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-doxicycline (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
### Intervention study ASMQ – Acre

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Marcos Boulos</th>
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<tbody>
<tr>
<td>Steering Committee</td>
<td>Roseli La Corte – MOH/UFSE</td>
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<td></td>
<td>José Ladislau – MOH</td>
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<td></td>
<td>Paola Marchesini – PAHO</td>
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<td>Isabela Ribeiro – DNDi</td>
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<td>Data Analysis</td>
<td>SVS/MS, OPAS/OMS, DNDi, USP, UERJ</td>
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<td>Regional Coordination</td>
<td>Suiane do Valle</td>
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<tr>
<td>Monitors</td>
<td>Ana Carolina Santelli – MOH</td>
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<td>André Daher – Fiocruz</td>
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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 + doxicycline + 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)

Methods

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

Type: Effectiveness study
Period: July/2006 to December/2008
Site: 3 municipalities in the Juruá Valley, Acre

Intervention: Artesunate-mefloquine *(Farmanguinhos)*
25+50 mg ou 100+200 mg
1-2 tablets/d po for 3 days

Follow-up: Thick smear D7 and D40

Selection Criteria – Study area

- Priority municipalities for the MOH (high risk areas IPA≥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

Inclusion Criteria

- All patients presenting to the health system
- Age > 6 months
- Microscopic diagnosis of *P. falciparum*
- Parasitaemia* 250 to 100,000/uL or < +++
- Consent from patient or legal representative

*RDTs were accepted for inclusion after introduction as programmatic routine*
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Exclusion criteria

- Pregnancy: amenorrhea > 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
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

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
  – Polynomial 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
Description of population

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

Monthly malaria cases - 2003-2008

P. falciparum
P. vivax
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Monthly Falciparum/Vivax ratio - 2003-2008

Proportion of \(P. \text{falciparum}\) malaria – Acre 2003-2008

Presented at ASTMH09 - ASMQ Breakfast session
Intervention study ASMQ – Acre

Proportion of Patients with Recurrence of *P. falciparum*

<table>
<thead>
<tr>
<th>Year</th>
<th>Vale do Jurua</th>
<th>Outros municípios</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td>2005</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>2006</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>2007</td>
<td>6</td>
<td>28</td>
</tr>
</tbody>
</table>

*Lâminas positivas em até 40 dias após o tratamento*

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Proportion of slides with *P. Falciparum* gametocytes

<table>
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<th>Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>2005</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>2006</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>2007</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>

Presented at ASTMH09 - ASMQ Breakfast session
Intervention study ASMQ – Acre

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

The ASMQ Fixed-Dose Combination to treat Malaria
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Discussion
Intervention study ASMQ – Acre

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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