Malaria in Pregnancy: MMV Current and Potential Future Contributions

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MIPWG, Maputo
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2. MMV Current Contributions
   - MMV contribution to ongoing clinical trials in MIP
   - Update on the MMV supply grant (QA SP)
   - SP market research findings

3. MMV Future Contributions
   - Consider the development of Pyronaridine/Piperaquine
   - Prioritizing molecules and accelerating the development of antimalarials for pregnant women while developing next-generation antimalarials
Medicines for Malaria Venture

... a quick overview

- Swiss based non-for-profit foundation created in 1999

- Mission: to reduce the burden of malaria by **DISCOVERING, DEVELOPING** and **DELIVERING** new effective and affordable antimalarial drugs

- About 400+ partners worldwide including research / academia, pharmaceutical companies, governments, NGOs
MMV-supported projects

**Research**
- **Lead optimization**
  - Miniportfolio 2 series
    - GSK
- **Candidate profiling**
  - OZ609/MMV052
    - NebrasQ/STPHI
  - PAN9
    - TropiQ/RUMC
  - Phenotypic
    - Daiichi-Sankyo
  - Open Source Series
    - University of Sydney
  - Phe tRNA ligase
    - Broad Institute/Eisai
- **Pantothenates**
  - TroplQ/RUMC

**Translational**
- **Preclinical**
  - MMV253
    - Zydus Cadila
  - AN13762
    - Sanofi
  - SAR121
    - Sanofi
  - M5717
    - Merck KGaA
- **Human volunteers**
  - P218
    - Janssen
  - SJ733
    - Kentucky/Eisai
  - KAF156/Lumefantrine
    - Novartis
- **Patient exploratory**
  - Artefenumol/Ferroquine
    - Sanofi
  - Piperaquine
    - Novartis
- **Patient confirmatory**
  - Dihydroartemisinin-piperaquine dispersible
    - Alfasigma
  - Sulfadoxine-pyrimethamine+amodiaquine dispersible
    - 5 Kart worship
- **Regulatory review**
  - DSM265
    - Takeda
  - MMV048

**Product development**

**Access**
- **Approved/ERP**
  - Artemether-lumefantrine
    - Dispersible
    - Novartis
  - Artesunate for Injection
    - Gulin
  - Dihydroartemisinin-piperaquine
    - Alfasigma
  - Pyronaridine-artesunate
    - Shin Poong
  - Pyronaridine-artesunate granules
    - Shin Poong
  - Artesunate-amodiaquine
    - Sanofi
  - Artesunate-apyrimethamine
    - Cipla
  - Sulfadoxine-pyrimethamine+amodiaquine
    - Gulin
  - Rectal artesunate
    - Cipla
  - Rectal artesunate
    - Strides Shasun
  - Tafenoquine
    - GSK

MMV support to projects may include financial, in-kind, and advisory activities.

Footnotes:  
- Included in MMV portfolio after product approval and/or development. DNDi and partners completed development and registration of ASMQ and ASAQ.  
- Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing.  
- WHO Prequalified OR approved/positive opinion by regulatory bodies who are ICH members/observers.  
- Paediatric formulation.

Brand names:
1. Coartem® *Dispersible*  
2. Artesun®  
3. Eurartesim®  
4. Pyramax® tablets or granules  
5. ASQA Winthrop®  
6. SPAQ-CO™  
7. Krintafel/Kozenis (Trademarks owned or licensed by GSK)

(Status of tafenoquine & Strides Shasun rectal artesunate updated September 2018)
MMV Current Contributions

Defeating Malaria Together
Generating Safety Data in Pregnant Women

• Artemisinin use in the first trimester of pregnancy is restricted

• DHA-PQP has been recently introduced for malaria treatment in 1st trimester in Indonesia

• MMV is supporting a study in Indonesia with the Liverpool School of Tropical Medicine in conjunction with the Timika Research Facility, Indonesia, to enrich the growing body of safety data on pregnancy outcomes associated with DHA-PQP exposure in first trimester
Post-Marketing DHA-PQP studies in malaria in pregnancy

In an effort to identify alternative drug options for IPTp, MMV is involved in the conduct of 2 clinical studies:

- Cardio-safety of DHA-PQP and PK of PQP amongst pregnant women in Tanzania – LSHTM

- Safety and efficacy of DHA-PQP for IPTp of malaria in HIV-infected pregnant women in Gabon and Mozambique (MAMAH study) - ISGlobal
Unitaid supply grant– filling QA SP Gap

- 4-year project which started in 2017

- Objective 1: secure QA SP market by bringing 2 new manufacturers of finished products to WHO prequalification

- Objective 2: development of packaging promoting IPTp
Filling QA SP GAP

... by supporting local manufacturing

• Key considerations
  • SP mainly procured with national budget – many countries buy it from local manufacturers (only 30% is procured from donors)
  • SP is on the import prohibition list in Nigeria to protect local manufacturing (*Nig key market*) – same situation in Uganda

