WHO guidelines for malaria, 30 November 2024

PICO tables, Section 5.2.1.7 “Anti-relapse treatment of *P. vivax* and *P. ovale*”

Summary of findings tables

1. Efficacy (7 mg/kg versus 3.5 mg/kg total dose primaquine)

Question: Is high (7 mg/kg) total dose primaquine more efficacious than low (3.5 mg/kg) total dose primaquine at preventing relapses to day 180 in patients with uncomplicated vivax malaria?

Population: People with *P. vivax* malaria

Intervention: 7 mg/kg dose primaquine (high total dose including 7-day and 14-day regimens)

Comparison: 3.5 mg/kg dose primaquine (low total dose including 7-day and 14-day regimens)

Outcome	Population	Study[a]	Comparator 3.5 mg/kg primaquine (risk per 1000)	Intervention 7 mg/kg primaquine (risk per 1000)	Relative effect Effect (95% CI)	Certainty of evidence	Plain language summary
Critical							
Risk of *P. vivax* recurrence by day 180	All participants	Individual patient data meta-analysis of 5380 patients from 23 studies (15 randomised, 8 observational) [1]	193 (169-219)	92 (70-121)[b]	AHR=0.45 (0.34-0.60)	Moderate[1] Downgraded for risk of bias, inconsistency and indirectness, upgraded for dose effect and size of effect	There may be a moderate to large reduction in *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine
	Age <5 years	Individual patient data meta-analysis of 377 patients from 13 studies (8 randomised, 5 observational) [1][c,d]	288 (188-425)	93 (43-212)[b]	AHR=0.30 (0.13-0.70)	Moderate[2] Downgraded for risk of bias and indirectness, upgraded for dose effect and size of effect	There may be a moderate to large reduction in *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine
	Africa	Individual patient data meta-analysis of 659 patients from 3 randomised controlled trials [1][c,d,e]	148 (102-211)	71 (41-120)[b]	AHR=0.46 (0.26-0.80)	High[3] Downgraded for risk of bias and indirectness, upgraded for dose effect and size of effect	There may be a moderate to large reduction in *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine
	Americas	Individual patient data meta-analysis of 824 patients from 8 studies (5 randomised controlled trials, 3 observational studies) [1][c,d]	354 (302-412)	134 (17-656)[b]	AHR=0.33 (0.04-2.44)	Very Low[4] Downgraded for risk of bias, indirectness and imprecision	The evidence is uncertain about the risk of *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine

	South Asia	Two stage individual patient data meta-analysis of 1852 patients from 9 randomised controlled trials (unpublished)[f,g]	23 (3-54)	7 (0-61)	RR=0.3 (-)[h]	Very Low[5] Downgraded for risk of bias, indirectness and imprecision	The evidence is uncertain about the risk of *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine
	East Asia/Oceania	Individual patient data meta-analysis of 3174 patients from 15 studies (10 randomised, 5 observational) [1][c]	153 (109-214)	89 (50-153)[b]	AHR=0.56 (0.31-1.00)	Low[6] Downgraded for risk of bias, indirectness and imprecision, upgraded for dose effect	There may be a small to moderate reduction in *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine
	Chloroquine	Individual patient data meta-analysis of 3457 patients from 19 studies (11 randomised, 8 observational) [1][c]	172 (147-200)	69 (50-95)[b]	AHR=0.38 (0.27-0.53)	Moderate[7] Downgraded for risk of bias, inconsistency and indirectness, upgraded for dose effect and size of effect	There may be a moderate to large reduction in *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine
	Dihydroartemisinin-piperaquine	Individual patient data meta-analysis of 1387 patients from 6 studies (5 randomised, 1 observational) [1][c,d,i]	329 (159-585)	64 (23-154)[b]	AHR=0.17 (0.06-0.43)	High[8] Downgraded for risk of bias and indirectness, upgraded for dose effect and size of effect	There may be a large reduction in *P. vivax* recurrences with 7 mg/kg versus 3.5 mg/kg total dose primaquine

Notes
AHR – adjusted hazard ratio; CI – confidence interval; RR – risk ratio (unadjusted)
a – Numbers reflect only patients and studies in the 3.5 mg/kg and 7 mg/kg total dose primaquine treatment groups; b – Intervention risk calculation = 1000 - (exp[ln(1-proportion of patients with event) x AHR]) x 1000; c – Based on subgroup analysis of dataset used for [1]; d – New formal analysis planned; e – All patients from Ethiopia; f – All patients from India, Nepal and Pakistan; g – Too few data from one stage individual patient data meta-analysis so two stage meta-analysis undertaken including aggregated data from studies where individual patient data were unavailable; h – 95% CI for hazard ratio based on pooled estimates not calculated; i – All patients from Indonesia and Thailand.

