STAYING AHEAD OF RESISTANCE & BUILDING TRANSFORMATIVE TOOLS

A quick look at the BMGF malaria vector control portfolio

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March 2022

CHARTING AN ERADICATION PATHWAY THAT MINIMIZES DEATHS

Three strategic goals define Pathway to Eradication

1 Drive down burden

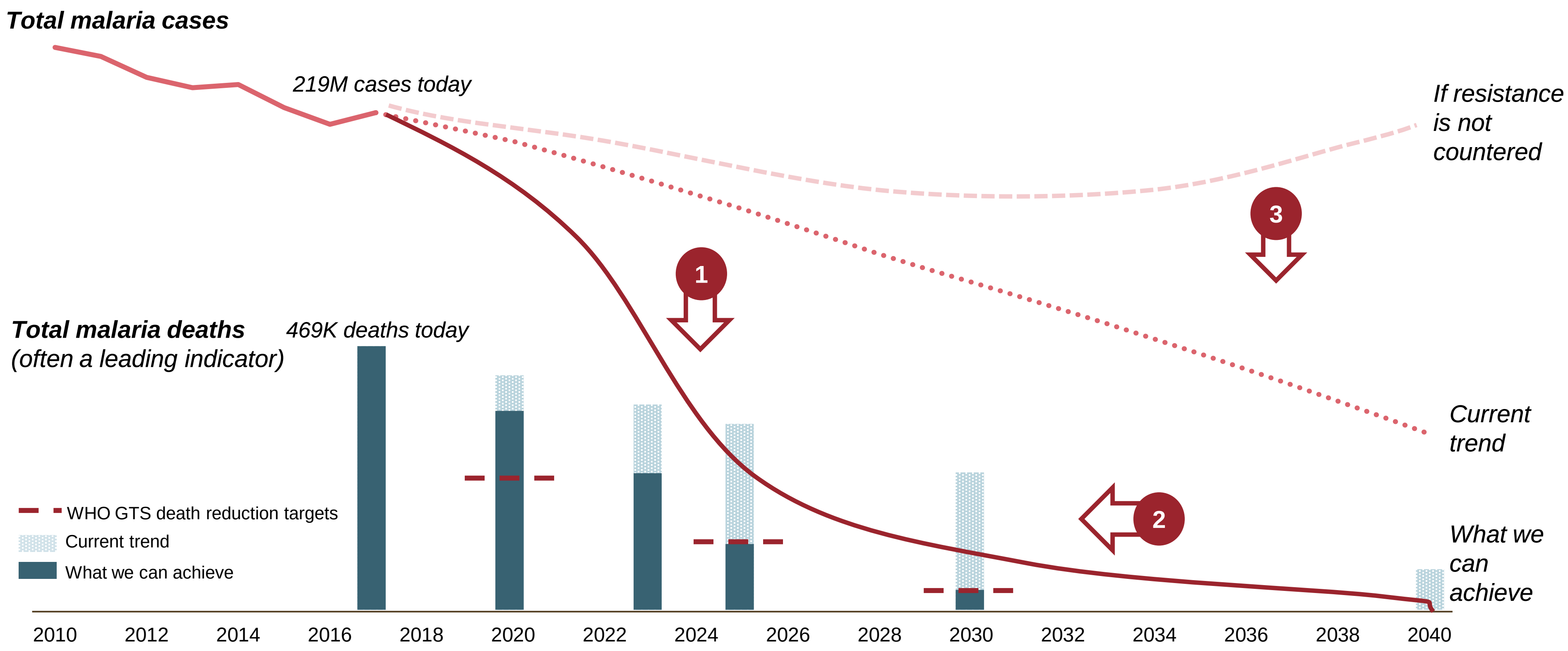
In the short- and medium- term, **scale surveillance + data-driven sub-national optimization, chemoprevention & case management in high burden settings** to reduce deaths and cases

2 Shorten the endgame

Create enabling environment for winning endgame in high endemic SSA by **investing in next-gen surveillance systems, MDR *Pf* elimination, and accelerating endgame R&D** today

3 Get ahead of resistance

Mitigate emergence of drug & insecticide resistance by **eliminating *Pf* in the GMS, developing a robust pipeline of AIs and analyzing entomological and genetic epi data** to quickly respond to threats



