• Similar effect of PQ on gametocyte appearance (P = 0.308) between day 7 (D7) (OR, 0.58; 95% CI, .33 to 1.01; P = .053) & D14 (OR, 0.30; 95% CI,0 .14 to 0.63; P = .002).<br><u>Gametocytaemia in detectable gametocytes at baseline:</u><br>• 23.4% (258/1101) on D7 vs 57.4% (316/551) (OR, 0.22; 95% CI, .17–.28; P < .001).<br>• Higher dose of PQ was associated with lower prevalence of gametocyte positivity on D7 & D14 (AOR, 0.69; 95% CI, .65–.74 and AOR, 0.58; 95% CI, .53–.64 for each 0.1-mg/kg increase in dose, respectively; both P < .001). AOR of 0.40 (95% CI, .34–.46) for D7 gametocyte carriage vs AOR 0.26 (95% CI, .20–.33) for D14 gametocyte carriage<br>• Addition of PQ reduced gametocyte carriage for both ACTs, differed between AL and DP (test for interaction, P = .010 for D7 & P < .001 for D14).<br>  ○ AL -reduction in gametocyte carriage probability achieved with 0.25-mg/kg PQ dose,<br>  ○ DP - higher doses of PQ were associated with additional substantial reductions in gametocyte carriage.<br>• 0.25 mg/kg PQ + AL reduced risk of gametocytemia on D7 to 26.0% (95% CI, 18.7%–34.9%) and D14 to 7.6% (95% CI, 4.3%–13.2%) vs 37.1% (95% CI, 27.6%–47.8%) & 18.2% (95% CI, 11.4%–27.9%) with DP. Gametocyte carriage risk significantly higher on D7 in patients treated with PQ on D2 or 3 vs patients treated with PQ on day 0 (AOR, 2.28; 95% CI, 1.66–3.69; P < .001). Not statistically significant by D14 (AOR, 1.74; 95% CI, .80–3.81; P = .164)<br><u>Gametocyte density</u><br>• Median values of 2.0% (interquartile range [IQR], 0.3%–10.2%) vs baseline by D7 vs 29.8% (IQR, 8.1%–77.4%) (P < .001). Values on D14 were 0.5% (IQR, 0.1%–5.6%) vs 9.6% (IQR, 1.5%–36.0%) (P < .001) | • Risk of bias is low - blinding on all measurements of gametocyte carriage.<br><br>AMSTAR assessment of the systematic review:<br>**Moderate quality.**<br>• Research questions and inclusion criteria for the review included the components of PICO? Yes<br>• Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Yes<br>• Review authors explained selection of the study designs for inclusion in the review? Yes<br>• Review authors used a comprehensive literature search strategy? Partial yes<br>• Review authors perform study selection and data extraction in duplicate? Yes<br>• Review authors provided a list of excluded studies and justify the exclusions? No<br>• Review authors described the included studies in adequate detail? Yes<br>• Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Yes<br>• Review authors reported on the sources of funding for the studies included in the review? No<br>• For meta-analyses, review authors used appropriate methods for statistical combination of results? Yes<br>• For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis? Yes |

| Citation | Study design | Population (n) | Treatment | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|
| | | | | | | • Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review? Yes<br>• Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? No<br>• For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review? No<br>• Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review? Yes<br><br>• Reviewed effect of PQ single dose (0.0625 to 0.75 mg/kg) on transmission potential of *falciparum malaria* infections, when coadministered with schizonticidal drugs.<br><br>• Single dose PQ has gametocyte clearing and sterilizing effects.<br><br>• Mosquito infections were rarely observed 1 week after administration of PQ (irrespective of other drugs) - caution - only in 3/14 studies |

*ACT= artemisinin-based containing therapy; Day=D; PQ = primaquine; RCT=randomised controlled trial; RR=risk ratio*

