

Efficacy of Three Regimens of Chloroquine and Primaquine for the Treatment of *P. vivax* Malaria in Cruzeiro do Sul, Acre, Brazil

Sarah-Blythe Ballard, MD, PhD
Alexandre Macedo de Oliveira, MD, MSc, PhD
Malaria Branch, Division of Parasitic Diseases and Malaria

Center for Global Health

Malaria Branch, Division of Parasitic Diseases and Malaria



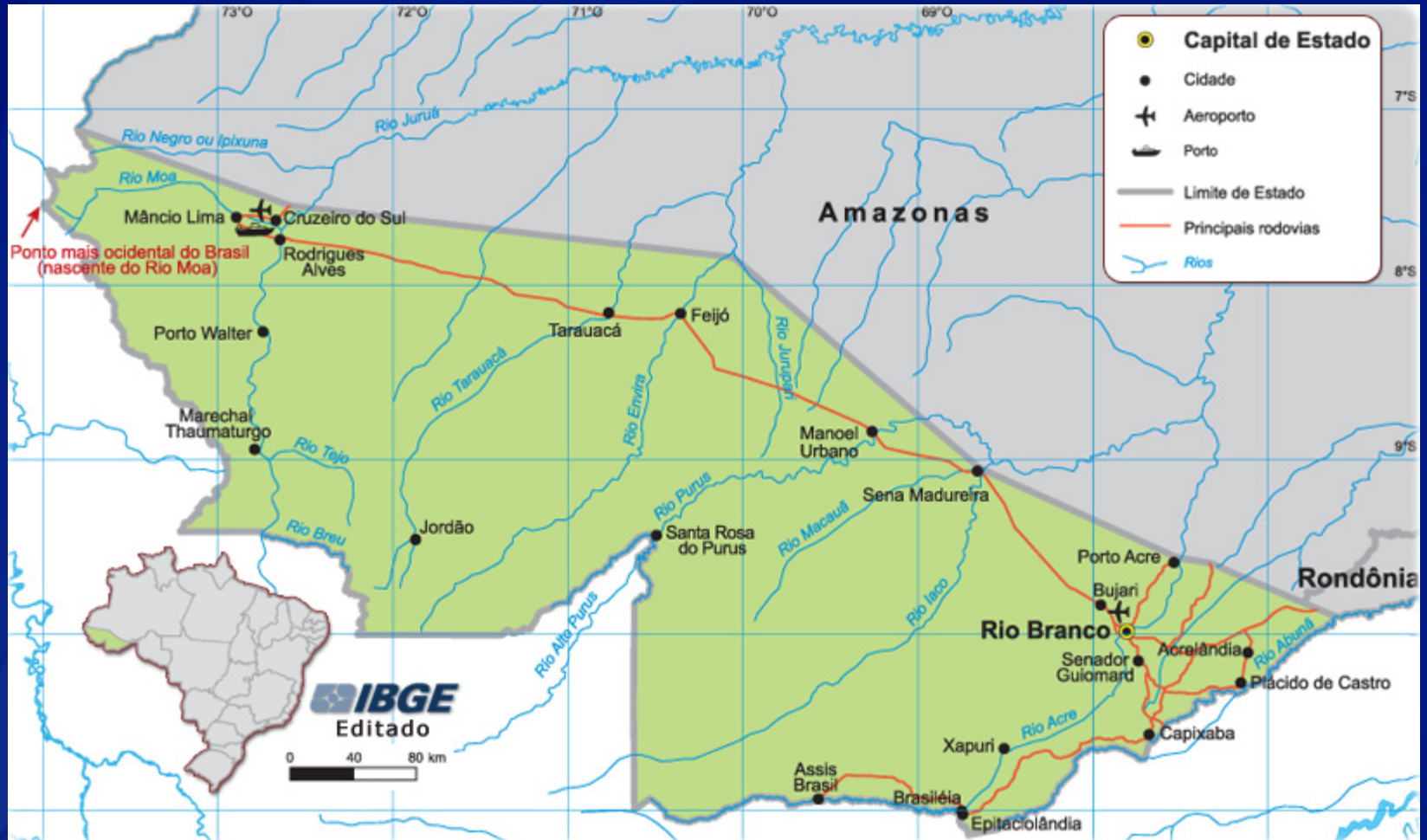
Agenda

- Explain reasons for conducting this study
- Share challenges in implementing *in vivo* efficacy trials in low -transmission settings
- Share some preliminary results (follow -up still on going)
- Challenge you to start thinking about next steps regarding radical treatment of vivax malaria