VECTOR CONTROL PORTFOLIO INVESTMENT AREAS

Insecticidal interventions

- Discover, optimize, and translate new insecticide active ingredients (AIs) to fight resistance
- Develop new AI combinations into LLINs and IRS to fight insecticide resistance
- Develop novel insecticide delivery systems for community transmission prevention
- Tools for improved surveillance
- Vector control product launch & life cycle management
- Develop long lasting endectocides

Genetically Based Vector Control

- Create & test platforms to test GM mosquitoes
- Develop self-limiting mosquito constructs
- Develop self-sustaining GM mosquito constructs with gene drive
- Develop endosymbiont-based interventions

Vector surveillance

- Tools for improved vector surveillance
- Improve entomological surveillance & data use

INSECTICIDAL INTERVENTIONS

Stage of development

Pre-development	Development	Field Trials	Implementation

• Active Ingredient insecticide discovery
  • 3 novel AIs (IVCC)
  • Exploration of traditional Chinese medicine library
	• LLINs
	  • 2 x novel AIs with pyrethroids (IVCC)
	  • 1 x PBO LLIN
		• IRS
		  • 2 x new molecules (submitted to PQ)
		• PBO net field stability
			• Next generation LLINs

• ATSB
  • Identifying long range attractants
  • Investigating alternative AIs
• Active ingredient discovery (volatiles/repellents)
	• ATSB
	  • Product development
	  • Product optimization
	  • Manufacturing scale-up)
		• Eave Tubes & window screening*
		• Spatial repellents**
		• ATSB	

* RCT complete; proof of concept of insecticidal window screens continuing

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HOW DO WE REPLACE PYRETHROIDS?

	Strengths	Weaknesses
New AI	Delivers new insecticide that fits TPP for intended use Offers novel target site mode of action No pre-existing background resistance	Very few companies capable of new AI development High cost Long time to market High failure rate even at late stages Relatively high CoGs for new AI
Repurposing	Eliminates highly risky development process Relatively short time to market Relatively low cost for of development Potential: Many companies do not screen for activity vs. resistant mosquitoes.	For LLIN especially – few insecticides meet the TPP requirements Very few compounds that provide BFI/Personal Protection hence combining with Pyrethroids Not always possible to access chemistry and regulatory package.

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ATTRACTIVE TARGETED SUGAR BAIT CONCEPT

→ **A device that presents an attractive sugar-meal laced with a lethal toxicant to mosquitoes and other flying, biting insects**

Use case

- **Outdoor** application
- Offers insecticide to mosquito through mechanism other than contact, opening up **wider choice of insecticides** and potential for **resistance management**
- Targets **both male and female** mosquito populations
- Reduces transmission by impacting adult mosquito survival, shifting towards greater proportion of younger uninfected females

GENETIC BASED VECTOR CONTROL

Stage of development

Pre-development	**Development**	**Field Trials**	**Implementation**
Lab development	**Regulatory approvals for field testing**	**Field Trials**	**Implementation**

• Self limited
  • *An. albimanus* & *An. stephensi* (Oxitec)
• Gene drive
  • Target Malaria
  • Transmission Zero
  • UCI*
	• Self-limited
	  • *An. gambiae* (Target Malaria)
		• No products for malaria control have made it to field trials yet	• Self-limited
			  • *Aedes aegypti* (DENV, ZIKV) (Oxitec)**

* Prior investment by BMGF, deprioritized in 2019
** Not funded by BMGF

DEFINITION OF PARADIGM/ PRODUCT CLASS

	Self-limited	Gene drive
Product description	A mosquito strain that is modified so that only male offspring are produced	A mosquito strain that is modified with a construct that copies itself. The construct can either decrease mosquito populations (suppression) or make them unable to transmit malaria (replacement).
Potential impact	Localized	Widespread
Timespan	Transgenic mosquitoes die off after releases halt	Transgenic mosquitoes continue to increase and spread after releases halt
Intended use	a) Malaria elimination in small foci b) Controlling urban malaria outbreaks c) Data from GM self-limited releases can contribute to decision-making on gene drive	To drive down malaria transmission across widespread, rural, high-burden areas where current tools are insufficient to get to elimination
Timeline	More likely to be available in the next 5 years	10+ years

ENDECTOCIDES

Stage of development

Discovery	Early / Preclinical	Mid / Proof of concept	Late Dev/ Launch
• Novel isoxazoline	• Long acting oral ivermectin formulation • Long acting injectable ivermectin	• Isoxazoline class	• Multiple trials of 1-3d standard ivermectin with and without DHA/PQP MDA (modelling suggest low impact)*