Certainty of evidence

1. **Risk of bias: Serious.** Downgraded 1 level. Although 8 of 23 studies were observational a sensitivity analysis restricted to 9 randomised controlled trials (RCTs) comparing primaquine treatment regimens did not change results substantially. 5 of these 9 RCTs had potential concerns for bias with missing outcome data or bias in the reported results. **Inconsistency: Serious.** There was heterogeneity in absolute risks between studies and some heterogeneity in the relative change in risk within studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: No serious.** The upper and lower limits of the 95% CI of the adjusted hazard ratio indicate appreciable benefit with high total dose primaquine. The total sample size was larger than the optimal information size. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Upgrading by one for dose effect and one for effect magnitude.
2. **Risk of bias: Serious.** Downgraded 1 level. Although 5 of 13 studies were observational a sensitivity analysis restricted to 4 RCTs comparing different primaquine treatment regimens did not change results substantially. 3 of these 4 RCTs included had potential concerns for bias with missing outcome data or bias in the reported results. **Inconsistency: No serious.** Although there was heterogeneity in absolute risks between studies the relative change in risk was similar within studies where able to be assessed. **Indirectness: Serious.** Downgraded two levels as trials did not directly compare interventions and the population was not consistently assessing individuals <5 years. **Imprecision: No serious.** The upper and lower limits of the 95% CI of the adjusted hazard ratio indicate appreciable benefit with high total dose primaquine. The total sample size was larger than the optimal information size. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Upgrading by one for dose effect and one for effect magnitude.
3. **Risk of bias: Serious.** Downgraded 1 level due to 1 of 3 RCTs having non-blinded interventions and potential concerns for bias with missing outcome data or bias in the reported results. All RCTs compared different primaquine treatment regimens. **Inconsistency: No serious.** Although there was heterogeneity in absolute risks between studies the relative change in risk was similar within studies where able to be assessed. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: No serious.** The upper and lower limits of the 95% CI of the adjusted hazard ratio

indicate appreciable benefit with high total dose primaquine. The total sample size was larger than the optimal information size. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Upgrading by one for dose effect and one for effect magnitude.

4. **Risk of bias: Serious.** Downgraded 2 levels. 3 of 8 studies were observational and although 3 RCTs compared different primaquine treatment regimens too few patients received high total dose primaquine to undertake a sensitivity analysis. 2 of 5 RCTs in the primary analysis had potential concerns for bias with missing outcome data or bias in the reported results. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results were able to be assessed. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few patients with high total dose primaquine. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Nil.
5. **Risk of bias: Serious.** 8 of 9 studies compared different primaquine treatment regimens. Downgraded due to some concerns about bias from randomisation, missing outcomes or selection of reporting results in 7 of 9 studies. **Inconsistency: No serious.** Although there was heterogeneity in absolute risks between studies the relative change in risk was similar within studies where able to be assessed. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Nil.
6. **Risk of bias: Serious.** Downgraded 1 level. Although 5 of 15 studies were observational a sensitivity analysis restricted to 6 RCTs comparing different primaquine treatment regimens did not change results substantially. 2 of these 6 RCTs included had potential concerns for bias with missing outcome data or bias in the reported results. **Inconsistency: No serious.** Although there was heterogeneity in absolute risks between studies the relative change in risk was similar within studies where able to be assessed. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The upper limit of the 95% CI of the adjusted hazard ratio does not indicate appreciable benefit of the high total dose primaquine. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Upgrading by one for dose effect.
7. **Risk of bias: Serious.** Downgraded 1 level. Although 8 of 19 studies were observational a sensitivity analysis restricted to 8 RCTs comparing different primaquine treatment regimens did not change results substantially. 4 of these 8 RCTs included had potential concerns for bias with missing outcome data or bias in the reported results. **Inconsistency: Serious.** There was heterogeneity in absolute risks between studies and some heterogeneity in the relative change in risk within studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: No serious.** The upper and lower limits of the 95% CI of the adjusted hazard ratio indicate appreciable benefit with high total dose primaquine. The total sample size was larger than the optimal information size. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Upgrading by one for dose effect and one for effect magnitude.
8. **Risk of bias: Serious.** Downgraded 1 level. Although 1 of 6 studies was observational a sensitivity analysis restricted to 1 RCT comparing different primaquine treatment regimens did not change results substantially although precision was reduced. **Inconsistency: No serious.** Although there was heterogeneity in absolute risks between studies the relative change in risk was similar within studies where able to be assessed. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: No serious.** The upper and lower limits of the 95% CI of the adjusted hazard ratio indicate appreciable benefit with high total dose primaquine. The total sample size was larger than the optimal information size. **Publication bias: No serious.** No expected reason given both high and low risks of recurrence important. **Upgrade:** Upgrading by one for dose effect and one for effect magnitude.

