4th New Tools, New Challenges in Vector Control Work Stream meeting
31 January 2019

The Ivermectin roadmap

Carlos Chaccour
Regina Rabinovich
Context

“The house is on fire”

• Residual transmission
• WMR 2016 – 2017
• Need for new tools to reach GTS goals
WHO preferred product characteristics: endectocide for malaria transmission control

JUNE 2017 INFORMATION NOTE
Objectives

1. Increase alignment of researchers, product developers and funders on the process for advancing ivermectin as a complementary tool to reduce malaria transmission.

2. Create critical path towards the Target Product Profile in at least two different eco-epidemiological settings.

3. Develop the regulatory pathway with greatest probability of success.
Methods

1. Experts with very different backgrounds “Roadmappers”
2. Kick off meeting at ASTMH 2017
3. Identification of potential *Use Scenarios*
4. Creation of seven work streams
5. Sequential drafting of each work stream document
6. Face to face synthesis meeting
7. Feedback on consolidated manuscript
8. Final product
Overview

Use scenarios
Active and planned trials
Potential impact assessment
Efficacy & Safety
Ethics
One Health
Resistance
Environmental
Regulatory
# Main use scenarios

<table>
<thead>
<tr>
<th>Transmission setting</th>
<th>Rationale for ivermectin use</th>
<th>Target blood source</th>
<th>Co-delivery</th>
<th>Rationale for co-delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>Reduce disease burden</td>
<td>Human</td>
<td>SMC (children)</td>
<td>Operational and vector control synergies</td>
</tr>
<tr>
<td>Higher</td>
<td>Accelerate to elimination</td>
<td>Human</td>
<td>ACT MDA</td>
<td>Ivermectin provides additional transmission reduction by targeting outdoor and early biting vectors</td>
</tr>
<tr>
<td>Higher</td>
<td>Reduce vectorial capacity</td>
<td>Livestock</td>
<td>Enhanced uptake of LLINs</td>
<td>Alternative blood source for ivermectin delivery. This strategy allows for use of long-lasting veterinary formulations</td>
</tr>
<tr>
<td>Higher</td>
<td>Reduce vectorial capacity</td>
<td>Human + Livestock</td>
<td>With or without ACT MDA</td>
<td>Covering two different blood sources could impact the most on local vector populations</td>
</tr>
</tbody>
</table>
# Other use scenarios

<table>
<thead>
<tr>
<th>setting</th>
<th>Rationale for ivermectin use</th>
<th>Target blood source</th>
<th>Additional co-delivery</th>
<th>Rationale for co-delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>Reduce vectorial capacity</td>
<td>Human</td>
<td>IRS timed around ivermectin MDA</td>
<td>Boost IRS efficacy by precipitating a sharp reduction in vectors around the IRS campaign</td>
</tr>
<tr>
<td>Any</td>
<td>Reduce disease burden</td>
<td>Human</td>
<td>NTD interventions such as Azithromycin or IDA for LF</td>
<td>Same impact, delivered in context of NTD program</td>
</tr>
<tr>
<td>Any</td>
<td>Insecticide resistance management</td>
<td>Human +/- livestock</td>
<td>PBO nets Other insecticide delivery vehicles i.e. ATSBs</td>
<td>As part of an insecticide resistance management strategy</td>
</tr>
<tr>
<td>Lower</td>
<td>As part of reactive interventions</td>
<td>Human +/- livestock</td>
<td>FMDA with ACT + ivermectin +/- other vector control tools</td>
<td>Management of secondary cases after successfully driving down transmission</td>
</tr>
<tr>
<td>Any</td>
<td>Manage outbreaks</td>
<td>Human +/- livestock</td>
<td>FMDA with ACT + ivermectin +/- other vector control tools</td>
<td>As a way to quickly reduce vectorial capacity</td>
</tr>
</tbody>
</table>