Malaria in Brazil, 2016

- 151,620 cases
- Species
 - 88% *P. vivax*
 - 12% *P. falciparum* or mixed infections
- Acre state
 - 35,209 cases
 - Higher risk in western region

Acre State



P. viva Efficacy Trials: Tougher Reality

- Around 120 patients per arm to account for higher chances of loss to follow up due to longer follow up (6 months)
- Often multiple sites for enrollment due to larger sample size (6 to 10 staff in total)
- Health facility –based enrollment but home -based follow -up
- Genotyping correction not agreed upon

Efficacy of Chloroquine and Primaquine for the *P. vivax* Malaria, Cruzeiro do Sul, 2014

- 168 days of follow -up (6 months)
- 3-day course with chloroquine
 - 1 daily dosing
 - Total adult dose: 1.5 g
- 7-day course with primaquine
 - Total dose: 3.5 mg/Kg over 7 days

Efficacy of Chloroquine and Primaquine for the *P. vivax* Malaria, Cruzeiro do Sul, 2014

- 119 patients enrolled
 - 26 *P. falciparum* infections during 6 -month follow -up
 - 28 (~30%) *P. vivax* infections during 6-month follow -up
 - 13 reinfections or relapses (different molecular profile)
 - 15 likely relapses (same molecular profile)
- Uncorrected Day 168 failure = 30.1% (28/93)
- Genotyping -corrected Day 168 failure = 18.8% (15/80)
- Moderate relapse rate within first 6 months

Primaquine Dose

- World Health Organization (2015)
 - Total dose: 3.5 or 7.0 mg/kg
 - 0.25 mg/kg/day over 14 days in temperate areas
 - 0.5 mg/kg/day over 14 days in tropical areas
- Countries in the Americas
 - Total dose: 3.5 mg/kg
 - 0.25 mg/kg/day over 14 days
 - 0.5 mg/kg/day over 7 days

Tafenoquine Study

	Chloroquine plus tafenoquine				Chloroquine plus primaquine (n=50)	Chloroquine alone (n=54)
	50 mg (n=55)	100 mg (n=57)	300 mg (n=57)	600 mg (n=56)		
Peru, n	22	24	23	23	22	22
Efficacy, % (95% CI)	45.5% (23–66)	39.5% (20–58)	81.1% (57–92)	84.0% (58–95)	58.7% (36–76)	12.2% (2–31)
Brazil, n	6	6	6	7	6	6
Efficacy, % (95% CI)	33.3% (5–68)	33.3% (5–68)	83.3% (27–97)	85.7% (33–98)	83.3% (27–97)	16.7% (1–52)
Thailand, n	16	16	19	16	16	16
Efficacy, % (95% CI)	60.0% (32–80)	67.3% (38–85)	94.7% (68–99)	100% (100–100)	92.9% (59–99)	56.3% (30–76)
India, n	11	11	9	10	6	10
Efficacy, % (95% CI)	90.9% (51–99)	80.0% (41–95)	100% (100–100)	100% (100–100)	100% (100–100)	90.0% (47–99)

No statistical comparisons were made at the country level.

Objective

- Evaluate the efficacy of chloroquine and three different regimens of primaquine for treatment of uncomplicated *P. vivax* malaria in Brazil
 - Standard “low dose” primaquine (7 days), unsupervised
 - Standard “low dose” primaquine (7 days), supervised
 - Doubled “high dose” primaquine (14 days), supervised

Study Design

- Three-arm clinical trial
- 168-day follow -up (6 months)
 - Day 28 as primary endpoint for acute treatment efficacy
- Enrollment at malaria diagnostic posts (Hospital Regional do Vale do Juruá post and others) in Cruzeiro do Sul
- Home-based follow -up

