AMPEN VIVAX WORKING GROUP:
THE TOOLBOX FOR VIVAX ELIMINATION

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BMGF
2007: AN AUDACIOUS GOAL

“Any goal short of eradicating malaria is accepting malaria; it’s making peace with malaria; it’s rich countries saying: ‘We don’t need to eradicate malaria around the world as long as we’ve eliminated malaria in our own countries. That’s just unacceptable.’

Melinda Gates, 2007

- Our goal is to eliminate all malaria, not just falciparum malaria
ACCELERATE TO ZERO BY BENDING THE CURVE AND SHORTENING THE TAIL

Global annual malaria parasite incidence

- “Bend the Curve”
- “Shorten the Tail”

Resurgence
Sustain progress
Accelerate to zero
WE ARE ELIMINATING VIVAX TODAY, AND WE BELIEVE THAT WE CAN BEND THE CURVE NOW

• Vivax is the predominant species in 70% of countries with 500 cases or fewer
• Beyond R&D, BMGF is involved in:
  • Elimination efforts in Mesoamerica
  • Surveillance and system-strengthening in the GMS
VIVAX: KNOWN CHALLENGES

1. INFECTION DETECTION: We struggle to detect vivax
   - Fail to diagnose all clinical cases
   - Often confused when co-infection
   - Cannot detect submicroscopic infections
   - Cannot detect any latent stage parasites

2. ELIMINATE/EPI: We poorly target interventions
   - Diagnostic lag limits surveillance as intervention
   - Incomplete maps of disease transmission
   - Inadequate disease transmission models
   - Limited operational expertise

3. ACHIEVE RADICAL CURE: We struggle to provide radical cure
   - Adherence to full regimens
   - G6PD or CYP 2D6deficient individuals
   - Unknown G6PD individuals
   - Pregnant and breastfeeding women
   - Infants, < 6 months

4. PREVENT TRANSMISSION: We face a varied parasite and vectors
   - Broader geographic and vector diversity
   - Residual transmission gaps
   - More diversity limits vaccine targets

Key R&D Question: Which priority research gaps can greatest accelerate the elimination of vivax malaria AND shorten the tail?
### THERE ARE FOUR INVESTMENT PILLARS TO TRANSITION OUR STRATEGY TOWARD VIVAX ELIMINATION

**Hypothesis:** Vivax elimination requires identifying the asymptomatic reservoir of disease, treating them with targeted and scalable radical cure, and finally closing any coverage gaps.

<table>
<thead>
<tr>
<th>Understand the threat</th>
<th>Optimize Radical Cure</th>
<th>New tools to accelerate elimination</th>
<th>Demonstrate Pv elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypnozoite biology</td>
<td>- Surveillance as an intervention</td>
<td>- Address residual transmission</td>
<td>- Define clear strategy for NMCPs on radical cure</td>
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<tr>
<td>- Map incidence</td>
<td>- Find limit of RC</td>
<td>- Additional prevent transmission tools, such as mAb, vaccine</td>
<td>- Show feasibility at cost in a co-endemic ‘hard place’</td>
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<td>- Submicroscopic reservoir</td>
<td>- Model TFQ use</td>
<td>- Diagnostics to stratify risk of vivax relapse</td>
<td>- Shorten the tail to elimination</td>
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<tr>
<td>- Hypnozoite detection</td>
<td>- Operational evaluation</td>
<td>- Non-hemolytic drug</td>
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<tr>
<td>- Model transmission dynamics</td>
<td>- Assess risk-stratified packages of interventions</td>
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<tr>
<td>- CYP2D6 prevalence</td>
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HOW FAR WILL OPTIMIZING CURRENT TOOLS TAKE US TOWARD ELIMINATION?

- **Modelling of current epi and tools will improve decision making**
  - Optimized vector control
  - Microscopy/improved RDT
  - 80% effective radical cure (blood schizonticide + 8-aminoquinoline)

