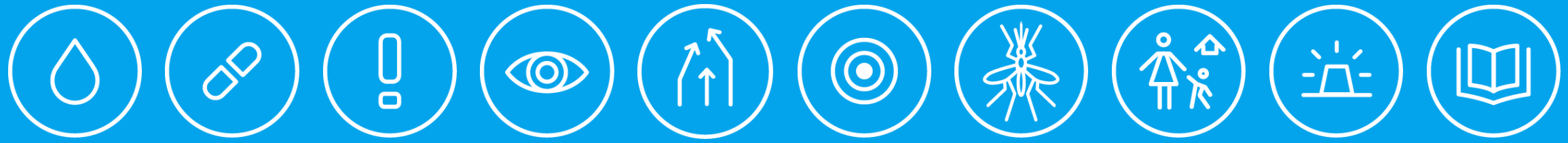
Meeting RBM CMWG

Antimalarial drug resistance in Africa and Strategy to respond



Kigali, 28 June 2022

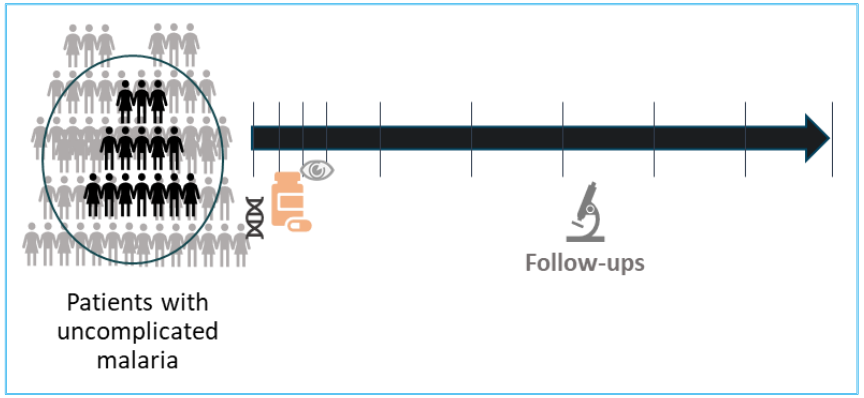
Global **Malaria** Programme

World Health Organization

Sources of information on drug efficacy and resistance

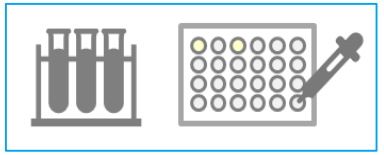
Therapeutic Efficacy Studies (TES)

- Gold standard for **monitoring drug efficacy** to inform treatment policy
- Follow-up and procedures in accordance with standard protocol
- WHO recommends that TES are done in sentinel sites at least once every 2 years.



In-vitro and ex-vivo studies

- Testing the **sensitivity of parasites** to precise concentration of antimalarial drugs.

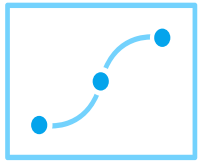


Molecular markers

- For drugs with molecular markers identified, **drug resistance can be confirmed, and trends monitored** with molecular techniques.
- Samples collected in surveys or TES.

Pharmacokinetics

- Blood level at day 7 and/or day of failure to confirm adequate blood level after treatment.



