IMPACT OF INSECTICIDE RESISTANCE ON MALARIA CONTROL AND RESIDUAL MALARIA

FLORENCE FOUQUE, TEAM LEADER VES/TDR/WHO
PRESENTED BY MARIAM OTMANI DEL BARRIO VES:TDR:WHO

VCWG RBM MEETING, 7TH TO 9TH FEBRUARY 2018, GENEVA
The overall objective of this study is to assess performances of LLIN/IRS in sites where Anopheles mosquitoes have developed resistance to insecticide in comparison to sites where Anopheles are susceptible to insecticides.

The specific objectives include:

1. **Update data on insecticide resistance** and determine resistance mechanism(s) in the 3 target countries.
2. **Monitor entomological, parasitological and socio-anthropological indices of LLINs/IRS efficacy** in selected study sites with and without insecticide resistance.
3. **Compare the performances of LLINs and IRS on entomologic indices (vector longevity, MBR and EIR) and malaria prevalence** in localities where Anopheles exhibit either the knock down resistance, metabolic-based resistance or both resistance mechanisms.
Malaria prevalence (%) in children (age 1-10 years) at baseline and 3, 6, 9, and 12 months post LLINs distribution

Mean indoor resting *Anopheles gambiae* s.s. per room per day at baseline and 3, 6, 9, 12 and 15 months following LLINs usage.

When mosquitoes have acquired 2 resistance mechanisms to insecticide, people are bitten by mosquitoes under the LLINs and stop using them, with consequences on malaria incidence.

<table>
<thead>
<tr>
<th>Respondents reasons for halt in LLINs usage</th>
<th>IMOTA (Kdr-w)</th>
<th>BAYEKU Kdr-w+ n450</th>
<th>ORETA (Kdr-w)</th>
<th>IGBOKUTA (none)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of LLINs (PermaNet 2.0) distributed</td>
<td>402</td>
<td>400</td>
<td>402</td>
<td>400</td>
</tr>
<tr>
<td>No. (%) Reduction in LLINs usage 15 months post distribution</td>
<td>35 (8.7%)</td>
<td>98 (24.5%)</td>
<td>22 (5.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Main reasons for reduction or halt in LLINs usage</td>
<td>No. (%) respondents n =35</td>
<td>No. (%) respondents n=98</td>
<td>No. (%) respondents n=22</td>
<td>No. (%) respondents n=2</td>
</tr>
<tr>
<td>'Got bitten by mosquito while sleeping under LLINs'</td>
<td>16(45.7)</td>
<td>69(70.4)</td>
<td>8(36.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>'See live mosquitoes resting on LLINs'</td>
<td>10(28.6)</td>
<td>21(21.4)</td>
<td>5(22.7)</td>
<td>0(0)</td>
</tr>
<tr>
<td>'Feeling hot sleeping under LLINs'</td>
<td>0(0)</td>
<td>0(0)</td>
<td>5(22.7)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>'Do not feel comfortable sleeping under LLINs'</td>
<td>9(25.7)</td>
<td>8(8.2)</td>
<td>4(18.2)</td>
<td>0 (0)</td>
</tr>
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</table>
OBJECTIVES AND EXPECTED OUTPUTS OF THE PROJECTS

The objectives of the selected research projects are to:

- **Produce updated data** from selected settings of low- to high-malaria transmission **on the magnitude** of residual malaria;

- **Produce scientific evidence on the causes** of this residual malaria through **investigations of entomological, social and environmental determinants**.

- These studies will form the **baseline scientific evidence for new recommendations and for further projects on more specific topics including the impact of new vector control tools.**
BURDEN AND CAUSES OF RESIDUAL MALARIA

- **Residual malaria hotspots in Peru and Brazil: setting the stage for testing improved**: PI Dionicia Gamboa Vilela, study sites in Brazil and Peru.
- **Understanding residual transmission for sustainable malaria control and enhancement of elimination efforts in Africa**: PI Joseph Mwangangi, study sites in Kenya, Cameroon and Ethiopia.
- **Residual Malaria Transmission in the Greater Mekong Subregion (GMS) - Studies to examine its magnitude and identify its causes**: PI Jeffrey Hii, study sites in Thailand and Vietnam.
- **Understanding human, parasite, vector and environmental interactions driving residual malaria transmission in Papua New Guinea**: PI Moses Laman, study sites are in Papua New Guinea.
- **Where and when is residual malaria transmission taking place? Investigating magnitude and drivers of persistent Plasmodium infections in East and West Africa**: PI Fredros Okumu, study sites in Burkina Faso and Tanzania.
RESIDUAL MALARIA TRANSMISSION IN THE GREATER MEKONG SUBREGION

