

The **ASMQ** Fixed-Dose Combination to treat Malaria
From Blueprint to Use in the Field
1 year after the launch in Brazil

**Effect of the artesunate mefloquine
fixed dose combination in the malaria
transmission in Amazon basin
communities**

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ASTMH, 19th November 2009

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Intervention study ASMQ – Acre

Background

- Malaria is a major public health problem in Brazilian Amazon: 500,000 cases/year
- Brazilian National Malaria Control Program deliver malaria diagnosis and treatment free of charge
- Concern about increasing antimalarial resistance to quinine-doxycycline (QD)
- In 2006, QD was first line treatment for Plasmodium falciparum malaria
- Artesunate-mefloquine new fixed-dose combination (ASMQ) in development, registration in the country in March '08

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Principal Investigator	Marcos Boulos
Steering Committee	Roseli La Corte – MOH/UFSE José Ladislau – MOH Paola Marchesini – PAHO Isabela Ribeiro – DNDi
Data Analysis	SVS/MS, OPAS/OMS, DNDi, USP, UERJ
Regional Coordination	Suiane do Valle
Monitors	Ana Carolina Santelli –MOH André Daher – Fiocruz



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Main objective

- To evaluate the impact of programmatic use of ASMQ in the reduction of falciparum malaria incidence in comparison with the standard regimen* used in Brazil

*Quinine + doxycycline + primaquine



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Secondary Objectives

- To evaluate the impact of ASMQ in the ratio of *Plasmodium vivax* / *Plasmodium falciparum*
- To evaluate the *P. falciparum* recurrence rate after 40 days
- To evaluate the proportion of slides with sexual forms of the parasite (gametocytes)



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Methods



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Type	Effectiveness study
Period	July/2006 to December/2008
Site	3 municipalities in the Juruá Valey, Acre
Intervention	Artesunate-mefloquine (<i>Farmanguinhos</i>) 25+50 mg ou 100+200 mg 1-2 tablets/d po for 3 days
Follow-up	Thick smear D7 and D40



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Selection Criteria – Study area

- Priority municipalities for the MOH (high risk areas IPA \geq 50/1.000 habitants)
- Monthly average > 20 cases of falciparum malaria
- Proportion of imported cases < 15%
- Cooperation of local health authorities



Intervention study ASMQ – Acre

Study area

- Acre State in Northeast Brazil at Amazon Basin
- Juruá Valley: 3 municipalities with 103,809 inhabitants, total
 - 86% of malaria cases in Acre State
- Tropical climate, 72-93°F, relative humidity 60-85%, rainy season Oct-April
- Seasonal malaria
- Malaria treatment through the public sector only



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Inclusion Criteria

- All patients presenting to the health system
- Age \geq 6 months
- Microscopic diagnosis of *P. falciparum**
- Parasitaemia* 250 to 100.000/uL or \leq +++
- Consent from patient or legal representative

*RDTs were accepted for inclusion after introduction as programmatic routine



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Exclusion criteria

- **Pregnancy: amenorrhea \geq 1 month**
- **Inability to tolerate oral medication**
- **Persistent vomiting (> 2 in the previous 24 h)**
- **Convulsions (> 1 in the previous 24 h)**
- **Lethargy/unconsciousness**
- **Severe malaria**
- **Mixed malaria**

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Safety monitoring

- **Pilot pharmacovigilance system in preparation to ACT roll-out**
- **Passive notification: all patients encouraged to report adverse events after administration of the drug to the local supervisor**
- **Standard forms from national regulatory agency available at the health facilities, diagnostic posts and to all health agents**
- **Training of health agents and local doctors on filling of the forms and instructions to patients**
- **All patients instructed to look for a health unit if they present any symptom related to the drug**

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Safety monitoring

- Cards with the therapeutic regimen and instructions on the need to seek assistance in case of adverse events were distributed to health agents and patients
- Notification forms were made available in all local hospitals.
- A letter with instructions to report adverse events was sent to every physician registered in local medical council
- The regional coordinator was a physician who could be reached at any time to clarify doubts or provide assistance. Her phone number was available in the informed consent given to each of the patients
- Toll-free number available for notification of events