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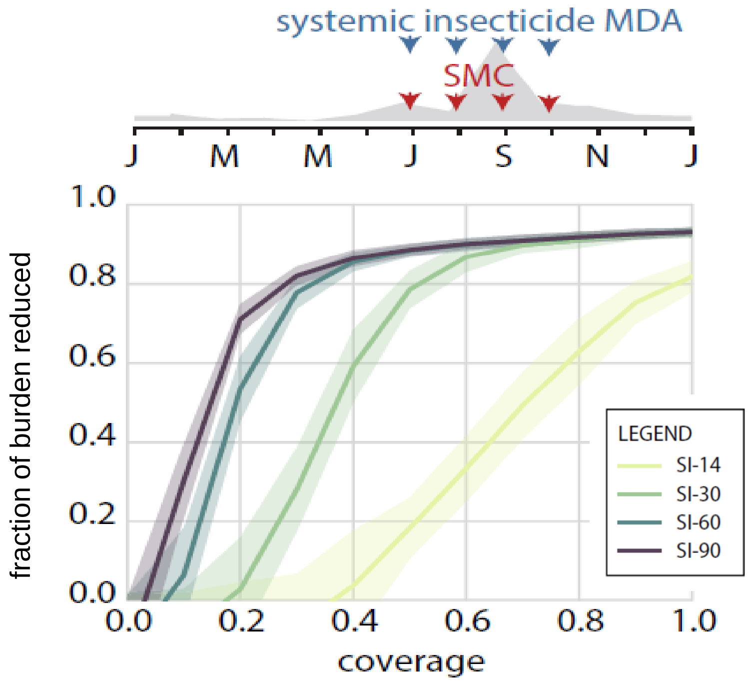
LONG-ACTING ENDECTOCIDES IN COMBINATION WITH OTHER INTERVENTIONS TO REDUCE COVERAGE NEEDS

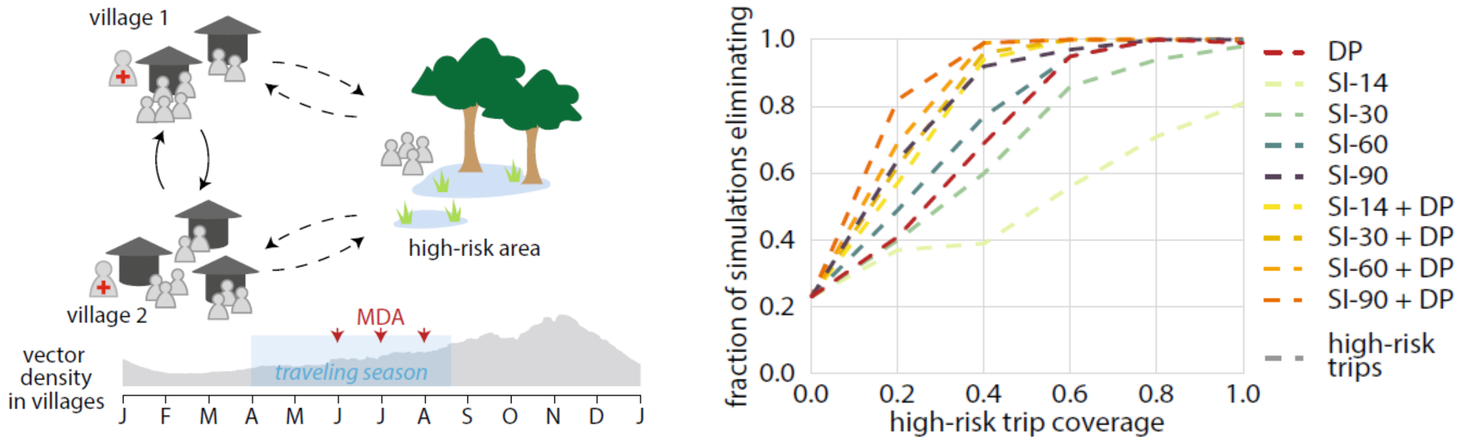
Use case: long-acting endectocide MDA with SMC in high-transmission areas



Longer duration of activity and multiple rounds of endectocide allow tradeoff with high coverage in SMC (above).