- To model, need longitudinal data and outcomes from standard interventions in archetypal settings
  - 2 models based off the PNG dataset
  - That is not enough…
<table>
<thead>
<tr>
<th>Country</th>
<th>G6PD Prev.</th>
<th>Primary Drug Regimen</th>
<th>Vector Control</th>
<th>Strong Political Will</th>
<th>Strong Surveillance Capacity</th>
<th>Microscopy vs RDT?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa Rica</td>
<td>0.4%</td>
<td>CQ + observed PQ (0.5 mg/kg over 7 days)</td>
<td>IRS, fogging, selective pyrethroid spraying, larvivorous fish/copepods, environmental management</td>
<td>X</td>
<td>X</td>
<td>Microscopy</td>
</tr>
<tr>
<td>El Salvador</td>
<td>3.3%</td>
<td>CQ + PQ (0.25 mg/kg over 14 or 5 days)</td>
<td>Focal IRS, Sustainable environmental management</td>
<td>X</td>
<td>X</td>
<td>Microscopy</td>
</tr>
<tr>
<td>Turkey</td>
<td>3.8%</td>
<td>CQ + PQ (0.25 mg/kg for 14 days)</td>
<td>IRS, larviciding, environmental management, surveillance</td>
<td>X</td>
<td>X</td>
<td>Microscopy with QC</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>2.9%</td>
<td>CQ + PQ (0.25 mg/kg for 14 or 5 days)</td>
<td>LLINs for 100% coverage, IRS in all endemic areas, Larvivorous fish + larviciding; growth regulators; environmental modification</td>
<td>X</td>
<td>X</td>
<td>Microscopy at district level with QC (RDTs where microscopy unavailable)</td>
</tr>
<tr>
<td>China</td>
<td>4.7%</td>
<td>PQ MDA if Pv in past year or contact (180 mg / 8 days), CQ + PQ treatment (180 mg / 8 days)</td>
<td>IRS only (100% foci with any malaria)</td>
<td>X</td>
<td>X</td>
<td>Microscopy at township or county level with QC (RDTs for remote areas/emergencies)</td>
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HYPOTHESIS: BETTER DIAGNOSIS WILL GREATLY ENHANCE RADICAL CURE UPTAKE AND ELIMINATION ACCELERATION

- **R&D VIVAX PRIORITIES:**
  1. Reliable detection of all symptomatic vivax to optimize case management
     - RDTs for vivax = quality microscopy
  2. Detection of **individuals** of high risk of relapse to target anti-relapse therapy
     - Detection of submicroscopic infections
     - Detection of those with viable hypnozoites, likely to relapse
  3. **Detection of High Risk Populations:** Understand transmission dynamics of Pv; detection of hotspots for targeted intervention
Initial work shows:

- Best Pan LDH test is 5-fold less sensitive than the current Pf RDT (5ng/mL)
- Best specific pvLDH test a full 25x less sensitive (25ng/mL)

Current pvRDT is likely to miss as much as 30-50% of symptomatic P. vivax cases

BMGF is investing to evaluate technical feasibility, then to work with manufacturers on prototypes

Technical feasibility assessment initiated to evaluate if sensitivity of current tests can be improved

- 2 manufacturers engaged; at least 8x improvement feasible
- Results in 6 months

TPP in progress with partners
## OPTIMIZING RADICAL CURE

### EXPANDING OUR EVIDENCE BASE TO USE TAFENOQUINE IN KEY EPIDEMIOLOGIC SETTINGS

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<th>Priority Tafenoquine studies</th>
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<tr>
<td><strong>Safety and combination trials with ACTs</strong></td>
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<tr>
<td>• Phase IVs as determined by regulatory agencies</td>
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<tr>
<td>• Enhanced pharmacovigilence</td>
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<td>• Vivax radical cure with ACTs : DHA-PIP, AS-PYR, AL</td>
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<th>Post-licensure longitudinal efficacy study</th>
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<tr>
<td>• 2 year WANECAM-like study of TQ 300mg single-dose versus PQ 30mg x14 with CQ or ACT in high relapsing region</td>
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<tr>
<td>• Ideally demonstrate non-inferiority, impact of post treatment prophylaxis</td>
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<th>Trials to drive policy</th>
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<td>• Real world use of the G6PD diagnostic with tafenoquine to demonstrate safety</td>
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<th>Optimizing tafenoquine prophylaxis</th>
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<tr>
<td>• Use in high risk mobile populations</td>
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<th>Pf gametocytocide</th>
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<td>• Single dose study in Pf population</td>
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OPTIMIZING RADICAL CURE
PRIORITY: IMPROVED G6PD DIAGNOSTICS

Qualitative G6PD test:
- need easier to use and read
- cutoff to <30% normal (men and homozygous women)

Quantitative G6PD Test
- PATH is evaluating 3 prototypes
  - spectrophotometry, colorimetric, and electrochemistry
- new products expected in 2018

Intermediate G6PD activity presents the clinical and diagnostic challenge…

…requiring a quantitative measurement solution
DON’T FORGET: TAFENOQUINE PROPHYLACTIC ACTIVITY

• Given weekly, tafenoquine at doses of >50 mg provides causal chemoprophylaxis again Pf and Pv
• 200mg dose weekly selected for chemoprophylaxis indication

• How long are you protected after a vivax treatment course? *Not known*

Lell 2000
Shanks GD 2001
TOP PRIORITY: NON-HEMOLYTIC RADICAL CURE

• Despite great progress in hypnozoite biology and drug screening, we have to recognize the next radical cure drug is still at least 10 years away
TRANSLATE INNOVATION INTO IMPACT

• Well defined, and user-focused (NMCP) use cases for our products

• Target product profiles based on epidemiology-driven modelling of key performance parameters

• Target policy profile developed with WHO and countries as part of development

• Regional (not national) regulatory review

• Innovative delivery planning and financing for elimination
THANK YOU!