Resistance definitions

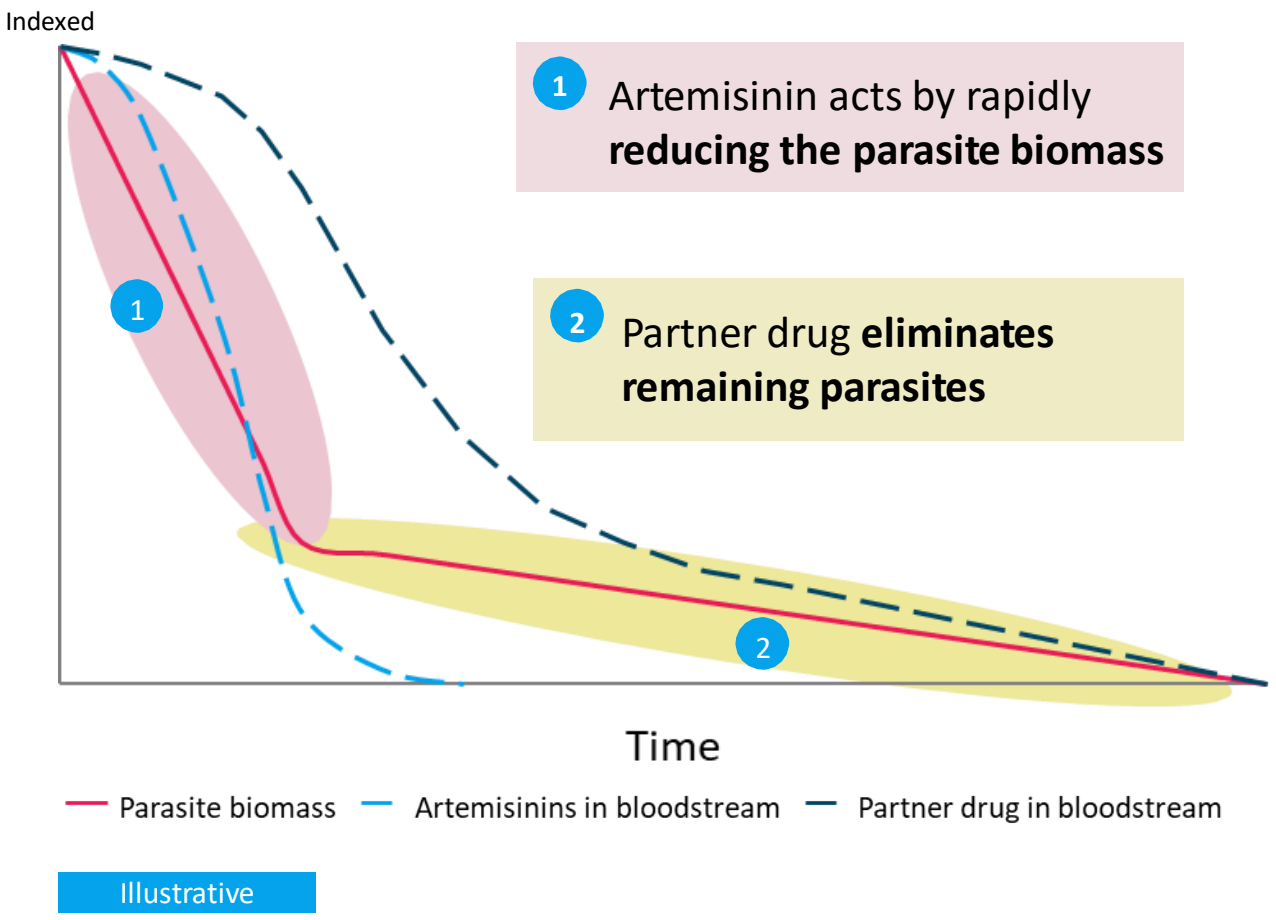
- **Antimalarial resistance** is defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject.

- ***Treatment failure (≠ resistance)*** is the inability to clear parasites from a patient's blood or to prevent their recrudescence after the administration of an antimalarial. Many factors can contribute to treatment failure, including incorrect dosage, poor patient adherence, poor drug quality, and drug interactions and resistance. Most of these factors are addressed in therapeutic efficacy studies.