• Opportunities
  • Build capacity – today only a few manufacturers based in Africa meet GMP standards and have WHO prequalified products
  • Experience with SP getting prequalification can apply for any other antimalarials (*e.g. Nigeria manufactures medicines product = 60% of West Africa market*)
## New QA SP: key milestones

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
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<tr>
<td>WHO ERC</td>
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<tr>
<td>BE study</td>
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<tr>
<td>WHO PQ*</td>
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<tr>
<td>Dossier review</td>
<td>12–14 m</td>
<td>★</td>
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<tr>
<td>Global Fund ERP**</td>
<td>Review 6 m</td>
<td>★</td>
<td></td>
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<tr>
<td>Country registration</td>
<td>6-18 months</td>
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</tbody>
</table>

### SP Universal Kenya

- **WHO ERC**: ★
- BE study: ★
- WHO PQ*: ★
- Dossier review: 12–14 m ★
- Global Fund ERP**: ★
- Review 6 m: ★
- Country registration: 6-18 months ★

### SP Nigeria manufacturer 1

- **WHO ERC**: ★
- BE study: ★
- WHO PQ*: ★
- Dossier review: 12–14 m ★
- Global Fund ERP**: ★
- Review 6 m: ★
- Country registration: 6-18 months ★

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**Key Milestones**

- **1st dossier submission to WHO PQ**: Q4 2019
- **2nd dossier submission to WHO PQ**: Q2 2020

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*WHO prequalification

**Global Fund Expert Review Panel
Development of adapted packaging for IPTp

... in a context of community health delivery

• **Objective**
  • To improve acceptance and compliance to IPTp
  • To generate demand

• **Materials tested:**
  • Blister
  • Patient leaflet
  • CHW job aid
Packaging field-testing - study design

• Lead: Sylvain Faye, UCAD, Dakar
• Feb-August 2018
• 3 countries: DRC, Nigeria and Mozambique
• Research questions:
  • Use and acceptability of SP packaging and communication materials
  • Perception of SP

• Qualitative and iterative: interview adapted to respondent; design adapted by response trends

• Mix of individual interviews and focus groups discussions
## Packaging field-testing - study design (2)

**Primary audience:**
- pregnant women (2\textsuperscript{nd}/3rd trimester) + last 6 months delivery
- community health workers / health workers / ANC supervisors
- partners/husbands

**Sample size: 294 respondents**

<table>
<thead>
<tr>
<th>Pays</th>
<th>Province</th>
<th>District</th>
<th>Total #interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDC</td>
<td>KWANGO</td>
<td>KENGE</td>
<td>107</td>
</tr>
<tr>
<td>NIGERIA</td>
<td>EBONYI</td>
<td>OHAUKWU</td>
<td>105</td>
</tr>
<tr>
<td>MOZ</td>
<td>SOFALA</td>
<td>NHAMATANDA</td>
<td>82</td>
</tr>
</tbody>
</table>
Summary of key findings: CHW’s perception of SP

- knowledge through wives/family members/relatives experiences (not through training)
- Fansidar often cited
- confusion between SP / Paracetamol
- reluctance to recommend SP due to:
  - side effects
  - no distinction with other drugs (e.g. white color)
  - fear of counterfeit
  - SP used for other intervention (e.g SMC)
- the absence of ‘specificity’, not own label, unsafe to distribute
Summary of key findings: pregnant women’s perception of SP

• Minority of respondents has a positive experience = malaria free pregnancy

• Negative perception due to:
  • side effects (e.g. nausea, vomiting)
  • quality of SP (e.g dispense in big jar = no hygiene measures, no info on expiry date)
  • smell and shape, size of SP tablet
  • no SP identity – loose white tablet (as paracetamol) raising concerns about counterfeit (e.g. Nigeria)
  • doubt with the effectiveness of the intervention
  • fear of harming their baby
Summary of key findings: blister

- **Blister**
  - Well appreciated by all audiences!
  - Perception of quality medicines
  - Create stronger SP identity
Summary of key findings: CHWs Job aid

Regularly give SP to pregnant women to protect them and their babies from malaria.

Administre regularmente la SP a las mujeres embarazadas para protegerlas y a sus bebes, contra el paludismo.

Regularmente tome SP para proteger você e seu bebê da malária.

**MALARIA-FREE PREGNANCY**

**GROSSESSE SANS PALUDISME**

**WITH**

**AVEC**

**SP: SULFADOXINE/ PYRIMETHAMINE**

This treatment can be safely administered until the time of delivery.

Gave a full 3 tablet dose of SP to prevent malaria, starting as early as possible in the second trimester, and at least three times during pregnancy, with individual doses given one month apart.