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Control strategies

- Strengthening of local management
- Active surveillance
- Vector control: indoor spraying
- Long lasting impregnated nets in Dec/07

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Data management and analysis

- Notification and data entry in routine vigilance (Sivep_Malaria)
- Evaluation pre and post intervention
- Time series analysis
 - Polinomial regression model: Pf and P. vivax (Pv) malaria incidence; Evaluation of difference in trends
 - Random-effects models for longitudinal data
- Covariates investigation: age, malaria cases at study initiation, proportion of imported cases, objective measures of control, number of settlements, temperature, humidity, pluviometric index, time from initiation of symptoms and treatment, gametocytes on day 0
- Comparison with other municipalities in the same state
- Software: Tableau 3.5, Microsoft Office Excel 2003, RecLink



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Results



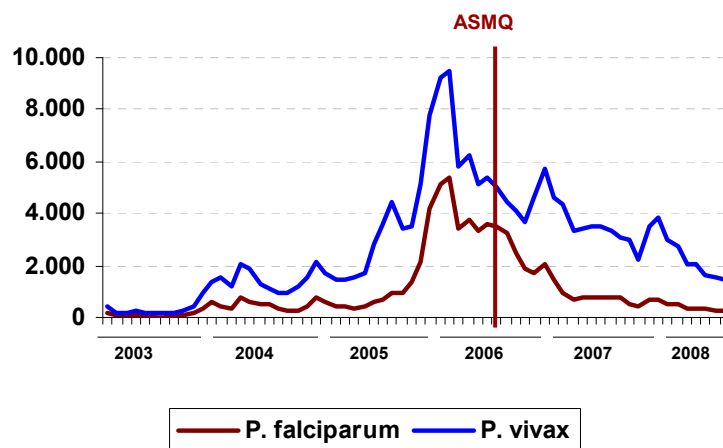
Intervention study ASMQ – Acre

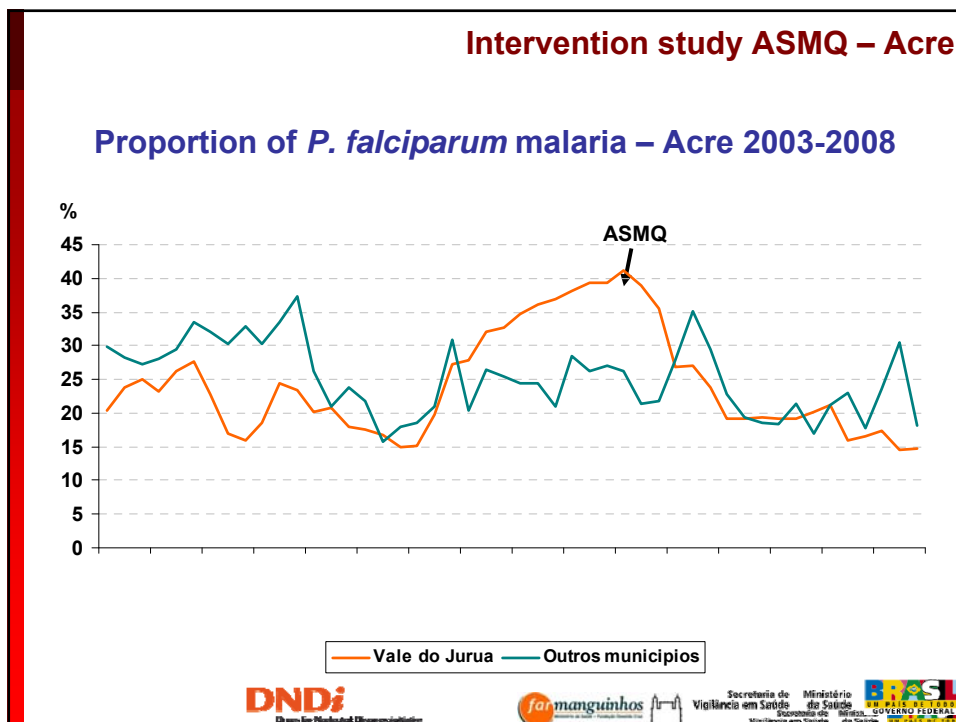
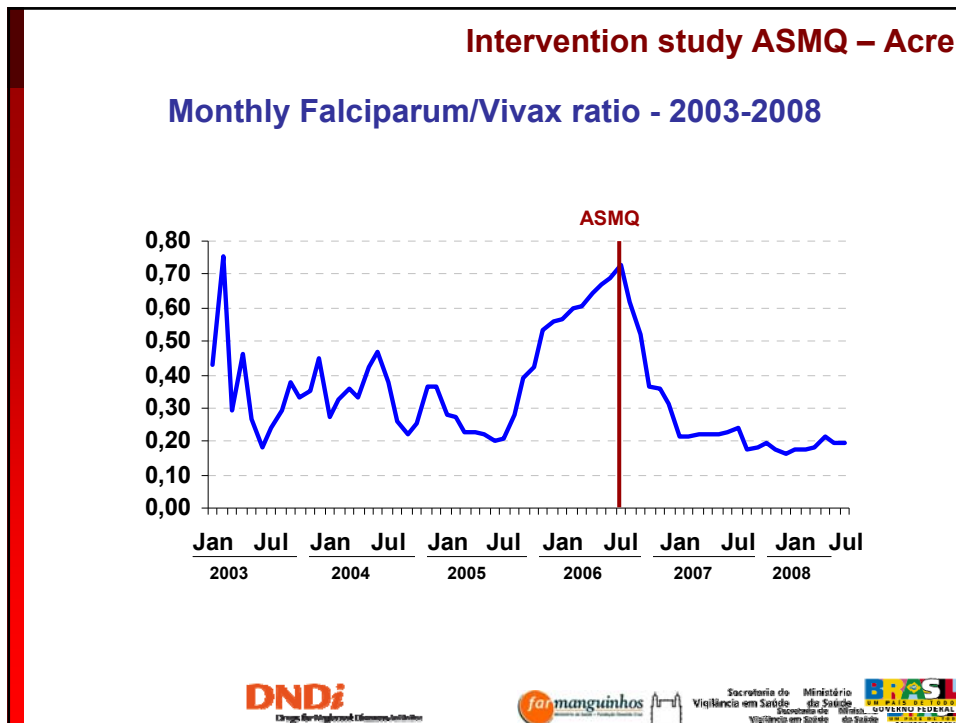
Description of population