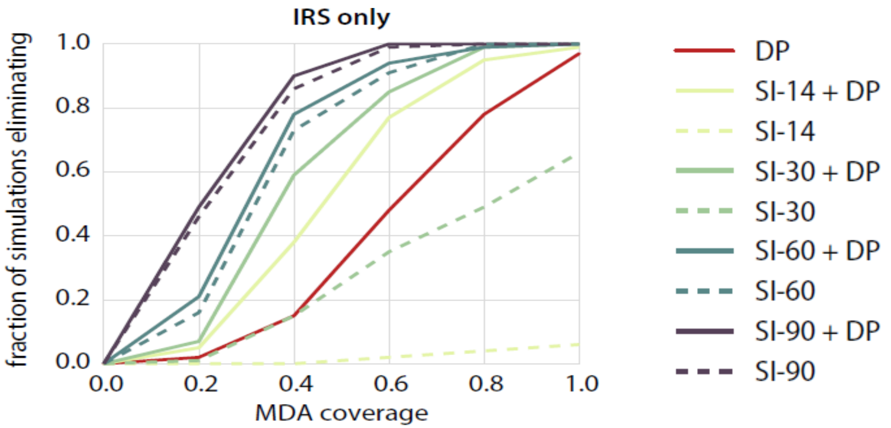
SI = systemic insecticide

Use case: targeting high-risk travelers in elimination settings



Endectocide MDA alone is effective when the duration is $\geq$ 60 days; however MDA combining an ACT with an endectocide of $\geq$14 days increase the impact above either alone (right).

Use case: boost household vector control (with ACT) in elimination settings



Endectocides have less impact in villages with effective household vector control; adding endectocide MDA can achieve elimination in functional coverage (above).

SOURCE: Selvaraj et al. *Malar J (2019) 18:307; Figs 2d,3 a & c,& 4d.*

VECTOR SURVEILLANCE

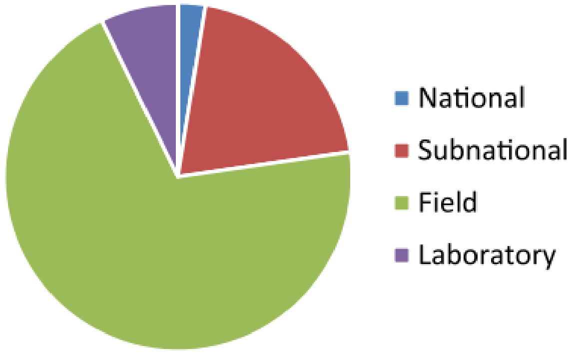


Fig. 8 Proportional shortfalls in staffing capacities of national malaria control programmes

Source: Russell et al. Malar J (2020) 19:422

Table 7 Summary assessment of laboratory analytical techniques for malaria vectors by expert informants

	Mosquito identification		Insecticide resistance		Sporozoite detection		Age grading		
Analysis	Morphology[1]	PCR[2]	WHO	CDC bottle	CS-ELISA	PCR	Ovarian dilatations	Parity dissection	NIR
Training requirement	Yellow	Red	Yellow	Yellow	Red	Red	Red	Red	Red
Human Resource Needs	Red	-[3]	Red	Red	Red	Red	Red	Red	Red
Complexity of Method	Red	Red	Red	Red	-	Red	-	Red	-
Costs/Logistics/Supplies[3]	Green	Red	Red	Red	Red	Red	Red	Red	Red
Specimen quality	Red	Red	Red	Red	-	Red	-	Red	
In-country capability	Green	Yellow	Green	Green	Green	Yellow	Green	Green	-
Interpretation of result[4]	-	-	Yellow	Yellow	-		Yellow	Yellow	Yellow
Technical consistency	Yellow	-	-	-	-	Yellow	Yellow	Yellow	

[a] Yellow indicates a moderate level of training required

[b] Red indicates significant requirements for use including high level of training, human resources, complex methodology, costs, need for quality specimens, which impacts technique uptake and use

[c] Green indicates few impediments (few logistics concerns, low costs or in country capability present) for use

[d] Yellow indicates variability in interpretation of results and technical consistency

[e] "-", not expressly addressed by informants

Source: Farlow et al. Malar J (2020) 19:432

PRIORITIES FOR NEW TECHNIQUES

- **Human Landing Catch replacement** to determine biting rates
- **Age grading of mosquitoes** to determine age structure of mosquito populations, with new techniques
- **Surface active ingredient detection** using a quantitative, non bioassay method
- **Field applicable rapid assays** for species identification, insecticide resistance frequency and mechanisms, sporozoite rates
- **Automated multiple parameter analyses** for:
  - adult density, species ID, insecticide resistance status and sporozoite infection
  - Characterization of larval habitats (remote sensing with drones, satellite imagery, other)

Thank you for listening