Artemisinin-based combination therapies

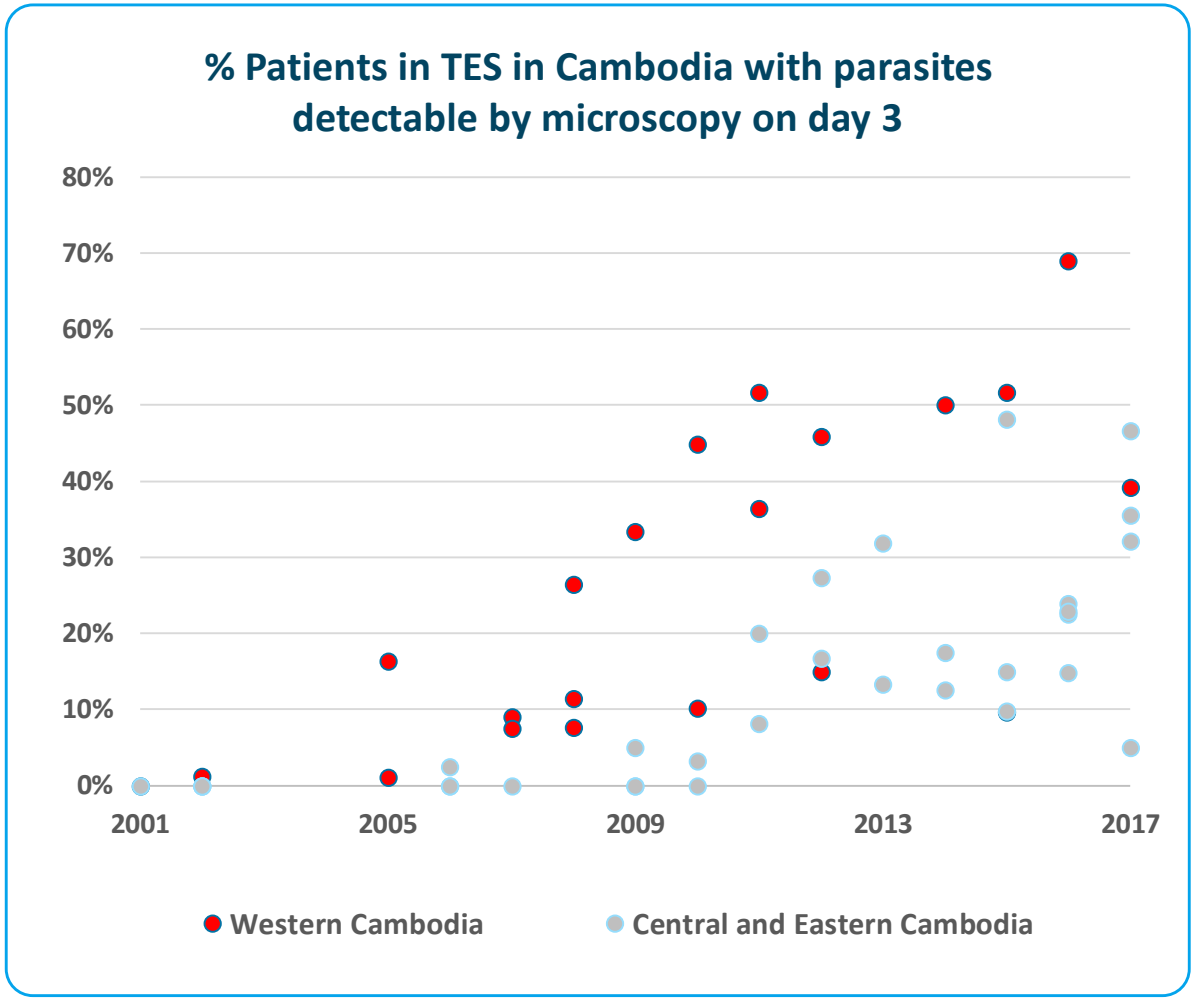
- Artemisinin-based combination therapies (ACTs) combine an artemisinin and partner drug
- The efficacy of ACTs is dependent of efficacy of both components
- All 6 partner drugs highly efficacious as monotherapies in absence of resistance
- Artemisinins rapidly lower the parasite biomass while partner drug completes elimination of the parasites

