Potential role of ivermectin and ivermectin-like compounds for malaria elimination

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[Logos for Universidad de Navarra, ISGlobal, Institute for Global Health, Roll Back Malaria]
The potential role of ivermectin for malaria elimination

- **Endectocide**
- **First concept: MDA**
  - ✅ Assuming good VC
  - ✅ Assuming good case management
- **Complementary** tool
How does it work?

- **Blood sources covered**
  - Treat livestock
  - Treat more sources:
    - Include children < 15 kg
    - Include pregnant women

- **Plasma levels reached**
  - Use higher doses (RME)
  - Reduce metabolism/elimination
  - Use more potent endectocides

- **Duration of Plasma levels**
  - Multiple doses
  - Slow release
  - RME

- **Efficacy of Ivermectin**

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How could we use it?
“Highlight the key linkages with policy”

• New use for malaria **would need to be** endorsed/approved
• **Gaps in the databased** identified and addressed
• New use for malaria **would need to be** recommended to NMCPs
• Need a framework to ensure **enough API is available** without affecting NTD programs
• It is **affordable** (funding source: GFATM, UNITAID, NMCPs...)

A ➔ B ➔ C
Prequalification

Target PRODUCT profile

Endorsement of the IDEA

Clinical development

Policy recommendation

Regulatory approval

Target POLICY profile
What evidence is needed?

- Efficacy
- Safety
- Acceptability
- Cost-effectiveness
- Feasibility

[Diagram showing regulatory approval and policy recommendation]

(endorsement)
What evidence is needed: **efficacy**

- Mosquito-killing effect
  - ✓ Insectary
  - ✓ Field
- Other effects (fertility, flying...)
- Modelling (Slater et al – JID 2014)
- Reduces malaria incidence
  - ✓ **RIMDAMAL** (Foy et al – Burkina Preliminary data ASTMH)
  - ✓ 150 mcg/kg every three weeks (x 6) during rainy season
  - ✓ 575 cases averted per 1000 children treated (NNT < 2)
What evidence is needed: Safety

- Dose & formulation
  - ✓ 150-200 mcg/kg once
  - ✓ Repeated dose
  - ✓ High dose
  - ✓ Slow release formulation

- **ACTIVE** (Burkina – Ouedraogo et al) Artemether-Lumefantrine
- **IVERMAL** (Kenia – Ter-Kuile) DHA-Piperaquine
- **NCT02568098** (Thailand - Jittamala) PQ + DHA-Piperaquine

- **The (potential) role of WHO-Prequalification**
What evidence is needed?

• Key question: total dose and spacing?
  
  *Data will inform whether current formulation is enough to meet the required effect*

• Key question: current vs new formulation?

  *Formulation discussions need a clear definition of the desired entomological/epidemiological targets*
What evidence is needed?

• What regulatory agency?
  
  *FDA seems receptive*

• What pathway?
  
  ✓ Repurposing: 505(b)(2)
What evidence is needed: **Acceptability**

- By the population
  - ✔ “only” transmission blocking
  - ✔ Community vs individual impact

- By other programmes (NTDs)
  - ✔ Concerns regarding resistance & procurement
  - ✔ Synergies
What evidence is needed: **Cost-effectiveness**

- **Current costs**
  - ✓ Mectizan donation program: 1.50/3-mg-tablet
  - ✓ Veterinary market: 18Eu/800 mg (1 ltr)

- **The role of competition**
  - ✓ What is an acceptable price for vector control?
  - ✓ What is the expected annual volume?

- **Procurement through GFATM**
  - ✓ Pre-qualification
What evidence is needed: **Feasibility**

- **Production**
  - ✓ Current: 150 tons/year
  - ✓ Less than 1.5% is for human use

- **Programmatic suitability**

- **Do we need a new formulation?**
Who would need to assess the evidence?

*Different perspectives*

- ERG
- VCAG
- MPAC
- NTD program
- WHO-PQ
What is the way forward? (1)

• Generate evidence using current formulation
  ✓ Different eco-epidemiological scenarios
  ✓ Does it really add value to the current paradigm?

• Start conversations for endorsement of the concept
  GMP/VCAG/MPAC

• Start conversations for regulatory approval (new indication)
  Using the current formulation to generate data
What is the way forward? (2)

• Define what MPAC and NTDs would need in order to give a recommendation

• Start pre-qualification process (>1 dossier)
  ✓ Healthy competition (reduce prices)
  ✓ Assure scalability
How does it work?

Second concept: how it works (PK)
*How does it work?*

**LC50**

The plasma concentration needed to kill 50% of the biting *mosquitoes* in a given time

A measure of efficacy similar to the MIC\textsubscript{50} and MIC\textsubscript{90} used in microbiology
How does it work?

MW = 7 hours

$\text{LC}_{50} = 25 \text{ ng/ml}$

Kobylnski 2010
How does it work?

MW = 55 hours

\[ LC_{50} = 6 \text{ ng/ml} \]

Ouedraogo 2013
How does it work?

Sub-lethal effects