*ii) Systematic review:*

| Citation | Study design | Population (n) | Treatment | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|
| Graves et al, 2018 | Systematic review of 24 RCTs and 1 quasi-RCT<br><br>14 RCTs evaluated ACT; 9 RCTs evaluated | *Study participants:* Adults or children with *P. falciparum* infection or a mixed infection of *P. falciparum* and other *Plasmodium* species treated with ACT | PQ with ACT<br>***vs***<br>no PQ<br><br>*PQ doses varied:*<br>• low: 0.2 to 0.25 mg/kg<br>• moderate: 0.4 to 0.5 mg/kg | • Infectiousness (people infectious and mosquitoes infected)<br>• Potential infectiousness (gametocyte measures assessed by microscopy or PCR)<br>• Severe haemolysis | ***PQ (+ACT) vs no PQ***<br><br><u>Infectiousness, day 3 or 4:</u><br>*Low dose:* RR 0.12, 95%CI 0.02 to 0.88, 3 RCTs; n=105; 2% vs 14% (*low certainty evidence*)<br>*Moderate dose:* RR 0.13, 95% CI 0.02 to 0.94; 3 RCTs, n=109 (low *certainty evidence*) | There was a paucity of direct evidence for malaria transmission, as no community cluster-RCTs measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate) could be sourced. Thus, indirect evidence from feeding studies or measurement of reduced *P. falciparum* gametocytaemia was considered reasonable to determine potential reduced infections acquired by |

| Citation | Study design | Population (n) | Treatment | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|
| | non-ACT; 2 RCTs included both ACT and non-ACT arms<br><br>2 trial arms used bulaquine; 7 PQ arms used low dose of 0.2 to 0.25 mg/kg (6 with ACT); 11 PQ arms used moderate dose of 0.4 to 0.5 mg/kg (7 with ACT); remaining arms used high dose of 0.75 mg/kg | *Settings:* Mali, Burkina Faso, The Gambia, Tanzania, Senegal<br><br>*G6PD status:* 11 RCTs excluded participants with G6PD deficiency; 1 RCT included only those with G6PD deficiency; and 3 RCTs included all, irrespective of status. 10 RCTs did not report on testing.<br><br>*Time of follow-up* was restricted to eight days after treatment to enable maximum comparison between trials. | • high: 0.75 mg/kg | | *High dose:* RR 0.2, 95% CI 0.02 to 1.68, 1 RCT, n=101 (*low certainty evidence*)<br><br><u>Infectiousness, day 8:</u><br>*Low dose:* RR 0.34, 95% CI 0.07 to 1.58, 4 RCTs, n= 243 participants; 1% vs 4% (*low certainty evidence*)<br>*Moderate dose:* RR 0.33, 95% CI 0.07 to 1.57; 4 RCTs, n=246 (low *certainty evidence*)<br>*High dose:* RR 0.18, 95% CI 0.02 to 1.41, 2 RCTs, n=181 (*low certainty evidence*)<br><br><u>Gametocytes detected by PCR, at day 3 or 4:</u><br>*Low dose:* RR 1.02, 95% CI 0.87 to 1.21; 3 RCTs; n=414 (*moderate certainty evidence*)<br>*Moderate dose:* RR 1.09, 95% CI 0.93 to 1.28; 3 RCTS; n=418 (*moderate certainty evidence*)<br>*High dose:* RR 0.92, 95% CI 0.75 to 1.13; 2 RCTS; n=394 (*low certainty evidence*)<br><br><u>Gametocytes detected by PCR at day 8</u>:<br>*Low dose:* RR 0.52, 95% CI 0.41 to 0.65; 4 RCTs, n=532 (*high certainty evidence)*<br>*Moderate dose:* RR 0.37, 95% CI 0.29 to 0.48; 5 RCTs; n=758 (*high certainty evidence)*<br>*High dose:* RR 0.31, 95% CI 0.23 to 0.43; 5 RCTs; n=793 (*high certainty evidence)*<br><br><u>Severe haemolysis:</u> | mosquitoes from malaria-infected persons (infectiousness).<br><br>AMSTAR assessment of the systematic review: **High quality.**<br>• Research questions and inclusion criteria for the review included the components of PICO? Yes<br>• Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Yes<br>• Review authors explained selection of the study designs for inclusion in the review? Yes<br>• Review authors used a comprehensive literature search strategy? Yes<br>• Review authors perform study selection and data extraction in duplicate? Yes<br>• Review authors provided a list of excluded studies and justify the exclusions? Yes<br>• Review authors described the included studies in adequate detail? Yes<br>• Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Yes<br>• Review authors reported on the sources of funding for the studies included in the review? Yes<br>• For meta-analyses, review authors used appropriate methods for statistical combination of results? Yes (Random- vs fixed-effects)<br>• For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis? Yes<br>• Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review? Yes<br>• Review authors provided a satisfactory explanation for, and discussion of, any |

