Evidence summaries present new developments, innovations and research relevant to the work of National Malaria Control Programs in the Asia Pacific region. This brief was prepared by Dr Kamala Ley-Thriemer from the APMEN Vivax Working Group Coordinating Team to provide a general overview, to stimulate discussion and planning within country programs and the APMEN Vivax Working Group.

RATIONALE:

In most vivax endemic countries chloroquine (CQ) is the first line treatment against acute illness. Resistance towards this drug was first reported 25 years ago, but has received significantly less attention than resistance in P. falciparum. Treatment with partially effective drugs leads to increased recurrences and anaemia, associated with higher morbidity and mortality burden. Artemisinin combination therapies (ACT) are used in areas with chloroquine resistance (CQR) and are suggested as universal antimalarial therapy in areas where falciparum and vivax malaria are co-endemic. Primaquine (PQ) is currently the only available drug effectively killing liver stages of the parasite; however its effectiveness is limited by a long treatment course and concerns over haemolytic events.

INCLUSION CRITERIA:

Clinical trials published between January 2013 and December 2014 on the treatment of vivax malaria in the Asia-Pacific region:

- To assess efficacy of blood schizontocidal efficacy
- Trials assessing efficacy of primaquine (PQ) for radical cure are included.

CHLOROQUINE EFFICACY STUDIES:

Chloroquine is the first line treatment for P. vivax malaria in the majority of countries. However drug resistance emerged and constant monitoring is therefore warranted. A total of 5 studies have been published since 2013 investigating the efficacy of chloroquine in the Asia Pacific region.

All 5 studies [1-5] reported high efficacy of chloroquine for *P. vivax*. However a recent global review[6] including 155 trials assessing efficacy against blood stages of the *Plasmodium vivax* parasite reported evidence for CQR vivax in more than half of the site estimates and suggests that the extend of CQR is larger than expected. This review also draws attention to the heterogeneity between studies calling for better standardization of methods to measure drug efficacy in vivax malaria (see table at the end of the brief).
CHLOROQUINE VS ACT COMPARATIVE STUDIES:
ACT for the treatment of vivax malaria is recommended in areas with CQR vivax malaria. Universal treatment with ACTs for all malaria species might simplify treatment schedules. We found one comparative study


### ACT EFFICACY STUDIES

In areas where CQR is present ACTs are recommended. This unified treatment policy for different malaria species has pragmatic advantages. With emerging artemisinin resistance against *P. falciparum*, monitoring its efficacy in *P. vivax* is important. We found 4 trials assessing schizontocidal efficacy either as primary endpoint or as secondary endpoint in a study with longer follow up to assess radical cure with PQ.


### Study Efficacy Interpretation

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Leang et al, 2013</td>
<td>Day 28 CQ risk of recurrence between 0% (n=53) and 17.4% (n=46) depending on site Day 28 DHA-PIP 0% (n=60) risk of recurrence</td>
<td>DHA-PIP appears to be an appropriate new first line treatment for vivax malaria in Cambodia.</td>
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<tr>
<td>Senn et al, 2013</td>
<td>Day 28 AL 2.2% risk of recurrence (n=594) Day 42 AL 12% risk of failure (n=594)</td>
<td>AL provides a rapid clinical response against <em>P. vivax</em> malaria, but is associated with a high rate of <em>P. vivax</em> recurrent clinical episodes between days 28 and 42 in Papua New Guinea.</td>
</tr>
<tr>
<td>Pasaribu et al, 2013</td>
<td>Day 42 AAQ*+PQ 9% risk of recurrence (n=167) Day 42 DHA-PIP+PQ 6% risk of recurrence (n=164)</td>
<td>AAQ and DHA-PIP, both combined with primaquine, were effective for blood stage parasite clearance of uncomplicated <em>P. vivax</em> malaria in Sumatera, Indonesia</td>
</tr>
<tr>
<td>Liu et al, 2013</td>
<td>Day 42 ANQ** 1.6% risk of recurrence (n=128) Day 42 CQ-PQ 3.9% risk of recurrence (n=132)</td>
<td>ANQ is non-inferior to CQ-PQ in Yunnan Province, China</td>
</tr>
<tr>
<td>Lon et al, 2014</td>
<td>42 Day DHA-PIP (2 days) 9% risk of recurrence (n=40) 42 Day DHA-PIP (3 days) 4% risk of recurrence (n=40)</td>
<td>3 days DHA-PIP for vivax is still effective in Cambodia</td>
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</table>

*Artesunate-Amodiaquine  
**Artemisinin-Naphtoquine

Treatment with artemether-lumefantrine (AL) was found to have high cure rates at day 28 but considerably lower efficacy at day 42 in Papua New Guinea, most likely attributable to *P. vivax* occurring after day21 following a regimen with a relatively short post-treatment prophylaxis [7]. All the other clinical studies showed high cure rates with different ACTs [8, 9]. The study in Cambodia showed that a 3 day course of DHA-PIP is still effective (with lower cure rates for a 2 day course) [10].
CLINICAL TRIALS FOR P. VIVAX RADICAL CURE:

Studies assessing antirelapse efficacy are challenging to conduct and interpret. They require a long follow up to capture late relapses and are limited by the difficulty in distinguishing between relapse, recurrence and reinfections. The recent published studies presented their results as the risk of cure and/or recurrence (time to first event) at different follow up times. Since 2013 data from a total of 4 trials in the Asia Pacific region have been published.