### Always present (per national policy)
- LLINs or IRS
- Case mgnt
- IPTp
# Active and planned trials

<table>
<thead>
<tr>
<th>Lead</th>
<th>Country</th>
<th>Dose</th>
<th>Combination</th>
<th>First results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC Gambia LSHTM</td>
<td>The Gambia</td>
<td>300 x 3</td>
<td>DHA-P MDA</td>
<td>2019</td>
</tr>
<tr>
<td>CSU</td>
<td>Burkina Faso</td>
<td>300 x 3</td>
<td>SMC</td>
<td>2020</td>
</tr>
<tr>
<td>ISGlobal*</td>
<td>Mozambique, Tanzania</td>
<td>400 x 1</td>
<td>Ivermectin alone + livestock</td>
<td>2020</td>
</tr>
<tr>
<td>LSHTM</td>
<td>Guinea-Bissau</td>
<td>300 x 3</td>
<td>DHA-P MDA</td>
<td>2021</td>
</tr>
<tr>
<td>MORU</td>
<td>Thailand</td>
<td>400 x 1</td>
<td>Ivermectin alone</td>
<td>2020</td>
</tr>
<tr>
<td>MIVEGEC Montpellier</td>
<td>Burkina Faso</td>
<td>Slow release</td>
<td>Livestock + ?</td>
<td>?</td>
</tr>
</tbody>
</table>

*Pending funding decision*
Active and planned trials

TOTAL PROJECTS: 24  
- 5 active

TOTAL FUNDING: $21.7M  
- $11.5M active

PROJECT SITES: 16  
- 4 active

Research Area Total Projects

- Effect of ivermectin: 11
- Clinical trials: 10
- Modelling the effect: 2
- New formulations: 2
- Effect of ivermectin: 2
- Roadmap development: 1

Project Timeline


View Projects
Impact assessment

Modelling by Hannah Slater
Projected Impact 2023-2027

- Ivermectin trials
- Mectizan donation
- No Loa
- No fragile states
- Experience with SMC/MDA
# Impact assessment

All numbers in millions

<table>
<thead>
<tr>
<th>Year</th>
<th>Population protected</th>
<th>Tablets per year</th>
<th>Drug costs/year</th>
<th>Distribution cost/year</th>
<th>Total costs/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2023</td>
<td>10</td>
<td>66</td>
<td>10</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>2024</td>
<td>16</td>
<td>110</td>
<td>16</td>
<td>15</td>
<td>32</td>
</tr>
<tr>
<td>2025</td>
<td>33</td>
<td>220</td>
<td>33</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>2026</td>
<td>47</td>
<td>311</td>
<td>47</td>
<td>43</td>
<td>90</td>
</tr>
<tr>
<td>2027</td>
<td>61</td>
<td>406</td>
<td>61</td>
<td>56</td>
<td>117</td>
</tr>
<tr>
<td>Totals</td>
<td>167</td>
<td>1113</td>
<td>167</td>
<td>153</td>
<td>323</td>
</tr>
</tbody>
</table>
Scenarios for the GTS

Griffin et al. 2016
Impact assessment

Change in malaria incidence due to ivermectin MDA for different Griffin scenarios change scenario in 20 eligible African countries implementing BOHEMIA 2023-27.
Cumulative averted incidence cases, 20 African countries, 2023-2027

- **Sustain**: 32,000,000 (40% efficacy), 16,000,000 (20% efficacy)
- **Innovate**: 10,500,000 (40% efficacy), 5,200,000 (20% efficacy)
- **Accelerate 2**: 14,300,000 (40% efficacy), 7,100,000 (20% efficacy)
- **Accelerate 1**: 22,600,000 (40% efficacy), 11,300,000 (20% efficacy)
- **No change**: 26,700,000 (40% efficacy), 13,500,000 (20% efficacy)
One Health -- Veterinary

• Increases killing effect
• Zoophily-driven residual transmission
• Existing and approved longer lasting formulations
• Possibility of using other endectocides (protects ivermectin)
• Mosaics
• Indirect economic benefits for small livestock holders
One Health