Este tratamiento puede ser administrado hasta el momento de la entrega.

Tome uma dose completa de 3 comprimidos de SP para prevenir la malária, com o maior numero de vezes possivel no segundo trimestre, pelo menos três vezes durante a gravidez com doses individuais com pelo menos um mês de intervalo.

**Meses**

**Números de comprimidos de SP**

Se a gestante apresentar febre ou sinais de malária, tive a malária...

... se ela for positiva, administrar um tratamento eficaz.

Pergunta-se se a gestante já recebeu algum medicamento. De criar a medicamento continuado ou então, consulte um profissional de saúde.

As mulheres que receberem a medicamento e não devam tomar SP devido à malária não devem tomar SP.

**No administration SP antes da 13ª semana de gravidez (2 meses).**

**Nima absence de gravidez (3 meses).**

**Cuidado** para que a mulher grávida não receba SP além do terceiro trimestre.

**Inclua a data em que a gestante tomou a medicamento no cartão do paciente.**

**Depois de frico vá, quando inicia ou é iniciada a desinfeção de espécimes, devida-se a amostra de SP para os laboratórios.**

**Meses**

**Número de comprimidos de SP**

Este tratamento pode ser administrado como segurança até o momento da entrega.

Tome uma dose completa de 3 comprimidos de SP para prevenir uma infecção por malária, começando o mais cedo possível no segundo trimestre, pelo menos três vezes durante a gravidez com doses individuais com pelo menos um mês de intervalo.
Patient leaflet

IMPORTANT FOR PREGNANT WOMAN

Regularly take SP to protect yourself and your baby from malaria.

- From the 2nd trimester, have regular antenatal care contacts.
- Take a full 3-tablet dose of SP to prevent a malaria infection, starting as early as possible in the second trimester, and at least three times during your pregnancy with individual doses given at least one month apart.

If you get fever or signs of malaria, seek diagnosis immediately and, if tested positive for malaria, take effective treatment.

Protect yourself and later also your newborn from malaria by sleeping under a bednet each night.

Take iron and folic acid each day to prevent anaemia.

Usually SP is very well tolerated. If, however, you feel adverse drug reactions, consult your health worker.

Months | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Number of SP tablets per month | ! | ! | ! | ! | ! | ! | ! | ! | !

Next appointment dates
SUCCESSFUL GLOBAL CALL TO ACTION!
MMV Future Contributions

Defeating Malaria Together
Women & Gender Equity in Malaria

- Pregnant women are the main risk group among adults in most malaria-endemic areas.
- Choices of antimalarials during pregnancy are limited.
- Pregnant women are excluded from clinical trials:
  - Typically due to concerns around teratogenicity, embryotoxicity and safety
  - Also due to development complexity, liability and cost
- Attention to gender is high on Global agenda.
- Risk management: Women should not be protected from research but through research.
## Antimalarials for Pregnant Women
### Teratogenicity and Drug Label Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Teratogenic Potential</th>
<th>Label Warning Section Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>NO</td>
<td>USPI - Pregnancy Category B. Use in pregnancy only if clearly needed.</td>
</tr>
<tr>
<td>Quinine</td>
<td>YES</td>
<td>USPI - Pregnancy Category C. Use only if potential benefit justifies the risk.</td>
</tr>
<tr>
<td>SP</td>
<td>YES</td>
<td>USPI - Pregnancy Category C. Use only if potential benefit justifies the risk to the fetus</td>
</tr>
<tr>
<td>Artesunate (AS)</td>
<td>YES</td>
<td>WHO SmPC. Should only be used during pregnancy especially in 1st trimester when the benefit is considered to outweigh the potential risks and alternate drugs are not available.</td>
</tr>
<tr>
<td>Artemether-Lumefantrine</td>
<td>YES</td>
<td>USPI - Pregnancy Category C. Safety from obs study (500 incl.1/3 1st trimester) + published data (&gt; 1000) showed no increased adverse pregnancy outcomes or teratogenic effect. Coartem tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</td>
</tr>
<tr>
<td>AS/AQ</td>
<td>AS: YES</td>
<td>WHO SmPC. During 1st trimester should not be used unless clearly necessary. During 2nd and 3rd, may be used with caution, only if other antimalarials are unsuitable.</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>YES</td>
<td>USPI - Pregnancy Category C. Should be used only if the potential benefit justifies the potential risk to the fetus.</td>
</tr>
<tr>
<td>DHA/PQP</td>
<td>Piperaquine: NO</td>
<td>EU SmPC. Should not be used during pregnancy in situations where other suitable and effective antimalarials are available.</td>
</tr>
<tr>
<td>PYR/AS</td>
<td>Pyronaridine: NO</td>
<td>Art 58 SmPC. Should only be used in 2nd and 3rd trimester when other treatments are considered unsuitable.</td>
</tr>
</tbody>
</table>
### Consider Developing PYR-PQP