2. Tolerability and safety (1 mg/kg/day versus 0.25 mg/kg/day primaquine)

Question: Does high (1 mg/kg) daily dose primaquine cause more gastrointestinal symptoms or adverse haemoglobin changes compared to low (0.25 mg/kg) daily dose primaquine?
Population: People with *P. vivax* malaria
Intervention: 1 mg/kg/day primaquine (high daily dose)
Comparison: 0.25 mg/kg/day primaquine (low daily dose)

Outcome	Population	Study[a]	Comparator 0.25 mg/kg/day primaquine (g/dL)	Intervention 1 mg/kg/day primaquine (g/dL)	Relative effect	Absolute effect	Certainty of evidence	Plain language summary
Critical								
Change in Hb to days 2-3	G6PD activity ≥30%	Individual patient data meta-analysis of 2040 patients from 12 studies (11 randomised, 1 observational) [2]	-0.7 (-0.8 to -0.5)[b]	-0.5 (-0.7 to -0.4)[b]	-	0.14 (0.02 to 0.27)	Very low[1] Downgraded for risk of bias, indirectness and imprecision	The evidence is uncertain about a difference in mean haemoglobin change at day 2/3 following 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	G6PD activity 30-<70%	Individual patient data meta-analysis of 25 patients from 4 studies (3 randomised, 1 observational) [2]	-1.3 (-2.8 to 0.3)[b]	-1.5 (-2.0 to -0.9)[b]	-	-0.22 (-1.79 to 1.36)	Low[2] Downgraded for indirectness and imprecision	There may be no difference in the mean haemoglobin change at day 2/3 following 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	G6PD activity ≥70%	Individual patient data meta-analysis of 693 patients from 6 studies (5 randomised, 1 observational) [2]	-0.6 (-0.8 to -0.4)[b]	-0.5 (-0.7 to -0.2)[b]	-	0.12 (-0.09 to 0.34)	Low[3] Downgraded for indirectness and imprecision	There may be no difference in the mean haemoglobin change at day 2/3 following 1 mg/kg/day versus 0.25 mg/kg/day primaquine

Outcome	Population	Study[a]	Comparator 0.25 mg/kg/day primaquine (risk per 1000)	Intervention 1 mg/kg/day primaquine (risk per 1000)	Relative effect	Absolute effect	Certainty of evidence	Plain language summary
>25% fall in Hb to <7 g/dL from day 0 to days 1-13	G6PD activity ≥30%	Individual patient data meta-analysis of 2162 patients from 13 studies (12 randomised, 1 observational) [2]	0 (0-4)	5 (2-10)	Not estimated due to small unadjusted numbers	5 (1 to 9)[c]	Very low[4] Downgraded for risk of bias, indirectness and imprecision	The evidence is uncertain about the risk of a fall >25% to <7 g/dL with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	G6PD activity 30-<70%	Individual patient data meta-analysis of 25 patients from 4 studies (3 randomised, 1 observational) [2]	0 (0-708)	91 (11-292)	Not estimated due to small unadjusted numbers	91 (-29 to 211)[c]	Low[5] Downgraded for indirectness and imprecision	There may be an increase in the risk of a fall >25% to <7 g/dL with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	G6PD activity ≥70%	Individual patient data meta-analysis of 720 patients from 6 studies (5 randomised, 1 observational) [2]	0 (0-13)	2 (0-13)	Not estimated due to small unadjusted numbers	2 (-2 to 7)[c]	Very low[6] Downgraded for risk of bias, indirectness and imprecision	The evidence is uncertain about the risk of a fall >25% to <7 g/dL with 1 mg/kg/day versus 0.25 mg/kg/day primaquine. There may be no difference in risk.
Important								
Vomiting, diarrhoea or abdominal pain at days 1-2	All people	Individual patient data meta-analysis of 1751 patients from 10 studies (6 randomised, 4 observational) [1]	182 (81-284)	221 (118-323)	ARR=1.21 (0.85-1.72)	-	Very low[7] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about any change in GI symptoms at days 1-2 with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	Age ≥15 years	Individual patient data meta-analysis of 987 patients from 10 studies (6 randomised, 4 observational) [1][d]	184 (76-292)	246 (136-356)	ARR=1.33 (0.90-1.99)	-	Very low[8] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about any change in GI symptoms at days 1-2 with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	Age 5-<15 years	Individual patient data meta-analysis of 631 patients from 8 studies (5 randomised, 3 observational) [1][d]	186 (71-302)	200 (91-309)	ARR=1.07 (0.69-1.68)	-	Very low[9] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about any change in GI symptoms at days 1-2 with 1