Evolution of parasite biomass in the body following ACTs administration



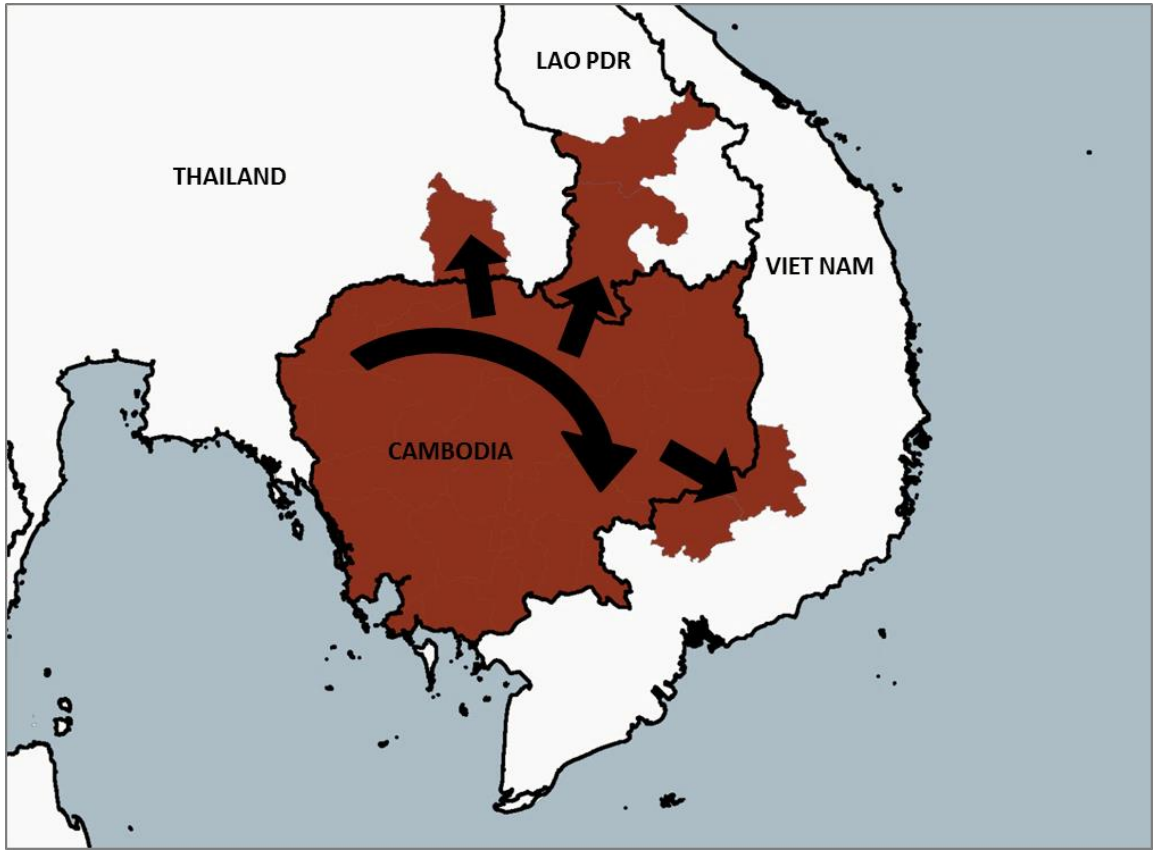
Artemisinin partial resistance

- Delayed clearance after treatment with an artemisinin was first detected on the border of Cambodia and Thailand
- 7-day artesunate treatment showed > 90% efficacy even in areas of high prevalence of delayed clearance
- **Artemisinin partial resistance** is seen as delayed parasite clearance following treatment with artemisinin-based monotherapy or with an ACT
- Delayed clearance alone does not lead to a significant increase of ACT treatment failure
- However, in combination with partner drug resistance, very high failure rates have been seen