Partner Institutions

- Brazilian National Malaria Control Program
- Secretaria Estadual de Saúde do Acre (SESACRE), Acre State Health Secretariat
- Instituto Evandro Chagas (a Brazilian national institute of health)
- Universidad de los Andes, Santiago, Chile
- PAHO
- CDC

Inclusion Criteria

- Age ≥ 5 years
- Fever (temp $>37.5^{\circ}$ C) or history of fever in previous 48 hours
- *P. vivax* monoinfection
 - 100 to 200,000 parasites/ μ l
- Informed consent and assent
- No signs of severe malaria

Total Sample Size (n=257)

- Group 1: 40% recurrent infection
 - 39 patients to compare Groups 1 and 3
 - 50 patients WHO minimum
 - 65 patients final
- Group 2: 30% recurrent infection
 - 74 patients to compare Groups 2 and 3
 - 96 patients final
- Group 3: 10% recurrent infection
 - 74 patients to compare Groups 2 and 3
 - 96 patients final

Study Arms

- Group 1
 - Unsupervised primaquine with usual primaquine dose of 3.5 mg/kg (0.50 mg/kg/day for 7 days)
- Group 2
 - Supervised primaquine with usual primaquine dose of 3.5 mg/kg (0.50 mg/kg/day for 7 days)
- Group 3
 - Supervised primaquine with increased primaquine total dose of 7.0 mg/kg (0.50 mg/kg/day for 14 days)

Treatment

- **3-day course with chloroquine**
 - 1 daily dosing
 - Total adult dose: 1.5 g
- **7- or 14-day course with primaquine**
 - After G6PD result
 - Total dose: 3.5 mg/Kg or 7.0 mg/Kg
 - Weight adjustment
- **All doses supervised (except primaquine for Group 1)**

Enrollment and Follow -up

- Outpatient clinic at Hospital Regional do Jurua
 - Days 0 to 3
 - Study nurse mandatory
- Home visits
 - Primaquine doses (not for Group 1)
 - Days 7, 14, 21, 28, 56, 84, 112, 140, 168
 - Nurse assistant

Home Follow-up



Microscopy

- Slide prepared at outpatient clinic or during home visits
- 2 independent readings
 - First reading on the day of visit
 - Second in up to 48 h
- Third reading if discordant (>50% in parasitemia or species)