								mg/kg/day versus 0.25 mg/kg/day primaquine
	Age <5 years	Individual patient data meta-analysis of 133 patients from 7 studies (4 randomised, 3 observational) [1][d]	294 (125-463)	163 (60-266)	ARR=0.55 (0.32-0.97)	-	Very low[10] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about any change in GI symptoms at days 1-2 with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
Vomiting, diarrhoea or abdominal pain at days 5-7	All people	Individual patient data meta-analysis of 1915 patients from 11 studies (7 randomised, 4 observational) [1]	62 (3-122)	110 (57-164)	ARR=1.77 (0.98-3.18)	-	Very low[11] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about a moderate increase in GI symptoms at days 5-7 with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	Age ≥15 years	Individual patient data meta-analysis of 1077 patients from 11 studies (7 randomised, 4 observational) [1][d]	47 (3-90)	127 (69-184)	ARR=2.71 (1.47-4.98)	-	Very low[12] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about any change in GI symptoms at days 5-7 with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	Age 5-<15 years	Individual patient data meta-analysis of 672 patients from 9 studies (6 randomised, 3 observational) [1][d]	97 (6-188)	99 (47-151)	ARR=1.01 (0.54-1.91)	-	Very low[13] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about any change in GI symptoms at days 5-7 with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	Age <5 years	Individual patient data meta-analysis of 166 patients from 8 studies (5 randomised, 3 observational) [1][d]	76 (0-156)	45 (0-99)	ARR=0.59 (0.28-1.21)	-	Very low[14] Downgraded for risk of bias, inconsistency, indirectness and imprecision	The evidence is uncertain about any change in GI symptoms at days 5-7 with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
Acute vomiting within 1 hour of primaquine on days 3-14	All people	Individual patient data meta-analysis of 1687 patients from 6 studies (5 randomised, 1 observational [1]	14 (3-40)	3 (1-7)	Not estimated due to small unadjusted numbers	-11 (-27 to 5)[c]	Low[15] Downgraded for indirectness and imprecision	There may be no change in acute vomiting with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	Age ≥15 years	Individual patient data meta-analysis of 915 patients from 5 studies (4 randomised, 1 observational [1][d]	8 (0-44)	4 (1-11)	Not estimated due to small unadjusted numbers	-4 (-20 to 12)[c]	Low[16] Downgraded for indirectness and imprecision	There may be no change in acute vomiting with 1 mg/kg/day versus 0.25 mg/kg/day primaquine

	Age 5-<15 years	Individual patient data meta-analysis of 637 patients from 6 studies (5 randomised, 1 observational [1][d]	27 (3-94)	2 (0-9)	Not estimated due to small unadjusted numbers	-25 (-62 to 12)[c]	Low[17] Downgraded for indirectness and imprecision	There may be no change in acute vomiting with 1 mg/kg/day versus 0.25 mg/kg/day primaquine
	Age <5 years	Individual patient data meta-analysis of 135 patients from 6 studies (5 randomised, 1 observational [1][d]	0 (0-195)	0 (0-31)	Not estimated due to small unadjusted numbers	0 (-)[c]	Low[18] Downgraded for indirectness and imprecision	There may be no change in acute vomiting with 1 mg/kg/day versus 0.25 mg/kg/day primaquine

Notes
ARR – adjusted relative risk; CI – confidence interval; Hb - haemoglobin
a – Numbers reflect only patients and studies in the 0.25 mg/kg/day and 0.5 mg/kg/day primaquine treatment groups; b – Covariate-adjusted estimated change in haemoglobin from day 0 to day 2/3; c – Risk per 1000; d – Based on subgroup analysis of dataset used for [1]

