WWARN Vivax Surveyor

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Overview

1. WWARN
2. Chloroquine resistance in *P. vivax*
3. Systematic review
4. Vivax Surveyor
5. Future directions
Collaborative network of over 268 research partners worldwide

Mission to support WHO and national governments to provide comprehensive, timely, quality assured evidence to track the emergence and spread of resistance and improve drug efficacy of existing medicine and new drugs in development.
Chloroquine

• First line *P. vivax* treatment in most endemic countries

• Resistance identified in 1989

• Present in 53% of 113 assessable sites

• Lack of detection and monitoring for resistance

*Price et al*, *Lancet Infectious Diseases*, 2014
Chloroquine resistance

**Category 1 evidence** constitutes greater than 10% recurrences by day 28 (with a lower 95% CI of >5%), irrespective of confirmation of adequate blood chloroquine concentration; occasional breakthrough recurrences do occur within 28 days of chloroquine treatment, but a risk greater than 10% in a large enough sample is very suggestive of resistance.

**Category 2 evidence** includes studies with at least 5% recurrences by day 28 but lower 95% CI of <5% in the presence of whole-blood chloroquine concentrations greater than 100 nm (ie parasite growth in the presence of high blood concentrations of the drug confirms resistance) or studies with at least 5% recurrences by day 28 and lower 95% CI of >5% irrespective of confirmation of adequate blood chloroquine concentration.

**Category 3 evidence** includes studies with at least 5% recurrences by day 28 (lower 95% CI of <5%), irrespective of confirmation of adequate blood chloroquine concentration; this category provides potential evidence of chloroquine resistance, which may have arisen from other factors such as poor drug absorption or drug quality.

**Category 4 evidence constitute trials highlighting chloroquine susceptibility**, confirmed in at least 10 patients with symptomatic malaria, treated with chloroquine monotherapy (no early primaquine) and fewer than 5% recurrences occurring within 28 days.
Aims

Open access database and map of vivax clinical trials

Identify trends in chloroquine resistance
Systematic review

• PRISMA guidelines

• Medline, Web of Science, Embase and the Cochrane Database of Systematic Reviews

• Inclusion criteria:
  • Prospective therapeutic efficacy studies of *Plasmodium vivax* mono-infection ≥28 days published since 1st Jan 1960
  • Case reports of resistance

• Extracted study metadata, site, treatment and efficacy data
17429 studies identified

1280 antimalarial clinical efficacy studies

292 studies enrolled patients with *P. vivax*

31 studies excluded:
- 15 retrospective
- 7 no vivax monoinfection
- 6 duplicate cohorts
- 3 prophylaxis trials

231 clinical trials (77,126 patients)

30 case reports
Percentage of published trials relating to *P. vivax*.
Vivax Surveyor

Mapping vivax drug studies

Study Details
- Type: Blood Stage Clinical Trial
- Site: Alor, Indonesia
- Number of sites: 1
- Years: 2001 - 2002
- Type of study: Blood Stage Clinical Trial
- Total number of patients enrolled: 36
- Treatment Arms: Chloroquine

Chloroquine Efficacy
- Primaquine Regimen: Primaquine
- Timing of Primaquine: End of Study
- Number of patients treated with CQ: 36
- % Failures by Day 28: 43.30% [27.40% - 60.80%]
- CQR Category: Category 1: >10% recurrence by day 28 and lower 95% CI > 5% with or without CQ levels
- Comments:
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www.wwarn.org/vivax/surveyor
**Study Details**

**Type:** Blood Stage & Antirelapse Clinical Trial  
**Site:** Bangkok, Thailand  
**Number of sites:** 1  
**Type of study:** Blood Stage & Antirelapse Clinical Trial  
**Total number of patients enrolled:** 593 Patients  
**Treatment Arms:** Chloroquine, Primaquine, Artemisinin, Arteether - Lumezantrine, Atovaquone-Proguanil, Azithromycin, Clarithromycin, Doxycycline, Tetracycline, Primaquine, Artesunate, Chloroquine, Sulfadoxine-Pyrimethamine, Other, Halofantrine, Mefloquine, Quinine, Chloroquine, Tafenoquine

**Chloroquine Efficacy**

**Primaquine Regimen:** -  
**Timing of Primaquine:** -  
**Number of patients treated with CQ:** 22  
**% Failures by Day28:** 0.00% [0.00% - 14.90%]  
**CQR Category:** Uncategorised

**Study Details**

**Type:** Blood Stage Clinical Trial  
**Site:** Miarivazo, Madagascar  
**Number of sites:** 3  
**Years:** 2006  
**Type of study:** Blood Stage Clinical Trial  
**Total number of patients enrolled:** 105 Patients  
**Treatment Arms:** Chloroquine

**Chloroquine Efficacy**

**Primaquine Regimen:** -  
**Timing of Primaquine:** -  
**Number of patients treated with CQ:** 70  
**% Failures by Day28:** 6.60% [2.60% - 15.70%]  
**CQR Category:** Category 3: >5% failures by day 28 but lower 95% CI <5% +/- CQ PK  
**Comments:**
Beyond the surveyor...

Individual Patient Pooled analysis

- Systematic review
- Original data provided by investigators
- Data pooled
- Analysis
The effect of dosing strategies on the therapeutic efficacy of artemether-lumefantrine for uncomplicated malaria: a meta-analysis of individual patient data

The WorldWide Antimalarial Resistance Network (WWARN) AS-AQ Study Group

WWARN pooled analyses for *P. falciparum*
P. vivax pooled analysis (1)

Recurrence risks

• What are the key host, parasite and pharmacological determinants of early recurrence including:
  • The mg/kg dose effect of different schizontocidal treatments
  • The mg/kg dose effect of different primaquine treatments

• What is the relationship between parasite clearance and early vivax recurrence?
P. vivax pooled analysis (2)

Haematological impact

• What is the effect of P. vivax on haemoglobin with and without primaquine?

• What component of anaemia is attributable to malaria compared to primaquine?
P. vivax pooled analysis – current status

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<td>37</td>
<td>8110 (24.0%)</td>
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<td>Planned total</td>
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6 unpublished studies
Acknowledgements

• Ric Price
• Kamala Ley-Thriemer
• Ben Ley

• Georgina Humphreys
• Hazel Ashurst
• Andrew Payne
• Prabin Dahal
• Dr Kasia Stepniewska
• Carol Sibley
• Philippe Guerin

• Julie Simpson

wwarn.org/vivax/surveyor

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