A

B

Imbahale et al. In review
One Health

A

B

Imbahale et al. In review
One Health
One Health

Median score

Percent of area at > median continent score
Resistance

Resistance can affect three different targets

• Human: filariae/STHs
• Veterinary: 30+ GI parasites
• Mosquito resistance
  • Via p450s (Gut vs cuticule)
  • Exposure of larvae (overlap with environmental workstream)
  • Via receptor expression
• Potential resistance management strategies
Conclusions

1. There is a regulatory and policy pathway
2. Evidence will be generated and presented in the next three years
3. There are enhanced discussions on dose/regimen selection and trial methods
4. There are strategies to evaluate risk of resistance, environmental impact and maximize community engagement and understanding
5. There is a pathway to industry engagement in this potential high-volume, low-cost market.
6. Remaining research questions have been identified, particularly operational.
<table>
<thead>
<tr>
<th>Peter Billingsley</th>
<th>Emily Kobayashi</th>
<th>Frank Richards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fred Binka</td>
<td>Kevin Kobylnski</td>
<td>Cassidy Rist</td>
</tr>
<tr>
<td>Ashley Birket</td>
<td>Ana Last</td>
<td>Jessica Rockwood</td>
</tr>
<tr>
<td>Tom Burkot</td>
<td>James Lavery</td>
<td>Francisco Saute</td>
</tr>
<tr>
<td>Carlos Chaccour</td>
<td>David Mabey</td>
<td>David Shoultz</td>
</tr>
<tr>
<td>Luis Ferrero</td>
<td>Leonard Mboera</td>
<td>Hannah Slater</td>
</tr>
<tr>
<td>Scott Filler</td>
<td>Charles Mbogo</td>
<td>Andrew Steer</td>
</tr>
<tr>
<td>Brian Foy</td>
<td>Tom McLean</td>
<td>Rick Steketee</td>
</tr>
<tr>
<td>Lee Hall</td>
<td>Scott Miller</td>
<td>Kang Xia</td>
</tr>
<tr>
<td>Julie Jacobson</td>
<td>David Olsen</td>
<td>Hetty Waskin</td>
</tr>
<tr>
<td>George Jagoe</td>
<td>Jetsumon Prachumsri</td>
<td>Edward Wenger</td>
</tr>
<tr>
<td>Caroline Jones</td>
<td>Regina Rabinovich</td>
<td>Rose Zulliger</td>
</tr>
<tr>
<td>Patrick Kachur</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thanks for your attention!

Correspondence:
regina.rabinovich@isglobal.org
Carlos.chaccour@isglobal.org

Funding:
Bill & Melinda Gates Foundation
Additional slides
Primary drivers of efficacy

- Levels reached
- Duration of levels
- Coverage

- Sporogony
- Fertility
- Mosquito fitness

• 

Malaria Ivermectin Roadmap
400 mcg/kg vs 300 x 3

Additional time with measurable concentration

Malaria Ivermectin Roadmap
400 mcg/kg vs 300 x 3

Additional AUC
## 300 x 3 vs 400 x 1

<table>
<thead>
<tr>
<th>Dose</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 x 3</td>
<td>• Modelled slightly higher impact</td>
<td>• Coverage/adherence?</td>
</tr>
<tr>
<td></td>
<td>• Regimen matches SMC/DHA-P</td>
<td>• Regulatory requirements for safety</td>
</tr>
<tr>
<td>400 x 1</td>
<td>• Proven coverage &amp; adherence (NTDs)</td>
<td>• Modelled slightly lower impact</td>
</tr>
<tr>
<td></td>
<td>• Dose in the current label</td>
<td>• Dose not used in all LF programs</td>
</tr>
<tr>
<td></td>
<td>• Simpler and aligned with NTDs</td>
<td></td>
</tr>
</tbody>
</table>