Certainty of evidence

1. **Risk of bias: Serious.** Downgraded 1 level. Although 1 of 12 studies were observational a sensitivity analysis restricted to 9 randomised controlled trials (RCTs) comparing primaquine treatment regimens did not change results substantially. 5 of these 9 RCTs had potential concerns for bias. **Inconsistency: No serious.** There was not substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
2. **Risk of bias: No serious.** Although 1 of 4 studies were observational, a sensitivity analysis restricted to 2 RCTs comparing primaquine treatment regimens did not change results substantially. **Inconsistency: No serious.** Few patients without substantial heterogeneity. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
3. **Risk of bias: No serious.** Although 1 of 6 studies were observational a sensitivity analysis restricted to 4 RCTs comparing primaquine treatment regimens did not change results substantially. **Inconsistency: No serious.** There was not substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
4. **Risk of bias: Serious.** Downgraded 1 level. Although 1 of 13 studies were observational a sensitivity analysis restricted to 9 RCTs comparing primaquine treatment regimens did not change results substantially. 5 of these 9 RCTs had potential concerns for bias. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
5. **Risk of bias: No serious.** Although 1 of 4 studies were observational, a sensitivity analysis restricted to 2 RCTs comparing primaquine treatment regimens did not change results substantially. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
6. **Risk of bias: Serious.** Although 1 of 6 studies were observational a sensitivity analysis restricted to 4 RCTs comparing primaquine treatment regimens did not change results substantially. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
7. **Risk of bias: Serious.** Downgraded 1 level. Although 4 of 10 studies were observational a sensitivity analysis restricted to 4 RCTs comparing primaquine treatment regimens did not change results substantially. 3 of these 4 RCTs had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
8. **Risk of bias: Serious.** Downgraded 1 level. Although 4 of 10 studies were observational a sensitivity analysis restricted to 4 RCTs comparing primaquine treatment regimens did not change results substantially. 3 of these 4 RCTs had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials

did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.

9. **Risk of bias: Serious.** Downgraded 1 level. Although 3 of 8 studies were observational a sensitivity analysis restricted to 3 RCTs comparing primaquine treatment regimens did not change results substantially. 2 of these 3 RCTs had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
10. **Risk of bias: Serious.** Downgraded 1 level. Although 3 of 7 studies were observational a sensitivity analysis restricted to 3 RCTs comparing primaquine treatment regimens did not change results substantially. 2 of these 3 RCTs had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
11. **Risk of bias: Serious.** Downgraded 1 level. Although 4 of 11 studies were observational a sensitivity analysis restricted to 4 RCTs comparing primaquine treatment regimens did not change results substantially. 3 of these 4 RCTs had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
12. **Risk of bias: Serious.** Downgraded 1 level. Although 4 of 11 studies were observational a sensitivity analysis restricted to 3 RCTs comparing primaquine treatment regimens did not change results substantially. 2 of these 3 RCTs had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
13. **Risk of bias: Serious.** Downgraded 1 level. Although 3 of 9 studies were observational a sensitivity analysis restricted to 4 RCTs comparing primaquine treatment regimens did not change results substantially. 3 of these 4 RCTs included had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
14. **Risk of bias: Serious.** Downgraded 1 level. Although 3 of 8 studies were observational a sensitivity analysis restricted to 4 RCTs comparing primaquine treatment regimens did not change results substantially. 3 of these 4 RCTs had potential concerns for bias with measurement of the outcome. **Inconsistency: Serious.** There was substantial heterogeneity between studies. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** The confidence interval of the ARR fails to exclude an important benefit or harm. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
15. **Risk of bias: No serious.** Although 1 study was observational, there was no substantial bias in measurement of the outcome identified with supervision of primaquine in all randomised studies except one treatment arm with partial supervision. All 5 RCTs compared different primaquine treatment regimens. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
16. **Risk of bias: No serious.** Although 1 study was observational, there was no substantial bias in measurement of the outcome identified with supervision of primaquine in all randomised studies except one treatment arm with partial supervision. All 4 RCTs compared different primaquine treatment regimens. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
17. **Risk of bias: No serious.** Although 1 study was observational, there was no substantial bias in measurement of the outcome identified with supervision of primaquine in all randomised studies except one treatment arm with partial supervision. All 5 RCTs compared different primaquine treatment regimens. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.
18. **Risk of bias: No serious.** Although 1 study was observational, there was no substantial bias in measurement of the outcome identified with supervision of primaquine in all randomised studies except one treatment arm with partial supervision. All 5 RCTs compared different primaquine treatment regimens. **Inconsistency: No serious.** Few events in all studies without substantial heterogeneity in relative results. **Indirectness: Serious.** Trials did not directly compare interventions. **Imprecision: Serious.** Few events. **Publication bias: No serious.** Not primary outcome, so no publication bias would be expected. **Upgrade:** Nil.

References