<table>
<thead>
<tr>
<th>Potential Advantages</th>
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</table>
| • No preclinical or clinical embryo-foetal toxicity signal | ➢ Target population: Pregnant women in 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> trimester.  
• Both are well tolerated, significant safety databases (esp. PQP)  
• Alternative in areas where SP-IPTp has lost efficacy due to SP resistance (parasites carrying sextuple haplotype mutation) and potentially in areas of artemisinin resistance  
• Both have long & matched duration ⇒ protects both subjects & drug components:  
➢ Each drug provides protection of the other from resistance development  
➢ Long post-dose prophylaxis (long elimination half-lives)  
➢ PQP is ‘fast acting’ (short parasite clearance time) |

<table>
<thead>
<tr>
<th>Potential Limitations</th>
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</tr>
</thead>
</table>
| • Maximum 3-day course, may be less but single dose is unlikely – Compliance and Cost-effectiveness?  
• Concerns around PQP cardiac and PYR liver safety during pregnancy? |
New FDA Guidance - Is the New Investigational Drug an Appropriate Alternative?

- Pre-requisites to administer new investigational drugs in pregnant women in pre-marketing setting, as per FDA draft guidance:
  1. No class and compound-specific reprotoxicity signal observed in adequate nonclinical studies (including studies on pregnant animals)
  2. The clinical trial holds out the prospect of **direct benefit** to the pregnant woman and/or fetus that is **not otherwise available** outside the research setting or cannot be obtained by any other means (e.g., the pregnant woman may **not have responded to other approved treatments** or there may **not be any treatment options**)
### 1st Pre-Requisite: Frontload Reprotox Studies to Prioritize the Development of Drugs Safe for Use in WOCBP and Pregnant Women

<table>
<thead>
<tr>
<th>Non-clinical reproductive and developmental toxicity studies</th>
<th>Inclusion of Women in Clinical Trials</th>
<th>Proposed Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose range finder embryo-fetal developmental (EFD) studies in 2 species (rodent and non-rodent)</td>
<td>Allows up to 150 WOCBP in Phase I and II with highly effective contraception</td>
<td>Before Phase I</td>
</tr>
<tr>
<td>EFD studies in 2 species (rodent and non-rodent)</td>
<td>WOCBP with contraception</td>
<td>Before Phase II</td>
</tr>
<tr>
<td>Fertility and early embryonic study (rodent)</td>
<td>WOCBP in large-scale trials (e.g. Phase III)</td>
<td>Before Phase III</td>
</tr>
<tr>
<td>Peri-postnatal developmental study (PPN) including neuro-behavioral parameters (rodent)</td>
<td>Pregnant women*</td>
<td>Before Phase III</td>
</tr>
</tbody>
</table>

*Need to have enough PhII data in women. Regulatory may ask for a juvenile tox study to be able to extrapolate the effects in children that can possibly be exposed through placenta or milk.
### Strategy to Address 2nd Pre-Requisite
To be discussed with HAs in the Countries*

<table>
<thead>
<tr>
<th>2nd Pre-Requisite</th>
<th>Arguments</th>
</tr>
</thead>
</table>
| Direct Benefit    | ➢ Advantage of a **single dose** treatment  
                     ➢ **Efficacy** |
|                   | ➢ **No approved treatment per se** in pregnancy  
                     i.e. most available therapies are recommended by WHO (e.g. ACTs) have **warning in the label**  
                     ➢ May not be considered as “approved” by Local Competent authorities/SRA |
|                   | ➢ e.g. clindamycin **not always available and expensive** |
| That is not otherwise available i.e. non responders to approved treatments | |
| Or there may not be any treatment options | |

• In case the above is considered not sufficient, add **“ACTs failure in artemisinin resistance areas”**.

* Based on the FDA Draft Guidance as a basis: to be discussed with Local HAs
Proposed Clinical Strategy to Inform Drug Label in Pregnancy

**GENERAL POPULATION: ADULTS INCLUDING WOCBP & CHILDREN**

- **Dose Finding Phase II**
  - Exposure-Ranging in adults and children
  - Efficacious Doses Identified

- **Pivotal Phase III program**
  - Optimal Combination Dose vs SOC in adults & children

**PREGNANT WOMEN (2\(^{ND}\) & 3\(^{RD}\) TRIMESTER)**

- **PBPK**
- **2-Part Open Label Ph III Sub-Study\(^{**}\)**
  - PK (n~20)
  - Safety/tol

  - Dose adjustment*

* Important to keep same drug ratio
** Continue data collection in pregnant women after NDA

WOCBP: women of childbearing potential
SOC: standard of care
NDA: new drug application
PBPK: physiologically-based PK modeling
Thank you