<table>
<thead>
<tr>
<th>Objectives (in SMART format)</th>
<th>Expected outcomes (the impact or changes in the field that the project will have contributed to)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. To determine the magnitude of RMT relative to the overall burden of malaria in a number of different transmission settings in the GMS [via a review of existing data by Malaria Consortium with WHO and NMCPs, with results available by June 2016].</td>
<td>A clearer understanding of the magnitude of RMT in a number of different transmission settings in the GMS and robust approaches for assessing RMT magnitude elsewhere in the region.</td>
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<tr>
<td>2. To produce scientific evidence on the causes of RMT through an in-depth investigation of entomological, epidemiological, social and environmental determinants in a representative selection of specific transmission settings in one endemic province in Thailand and one endemic province in Vietnam. [Fieldwork managed by Malaria Consortium in collaboration with partners and NMCPs, with results by October 2016].</td>
<td>A clearer understanding of the causes of RMT in the selected settings and development of robust protocols and tools for assessing the causes of RMT elsewhere in the region.</td>
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<tr>
<td>3. To develop simple, cost-effective protocols and tools that can be used more widely by partner agencies across different ecological and epidemiological settings globally. [Outputs finalized during TDR workshop for all TDR-RMT regional teams in late 2016]</td>
<td>Extensive development of new approaches and techniques resulting in increased capacity to understand the magnitude and causes of RMT globally.</td>
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MAIN RESULTS FROM THE GREATER MEKONG PROJECT

Malaria Drivers:

- Human-anopheles interaction in sites without LLIN/IRS and/or where LLIN cannot be used
  - High exophagy
  - High proportion of biting before/after sleeping hours
  - Non-use of LLIN and use of damaged/torn LLIN
- High population movement across international borders (endemic)/across other endemic districts
- *Plasmodium vivax* predominance

Are these drivers residual malaria?

Next Steps:

LLINs / IRS reached limit of effectiveness despite high coverage at village level, but no coverage out of villages.

**Personal protection tools are required for:**
- Pre-bedtime and wake-up time
- During night time hours in farm/forest - need to be light, durable, inexpensive

Next steps for research:
- Modelling of transmission in sites and testing of VC tools
- Quantify RMT across wet & dry seasons
COMMUNICATION MATERIALS

• Briefs on main findings for easy access to information by stakeholders and communities

• Scientific publications

• Materials for Vector Control advisory groups within WHO

• Data for scientific community and countries
RESIDUAL MALARIA HOTSPOTS IN PERU AND BRAZIL: SETTING THE STAGE FOR TESTING IMPROVED

The study will provide information of the impact of the use of treated nets in Mâncio Lima, Brazil and Mazán River, Peru (ITNs/LLINs, depending on the site) on the prevalence/incidence of malaria parasitemia. Results will facilitate the quantification of residual malaria in these hotspots.

**Objective 1.** To compare prevalence/incidence of parasitemia among households with and without bednet use (ITNs/LLINs) and with/without IRS.

**Objective 2.** To assess the socioeconomic, behavioral, and environmental determinants of residual malaria through a combination of household surveys and satellite imagery.

**Objective 3.** Determination of vector biology metrics (HBR, IR, EIR, HBI); quantification of environmental variables of aquatic mosquito habitats and genetic characterization of immature and adult *Anopheles darlingi* along Mazán River (Loreto Department, Peru) and in Mâncio Lima (Juruá Valley, Brazil)
KEY FINDINGS ON RESIDUAL MALARIA HOTSPOTS IN PERU AND BRAZIL

Key findings:

- *Anopheles darlingi* is the most abundant species, and the mosquitoes fed mostly outdoors (exophagic) in each community in both river basins.

- Of approximately 6,800 *An. darlingi* examined, 1.6% were infected with the malaria parasite (*Plasmodium falciparum* and *Plasmodium vivax*).

- Analysis of *An. darlingi* blood showed that the mosquitoes fed on humans more than they fed on chickens, cows and dogs.

- There was greater abundance of *An. darlingi*, a higher *An. darlingi* Human Biting Rate (HBR) and greater proportions of human blood meals in mosquitoes in the two Mazán River villages than in the two Napo River villages.

- More anopheline larvae (approx. 75% of 856) were present in water bodies within one kilometre of villages on the Napo River than in water bodies within one kilometre of villages on the Mazán River.

*Figure 3. High and low incidence malaria rate clusters in Mâncio Lima, Brazil.*
UNDERSTANDING RESIDUAL TRANSMISSION FOR SUSTAINABLE MALARIA CONTROL IN AFRICA

This study will be focusing on entomological, environmental and anthropogenic behavioral factors, which could contribute to residual malaria transmission where indoor based vector interventions are implemented in three settings with different ecological features across sub-Saharan Africa: Central Africa equatorial forest region (Cameroon), East Africa coastal areas (Kenya) and East Africa highlands (Ethiopia). This collaborative work will involve teams of 3 research institutions OCEAC (Cameroon), Jimma University (Ethiopia) and KEMRI (Kenya).

Objective 1: To characterize outdoor malaria transmission in focal points in different epidemiological settings with scaled up coverage of LLINs/IRS.

Objective 2. To determine the contribution of various mosquito behaviors to persistent malaria transmission despite high coverage of LLINs/IRS in different epidemiological settings.