| Citation | Study design | Population (n) | Treatment | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|
| | | | | | *Low dose:* RR 0.98, 95% CI 0.69 to 1.39; 4 RCTs, n=752 (*moderate certainty evidence)*<br>*Moderate dose:* RR 1.54, 95% CI 0.38 to 6.30; 2 RCTs; n=260 (*low certainty evidence*)<br>*High dose:* Trials did not systematically report evidence of haemolysis | heterogeneity observed in the results of the review? Yes<br>• For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review? No<br>• Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review? Yes<br>Where heterogeneity between trials was observed, a randoms effect RR (rather than fixed RR) was estimated.<br><br>Where evidence was graded as low certainty, this was mostly due to imprecision.<br><br>Risk of bias was assessed as low to moderate, with >50% RCTs assessed as low risk, and 20% assessed as high risk; whilst the remainder of the RCTs (mostly older RCTs) did not report sufficient information for assessment. The highest risk of bias was inadequate blinding of study participants and personnel. There were also insufficient trials to conduct a sensitivity analysis of the quality of the RCTs.<br><br>Publication bias was not assessed due to insufficient trials within each comparison. |

*RCT=randomised controlled trial; ACT= artemisinin-based containing therapy; PCR= polymerase chain reaction; PQ = primaquine; RR=risk ratio*

*iii) Randomised controlled study:*

| Citation | Study design | Population (n) | Treatment | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|
| Dysoley et al., 2019 | Open-label RCT | n= 109<br><br>≥1 year, ≥7 kg with acute (≤ 48 h), symptomatic (≥ 38 °C axilla/≥ 37.5°C aural/history of fever), uncomplicated | Dihydroartemisinin-piperaquine (DHAPP) + single low-dose PQ (SLDPQ, 0.25 mg/kg) vs. DHAPP alone | Primary<br>• D7 Hbconcentration | **G6PD deficiency (G6PDd) (n = 9)**<br>**vs.**<br>**G6PDn normal G6PD) (n = 46)**<br>Hb Concentration: Mean nadir Hb occurred on D7 (11.6, 95% CI6.4 to 15.6 g/dL) & was significantly lower (p = 0.040) in G6PD deficiency (G6PDd) (n = 9) vs. G6PDn (normal G6PD) (n = 46) | • The main study limitation was the very small number of G6PDd patients<br>• DHAPP+SLDPQ was associated with modest Hb declines in G6PD Viangchan, a moderately severe variant i.e. did not result in clinical significant haemolysis |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | falciparum malaria (≥ 1 asexual form/500 WBCs) Cambodia | | | • DHAPP+SLDPQ recipients: 10.9 vs. 12.05 g/dL, Δ = -1.15 (95% CI: -2.24 to -0.05) g/dL.<br>• 3 G6PDn patients had D7 Hb concentrations < 8 g/ dL; D7-D0 Hbs were 6.4to 6.9, 7.4 to 7.4, & 7.5 to 8.2 g/dl<br>• All patients - mean HemoCue measured nadir Hb was 12.4 g/dL (D7) increasing to 13.1 g/dL by D28. | • Mean nadir Hb occurred on D7 & was significantly lower G6PDd vs. G6PDn but was not clinically significant in terms of acute haemolytic anemia<br>• Evidence that SLDPQ is tolerated and appears safe in G6PDd patients |

*AS=Artesunate*; AL=*Artemether & Lumefantrine; DP=Dihydroartemisinin-piperaquine; Hb=Haeomoglobin; PQ=Primaquine; SP=*Sulphadoxine*/pyrimethamine; WBCs=white blood cells*

