Evidence Update

Malaria Series

Does primaquine prevent relapses in people with *Plasmodium vivax* malaria?

Evidence supports the World Health Organization's recommended course of primaquine (15 mg/kg/day for 14 days) plus chloroquine.

Inclusion criteria

Studies:

Randomized controlled trials and quasi randomized controlled trials.

Participants:

Adults and children with microscopically confirmed *P*. *vivax* malaria.

Intervention:

Intervention: primaquine (at a different dose or duration than the control) plus chloroquine.

Control: placebo or no drug or primaquine (15 mg/kg/ day for 14 days) plus chloroquine.

Outcomes:

Primary: *P. vivax* detected in the blood more than 30 days after starting primaquine.

Any adverse events.

Results

- Nine RCTs including 3423 participants met the inclusion criteria. Trials were conducted in India (3), Afghan refugee camps in Pakistan (3), Thailand (2), and Brazil (1). One trial had adequate allocation concealment.
- Groups taking primaquine for 5 days plus chloroquine had similar incidence of *P. vivax* in the blood after 30 days compared with those taking chloroquine alone (odds ratio 1.04, 95% confidence interval 0.64 to 1.69; 3 trials, 2104 participants).
- Groups taking primaquine for 14 days plus chloroquine had a lower incidence of *P. vivax* in the blood after 30 days than those taking chloroquine alone (OR 0.24, 95% CI 0.12 to 0.45; 6 trials, 1071 participants).
- Two trials compared the 5-day and 14-day primaquine plus chloroquine regimens and found a higher incidence of *P. vivax* after 30 days with the 5-day regimen (OR 13.33, 95% Cl 3.45 to 51.44, 2 trials; 186 participants).
- Mild adverse events of nausea, skin rash, and transient headache were reported.







Adapted from Galappaththy GNL, Omari AAA, Tharyan P. Primaquine for preventing relapses in people with Plasmodium vivax malaria. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD004389. DOI: 10.1002/14651858.CD004389.pub2. *Evidence Update* published in July 2007.

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Primaquine 5 days plus chloroquine versus chloroquine: *P. vivax* detected more than 30 days after starting primaquine

Study	PQ-5 days plus CQ n/N	CQ n/N	Odds Ratio (Random) 95% Cl	Weight (%)	Odds Ratio (Random) 95% Cl
01 Follow up: < or = 6 mon Gogtay 1999	ths 16/62	7/60		17.3	2.63 [1.00, 6.96]
Subtotal (95% CI) Total events: 18 (PQ-5 day Test for heterogeneity: nor Test for overall effect z=1	62 ys plus CQ), 7 (CQ) t applicable .95 p=0.05	60		17.3	2.63 [1.00, 6.96]
02 Follow up: > 6 months Rowland1999ii	128/250	129/250	-	42.4	0.98 [0.69, 1.40]
Yadav 2002	49/759	62/723		40.3	0.74 [0.50, 1.09]
Subtotal (95% CI) Total events: 177 (PQ-5 da Test for heterogeneity chi- Test for overall effect z=1	1009 ays plus CQ), 191 (CQ ·square=1.18 df=1 p=0. .03 p=0.3	973) 28 ⁼ =15.5%	•	82.7	0.86 [0.65, 1.14]
Total (95% CI) Total events: 193 (PQ-5 da Test for heterogeneity chi- Test for overall effect z=0	1071 ays plus CQ), 198 (CQ ·square=5.90 df=2 p=0. .15 p=0.9	1033) 05 I⁼=66.1%	-	100.0	1.04 [0.64, 1.69]
			0.1 0.2 0.5 1 2 Favours PQ-5 + CQ Favo	5 10 purs CQ	

Primaquine 14 days plus chloroquine versus chloroquine: *P. vivax* detected more than 30 days after starting primaquine

Study	log [OR] (SE)	OR (Random) 95% CI	Weight (%)	0R (Random) 95% Cl
01 Follow up <= 6 months Gogtay 1999	-2.88 (1.47)	•	4.5	0.06 [0.00, 1.01]
Pukrittayakamee 1994	-2.87 (0.91)	•	9.7	0.06 [0.01, 0.34]
Rajgor 2003	-2.23 (0.51)		19.5	0.11 [0.04, 0.29]
Walsh 2004	-1.22 (1.00)		8.4	0.30 [0.04, 2.12]
Subtotal (95% CI) Test for heterogeneity chi-s Test for overall effect z=5.	square=1.71 df=3 p=0.64 l° =0.0% 73 p<0.00001	•	42.2	0.11 [0.05, 0.23]
02 Follow up >=6 months Leslie 2004	-0.99 (0.24)		29.9	0.37 [0.23, 0.60]
Rowland 1999i	-0.71 (0.29)		27.9	0.49 [0.28, 0.87]
Subtotal (95% CI) Test for heterogeneity chi-s Test for overall effect z=4.	square=0.54 df=1 p=0.46 l° =0.0% 71 p<0.00001	•	57.8	0.41 [0.29, 0.60]
Total (95% CI) Test for heterogeneity chi-s	square=12.11 df=5 p=0.03 l= =58.71	. •	100.0	0.24 [0.12, 0.45]

Authors' conclusions

Implications for practice:

This review found evidence to support the World Health Organization's recommended course of primaquine 15 mg/kg/day for 14 days plus chloroquine to prevent relapse of *P. vivax* malaria. There is no evidence for the effectiveness of a 5-day course of primaquine.

Implications for research:

Large randomized controlled trials are needed to determine the optimum dose and duration of primaquine for preventing relapses of different strains of *P. vivax* malaria in different regions.

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