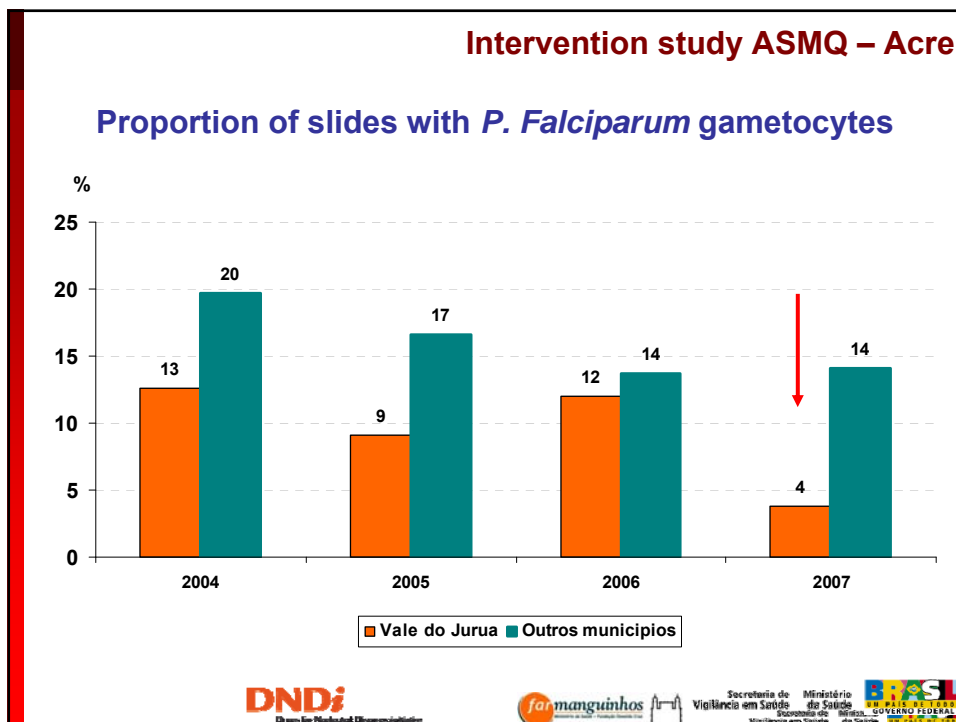
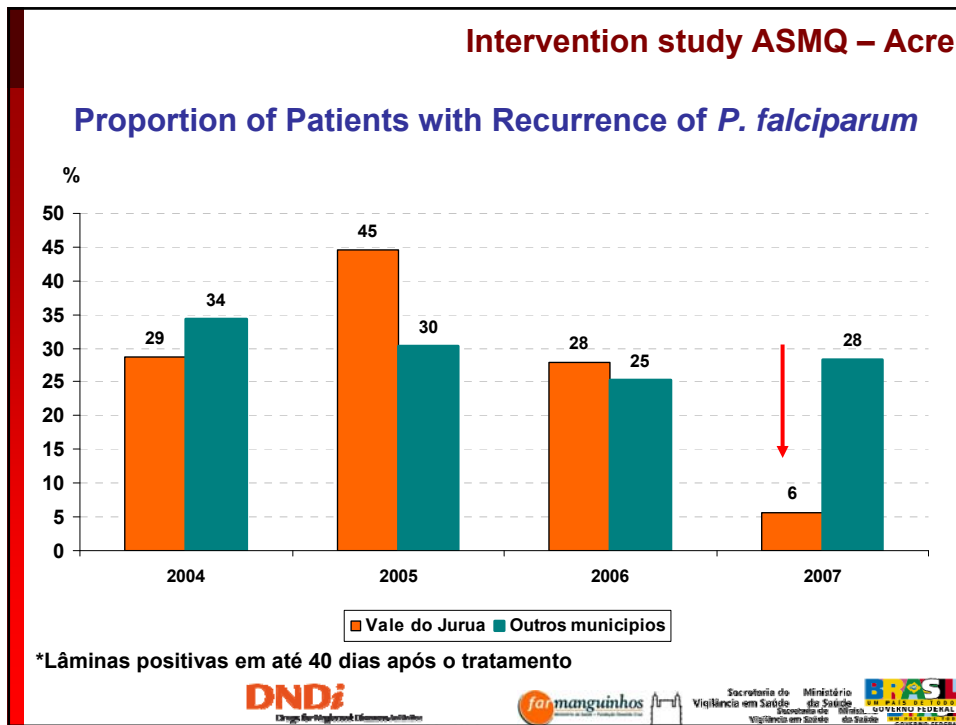
- Total population treated ASMQ: 31,453 patients
- Ratio female/male: 43%

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Monthly malaria cases - 2003-2008







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Safety

- No serious adverse events reported
- One single non-serious adverse report recorded in 2007
- No direct reports to the free-toll pharmacovigilance number from Farmanguinhos
- No reports to the national regulatory agency, ANVISA



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Discussion

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Conclusions

- **Successful study implementation in programmatic context, in collaboration with MoH and PAHO**
- **Significant impact of ASMQ in malaria reduction and change in Pf/Pv ratio after an epidemic period**
- **Lower positivity and gametocytes in follow-up smears**
- **No significant adverse events identified through passive notification system**

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Limitations

- **Intervention, ecological study, non-randomised**
- **Role of other control interventions: analysis ongoing**



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Thank you!

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