**Table 3: GRADE evidence profile**

**Question**: Primaquine compared to no primaquine for reducing community transmission of malaria
**Patient or population**: reducing community transmission of malaria
**Setting**: Burkina Faso, Colombia, Kenya, Mali, South Africa, Sudan, Tanzania, The Gambia, Uganda
**Intervention**: primaquine
**Comparison**: no primaquine

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Primaquine | no primaquine | Relative (95% CI) | Absolute (95% CI) | |
| **Community transmission (follow up: 7 days; assessed with: gametocyte carriage)** | | | | | | | | | | | |
| 14 | randomised trials | not serious | not serious | not serious [a] | not serious | publication bias strongly suspected [b] | 258/1101 (23.4%) | 316/551 (57.4%) | **OR 0.22** (0.17 to 0.28) | **345 fewer per 1,000** (from 387 fewer to 300 fewer) | ⊕⊕⊕◯ MODERATE |
| **Community transmission (follow up: 14 days; assessed with: gametocyte carriage)** | | | | | | | | | | | |
| 11 | randomised trials | not serious | not serious | not serious [a] | not serious | publication bias strongly suspected [b] | 106/931 (11.4%) | 202/471 (42.9%) | **OR 0.12** (0.08 to 0.16) | **346 fewer per 1,000** (from 372 fewer to 322 fewer) | ⊕⊕⊕◯ MODERATE |

*CI: Confidence interval; OR: Odds ratio*

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**
a. Studies conducted in higher transmission areas however the studies were sufficiently representative of the South African setting and we did not downgrade for indirectness
b. The IPD analysis could only include the available evidence from those willing or able to share study data.

## Appendix 1: Search strategy

| |
|---|
| **Cochrane library**<br><br>*Search:* "P. falciparum:ti,ab,kw AND primaquine:ti,ab,kw in Cochrane Reviews (Word variations have been searched)"<br><br>**Records retrieved: 6 (5 was not related to the PICO and 1 SR included in the review)** |
| **EPISTEMONIKOS**<br><br>**Search:**<br>(title:((title:(p. falciparum) OR abstract:(p. falciparum))) OR abstract:((title:(p. falciparum) OR abstract:(p. falciparum)))) AND (title:(primaquine) OR abstract:(primaquine)) – from 2018 to 2020<br><br>**Records retrieved: 4 (1 was a duplicate, 2 were not related to the PICO and 1 IPD analysis included for review)** |
| **PUBMED**<br><br>*Search:* ("plasmodium falciparum"[All Fields]) AND ("primaquine"[All Fields]) **Filters:** Randomized Controlled Trial, Humans, from 2018/07/01 - 2020/12/7<br><br>**Records retrieved: 11 (2 were duplicates, 8 were not related to the PICO and 1 RCT included in the review)** |