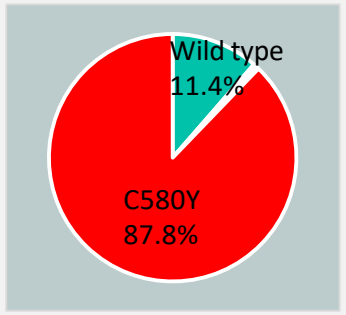
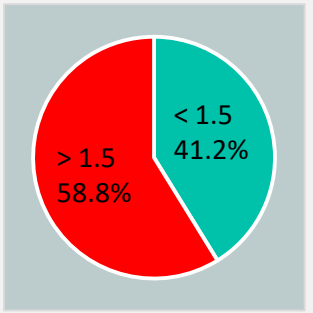
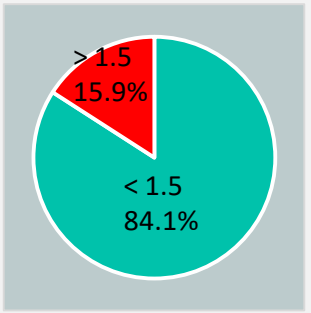
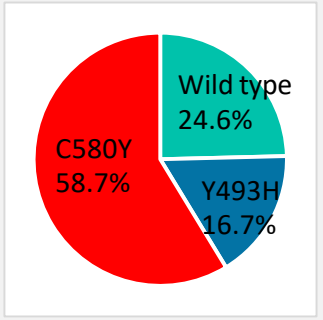
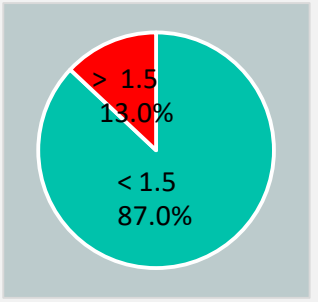
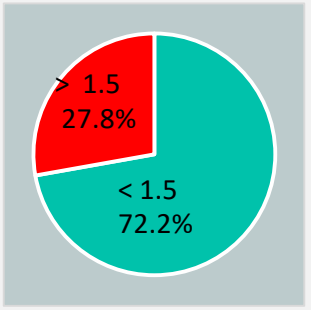
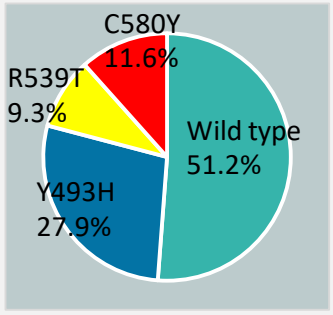
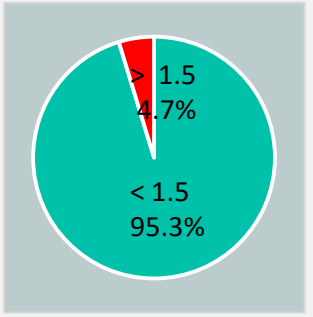
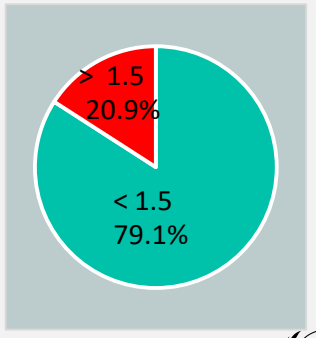
Spread of partner drug resistance

- In Southeast Asia, artemisinin partial resistance has not been seen to cause the emergence of partner drug resistance but may have helped spread piperaquine resistance through a strain with artemisinin partial resistance and piperaquine resistance
- The spread of the resistant parasites across the region linked to massive drug pressure
- However, change in first-line treatment in Cambodia does appear to select against this strain

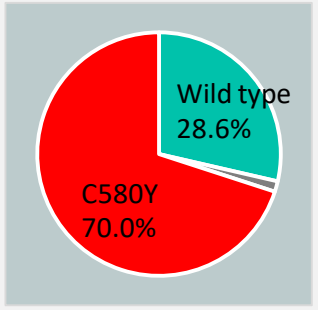
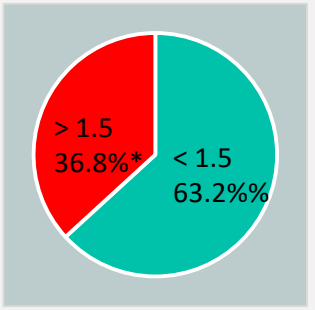
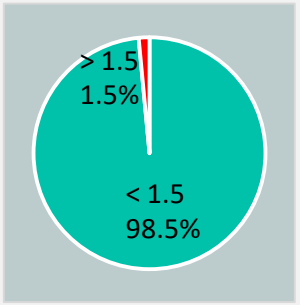
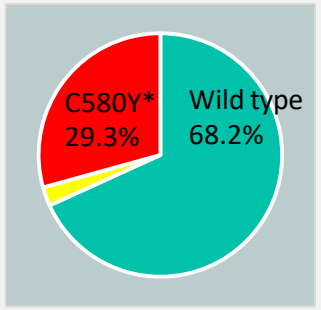
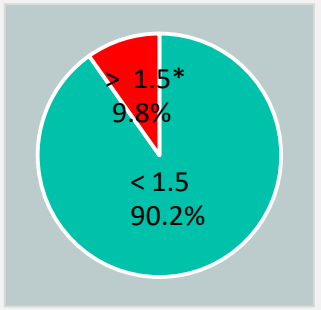
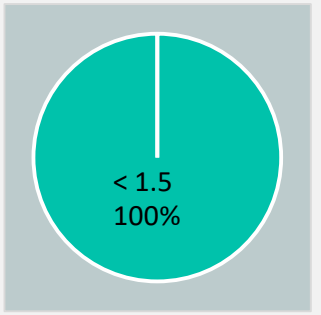
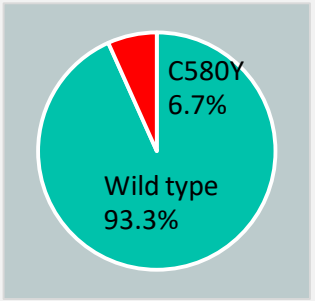
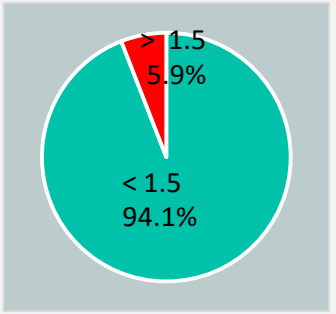
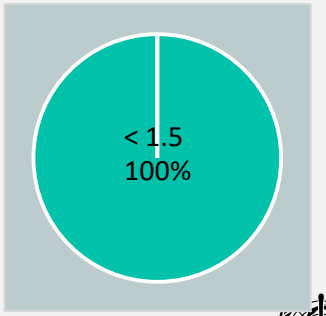