Objective 3. To investigate human behavioral/occupational factors associated with exposure to mosquito bites.
KEY FINDINGS ON RESIDUAL MALARIA HOTSPOTS IN KENYA, ETHIOPIA AND CAMEROON

- The primary & secondary vectors reported have increased biting outdoor
- The outdoor biting cycle is continuous mostly through out the night
- Mosquitoes collected outdoor are infected with malaria parasite
- There is need to develop sampling tools for outdoor mosquitoes
- Insecticide resistance is setting in the 3 sites and need strategies to manage spread/increase
- Human engage in activities which predispose them to mosquito bites in the evening and early morning
UNDERSTANDING HUMAN, PARASITE, VECTOR AND ENVIRONMENTAL INTERACTIONS DRIVING RESIDUAL MALARIA IN PAPUA NEW GUINEA

**Success indicator 1:** Spatio-temporal maps of residual malaria transmission and the key determinants of residual transmission.

**Success indicator 2:** Generated data incorporated into PhD thesis, laboratory standard operation procedures (SOPs) of new assays validated and in place; publications in peer-reviewed journals.

**Success indicator 3:** Project recommendations incorporated into the next iteration of the PNG National Malaria Control Strategic Plan, 2018-2023
SUMMARY FOR MALARIA IN PAPUA NEW GUINEA

**Mugil: north coast Madang Province**
High reported LLIN usage - 81-94%
Operational challenges with case management - inconsistent supply of RDTs/ACTs
Anticipate high prevalence of *Plasmodium* infection
*An. farauti* s.l, *An. punctulatus* s.l and *An. koliensis* were the predominant vectors
the majority of blood-fed mosquitoes were *An. koliensis*

**Lemakot: New Ireland Province**
Lower reported LLIN usage than in Madang Province
More consistent supply of RDTs/ACTs; anticipate much lower prevalence of infection
*An. farauti* s.l was the only anopheline species found in 2 of the Lemakot villages and they commonly bred in the tyre tracks and pig wallows
Variable biting behavior was observed in these 2 villages (earlier in Lavolai)
Alternative areas where villagers were likely to get infected with malaria were along the riverside when bathing and at the sports field
WHERE AND WHEN IS RESIDUAL MALARIA TRANSMISSION TAKING PLACE? IN EAST AND WEST AFRICA (TANZANIA AND BURKINA FASO)

**Activity 1:** Selecting one odour-baited mosquito trapping technology that could be used to representatively sample indoor and outdoor-biting malaria mosquitoes.

**Activity 2:** Estimating malaria incidence and contribution of ongoing outdoor malaria transmission to the current malaria burden.

**Activity 3:** Geospatial modeling and observations of residual transmission hotspots.

**Activity 4:** Identification of important variables at landscape level (between villages) and at fine scale (within villages) that affect biting risk and malaria transmission by residual vector species.

**Activity 5:** Mathematical Simulations.
KEY MESSAGES ON RESIDUAL MALARIA TRANSMISSION IN TANZANIA AND BURKINA FASO

• **Current Tools:** Insecticide-treated bed-nets and indoor residual spraying remain effective against malaria in both east and west Africa, but are increasingly compromised because of:
  ✓ Resistance to insecticide
  ✓ Outdoor biting behavior
  ✓ Activities of human population in places and when mosquitoes are biting.

• **An. funestus:** more than 80% of the ongoing residual malaria transmission is by *Anopheles funestus*, with need of need tools to collect them outdoors.

• **Resistance:** Malaria mosquitoes in east and west Africa are now extensively resistant to most insecticides,

• **Human behavior:** Need for complementary protection for people when they are outside bed nets.
Expected outputs of the Workshop

- Present and discuss the vectors and human behavioural factors associated with residual malaria.
- Discuss recommendations and guidance options for development of targeted malaria control tools.
- Provide baseline information to inform potential future research and training proposals, as well as standardized protocols for use in future research.
KEY MESSAGES FROM THE WORKSHOP

- The workshop discussions revealed a lack of agreement around the definition of residual malaria transmission.
- There are many similarities and differences seen in approaches to measuring and characterizing residual transmission. All studies included a vector and human component, however, few presented the results in an integrated way. Approaches and methods to link human and vector aspects should be evaluated and standardized.
- There are factors beyond residual transmission, including the quality of implementation of vector control tools (i.e. sub-optimal access and/or use of LLINs), which also need to be addressed in some contexts.
- Strong community engagement is essential for successful research and interventions.
- There is a clear and urgent need for context-specific strategies and interventions for addressing residual malaria transmission.
- The workshop played an important role in laying the groundwork for additional research and interventions. Ongoing coordination, and opportunities for collaboration, across research groups will be essential.
OVERALL CONCLUSIONS AND PERSPECTIVES

- In many situations, the current tools are not effective or cannot be implemented, or because the vector species are not targeted (outdoor biting).
- How to better define what is residual malaria, and what is malaria transmission not impacted by current tools.
- The results of the projects currently supported by VES/TDR on malaria will be published in a special issue.
- Case studies on implementation research, for situation in which LLINs and IRS are not appropriate.
- Activities on capacity building and exchange of information.
THANK YOU FOR YOUR ATTENTION