## Appendix 2: Evidence to decision framework

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| **QUALITY OF EVIDENCE OF BENEFIT** | **What is the certainty/quality of evidence?**<br>High ☐ Moderate ☒ Low ☐ Very low ☐<br>*High quality:* confident in the evidence<br>*Moderate quality:* mostly confident, but further research may change the effect<br>*Low quality:* some confidence, further research likely to change the effect<br>*Very low quality:* findings indicate uncertain effect | SLD PQ added to ACT for falciparum malaria to reduce infectiousness, gametocyte carriage, gametocyte PCR and disease transmission – reviewed evidence assessed overall as moderate (see table 1 for details):<br>***Stepniewska et al, 2020:***<br>• *Individual patient meta-analysis* of moderate to high quality.<br>***Grave et al, 2018:***<br>• *Participants' infectiousness at day 8 – PQ vs no PQ* – low quality evidence<br>• *Participants with gametocytes at day 8 by PCR – PQ vs no PQ*: high quality evidence. |
| **EVIDENCE OF BENEFIT** | **What is the size of the effect for beneficial outcomes?**<br>Large ☐ Moderate ☒ Small ☐ None ☐ | ***Stepniewska et al, 2020:***<br>• *Gametocyte carriage by D7*: 0.25 mg/kg PQ combined with AL reduced risk of gametocytemia to 26.0% (95% CI, 18.7% to 34.9%) *vs* 37.1% (95% CI, 27.6% to 47.8%) with DP alone.<br>• *Gametocyte carriage by D14*: 0.25 mg/kg PQ combined with AL reduced risk of gametocytemia to 7.6% *vs* 18.2% (95% CI, 11.4% to 27.9%) with DP alone.<br>• Gametocyte carriage risk reduction is influenced more positively on D7 if PQ is given on D0 vs D2 or D3: AOR, 2.28; 95% CI, 1.66 to 3.69; P < 0.001; though not statistically significant by D14.<br>***Grave et al, 2018:***<br>• *Participants' infectiousness at day 8 – PQ vs no PQ*: (4 RCTs, n=243) RR 0.34 (0.07 to 1.58); ARR 3% (95% CI -1.31% to 7.31%)<br>• *Participants with gametocytes at day 8 by PCR – PQ vs no PQ*: (4 RCTs, n=532) RR 0.52 (0.41 to 0.65); ARR 22% (95% CI 9.05% to 34.95%)<br>Paucity of RCTs measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate) in endemic communities; and therefore RCTS showing a reduction of gametocytaenia with PQ combined with ACT vs ACT alone has been considered. |

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE OF HARM</td><td>What is the certainty/quality of evidence?<br>High [ ] Moderate [X] Low [ ] Very low [ ]<br>High quality: confident in the evidence<br>Moderate quality: mostly confident, but further research may change the effect<br>Low quality: some confidence, further research likely to change the effect<br>Very low quality: findings indicate uncertain effect</td><td>See description of the quality of IPD analysis (Stepniewska et al, 2020), above.<br><br>The evidence in the Cochrane review (Grave et al, 2018) was downgraded from high to moderate certainty due to imprecision.</td></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?<br>Large [ ] Moderate [ ] Small [X] None [ ]</td><td>Results from an IPD analysis, Cochrane systematic review show that SLD PQ is well tolerated and appears safe in both normal G6PD and G6PD-deficient patients.<br><br>See text above for details of the low risk of severe haemolysis/acute haemolytic anaemia with SLD PQ.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?<br>Favours intervention [X] Favours control [ ] Intervention = Control or Uncertain [ ]</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?<br>Yes [ ] No [ ] Uncertain [X]</td><td>Primaquine is currently not registered with SAHPRA and is accessed via S21 application.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?<br>More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Direct medicine price/ treatment dose/ adult:
<table>
<tr><th>Medicine</th><th>Dose</th><th>Acquisition price (ZAR)*</th></tr>
<tr><td>Primaquine 15mg, tablet</td><td>15mg</td><td>15.15</td></tr>
</table>
* S21 price accessed by UCT from Equity pharmaceuticals - Email communication on file.<br>Estimated budget impact:<br>S21 application (2021) = 11000**<br>Estimated incremental budget expenditure for SLD PQ = estimated R166650.00<br>** Shared by SAMEC (Jan2021 – Dec2021) – communication on file</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?<br>Minor [ ] Major [ ] Uncertain [X]<br><br>Is the option acceptable to key stakeholders?<br>Yes [ ] No [ ] Uncertain [X]</td><td>No local survey data could be sourced to determine acceptability of technology by respective stakeholders.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?<br>Yes [ ] No [X] Uncertain [ ]</td><td>Primaquine access for reducing malaria transmission is only required in malaria endemic areas (i.e. lower socio-economic areas).</td></tr>
</table>

| Version | Date | Reviewer(s) | Recommendation and Rationale |
|---|---|---|---|
| First | 25 January 2021 | MR, TL, AG | SLD primaquine (0.25mg/kg), not be recommended for addition to the national EML. for elimination of *P. falciparum* malaria. There is uncertainty regarding the actual effect on reduction of transmission and malaria eradication. Furthermore, primaquine is not currently SAHPRA-registered. |

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