PQ antirelapse efficacy depends on the dose administered and treatment schedule. The study by Pasaribu and colleagues in Indonesia showed similar recurrence rates at 12 months between patients receiving Artesunate-Amodiaquine (AAQ) + PQ and those receiving dihydroartemisinin - piperaque (DHA-PIP) + PQ [8]. Similar efficacy was also seen at 12 months between CQ+PQ and artemisinin-naphthoquine (ANQ) in Yunnan province, China [9]. The study in India showed that the risk of recurrence at 6 months was lowest when PQ was given at a high dose regimen with 7mg/kg total dose over 14 days compared to other schedules [11]. Weekly PQ dosing was found to be similarly effective that standard 14 days schedules in a study in Cambodia [10].

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<td>Pasaribu et al, 2013</td>
<td>AAQ+PQ 11.4% (n=143) risk of recurrence at 12m</td>
<td>AAQ and DHA-PIP, both combined with primaquine, had similar efficacy at 12 months</td>
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<tr>
<td></td>
<td>DHA-PIP+PQ (n=164) 9.1% risk of recurrence at 12m</td>
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<tr>
<td>Liu et al, 2013</td>
<td>12 months ANQ 20.5% (n=128) risk of recurrence</td>
<td>ANQ is non-inferior to CQ-PQ in Yunnnan Province, China</td>
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<td>12 months CQ-PQ 17.7% (n=132) risk of recurrence</td>
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<tr>
<td>Lon et al, 2014</td>
<td>6 months: Weekly PQ vs standard both 39% risk of recurrence (n=72)</td>
<td>No difference between weekly dose and standard 14d dose in Cambodia</td>
</tr>
<tr>
<td>Rajgor et al, 2014</td>
<td>6 months CQ only 16.39% (n=305) risk of recurrence</td>
<td>The higher recurrence rate in no PQ as compared to PQ groups documents PQ antirelapse activity and need to add PQ to treatment</td>
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<td>CQ + PQ (Low dose 15 mg/day × 14d) 8.07% (n=322) risk of recurrence</td>
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<td>CQ + PQ (Low dose 30 mg/day × 7d) 10.07% (n=298) risk of recurrence</td>
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<td></td>
<td>CQ + PQ (High dose 30 mg/day × 14d) 6.62% (n=317) risk of recurrence</td>
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IMPLICATIONS FOR POLICY AND PRACTICE

- CQR vivax is increasingly reported from different parts of the world, with the greatest resistance in Eastern Indonesia and PNG. Data from Cambodia showed that some areas have resistance rates of up to 17%. However other studies show that chloroquine remains efficacy in parts of China and India.

- ACTs for the treatment of *P. vivax* malaria were found to be effective at day 28 in several recent studies from the Asia-Pacific region. However lower cure rates are found in Papua New Guinea at day 42, emphasizing the short post treatment prophylaxis of AL.

- PQ was effective in preventing relapse in a weekly dose compared to standard dose in Cambodia. In India a high dose regimen with 7mg/kg total dose divided over 14 days showed lowest risk of recurrences compared to other dosage schemes.

FACTORS CONTRIBUTING TO THE GEOSPATIAL UNCERTAINTY IN *PLASMODIUM VIVAX* DRUG EFFICACY

<table>
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<tr>
<th>Drug Sensitivity</th>
<th>Explanation</th>
<th>Recommendation</th>
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<tr>
<td>Enrolment of patients without clinical disease</td>
<td>Host immunity in asymptomatic patients enrolled from cross-sectional surveys might enable clearance of parasitaemia even after partly effective drug treatment</td>
<td>Restrict efficacy trials to patients presenting with clinical disease</td>
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<td>Co-administration of early primaquine</td>
<td>Early primaquine has schizonticidal activity that can increase parasite clearance and prevent recrudescence infections</td>
<td>Primaquine treatment should be delayed until the end of the follow-up</td>
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<td>Short duration of follow-up</td>
<td>Early evidence of resistance is shown by late recrudescence</td>
<td>Patients should be followed up for a minimum of 28 days</td>
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Incorrect diagnosis of resistance

- Incomplete treatment course
- Dose of chloroquine too low
- Poor absorption of drug
- Poor drug quality

**Recommendation**

- Poor patient adherence
- Prescription of inadequate mg/kg dose
- Either from poor quality drug or reduced gastrointestinal absorption
- Faulty product

**Supervision of drug treatment**

**Documentation of exact dose of drug administered**

**Measurement of drug blood concentrations on day 7 and the day of parasite recurrence**

**Confirmation of adequate drug concentrations, pharmacological assessment of study drugs and purchase only from certified, trusted producers**

A suggested protocol to assess vivax QCR in a standardized approach can be found at: http://www.wwarn.org/en/resistance/malaria/literature/chloroquine-resistant-plasmodium-vivax

RESEARCH GAPS:

- Standardized approaches are needed to evaluate drug efficacy for *P. vivax* which allow better comparison between studies and uniform interpretation.

- Comparison of crude risk of recurrence by 28 becomes difficult for regimens with different elimination half-life.

- PCR correction in *P. vivax* schizontocidal efficacy is less precise than for *P. falciparum* due to high rates of homologous recurrences from liver stages.
REFERENCES


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