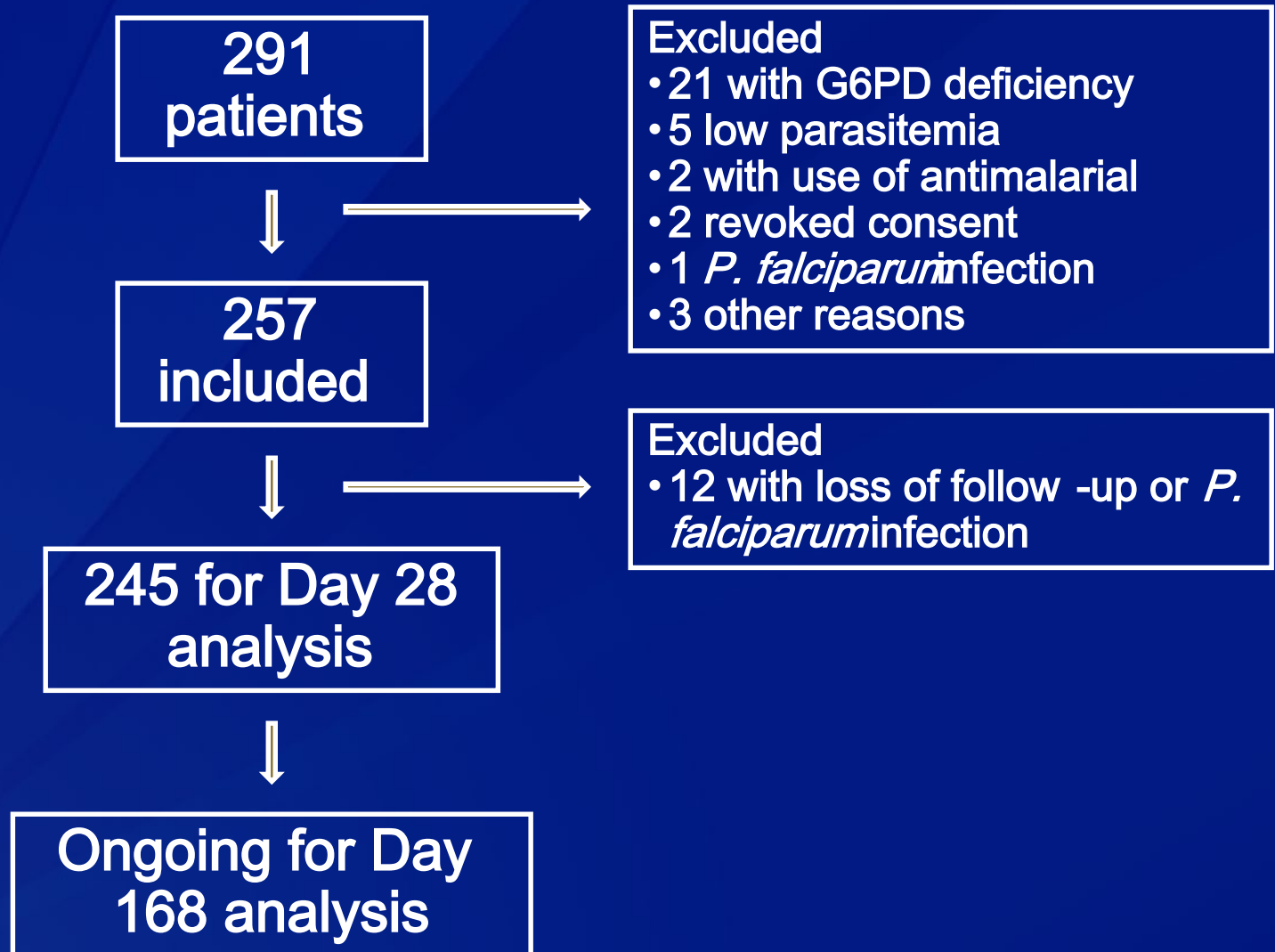
Challenges

- **Multi -arm study**
 - More patients
 - Randomization procedure
- **Late start**
 - Logistical challenges
 - PAHO assistance crucial
- **Low patient enrollment**
 - Creativity
 - Expansion to a rural area in Cruzeiro do Sul
 - Extra funds
 - Risky move

Results

- Enrollment
 - April 9 – August 30, 2018
- End of follow -up (study ongoing)
 - February 2019
- 291 patients conditionally included in study
 - 34 excluded

Results



Endpoint (Preliminary Results)

- Day 28
 - 245 patients reaching Day 28
 - 3 *P. vivax* infections
 - All from Group 2 (7 -day supervised primaquine)
 - Group 2
 - 97 patients included
 - 5 *P. falciparum* infections
 - Adequate clinical and parasitologic response (ACPR) = 96.7% (89/92)

Endpoint (Preliminary Results)

- Day 168
 - 49 reached Day 168 without recurrence
 - 6 new *P. falciparum* infections
 - 24 patients with loss of follow -up
 - 46 *P. vivax* infections
 - 15 in Group 1
 - 23 in Group 2
 - 4 in Group 3

Supervision

- Weekly conference calls with CDC
- 2 supervisory visits so far
 - During enrollment
 - Issues with patient enrollment
- Low patient enrollment
 - Expansion to rural areas
 - More challenging

Conclusions

- Chloroquine and primaquine efficacious for the treatment of the **acute phase** of uncomplicated *P. vivax* malaria in Cruzeiro do Sul
- Results on the prevention of relapse pending
- High-level performance of Acre staff and our partners

Next Steps

- Finalize patient follow -up (expected for February 2019)
- Engage in molecular processing and analysis
 - Not an easy task
 - Lack of agreement on techniques for *P. vivax*
 - South-to-South collaboration
- Maintain momentum with our portfolio in the region

Enf. Sâmela e Dra. Suiane



Muito Obrigada

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- Cassio Roberto Peterka
- Paola Marchesini, former
- Ana Carolina Santelli, former

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- Stella Maris Chenet Carrasco