Imwong et al. 2017 Lancet Inf Dis.

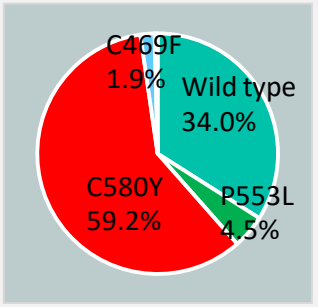
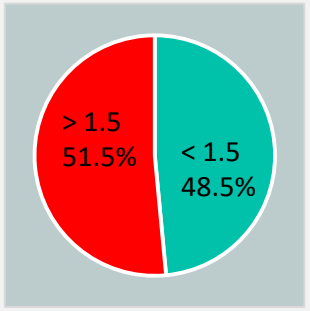
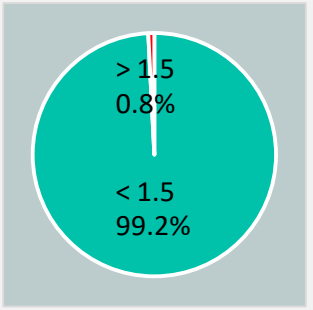
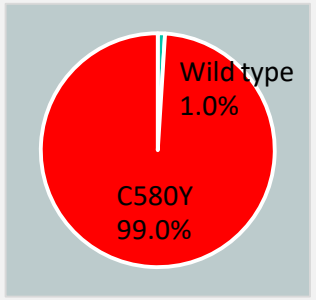
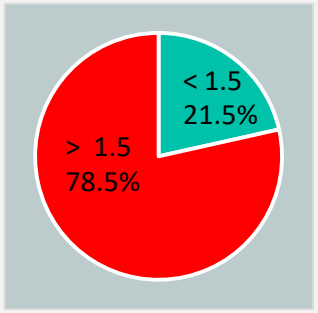
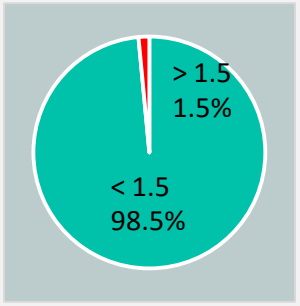
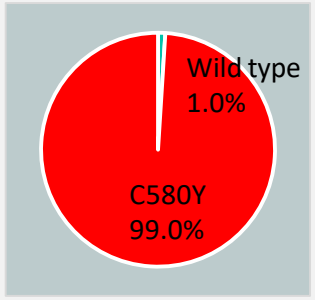
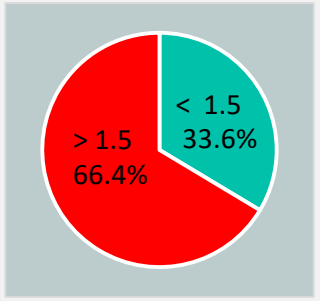
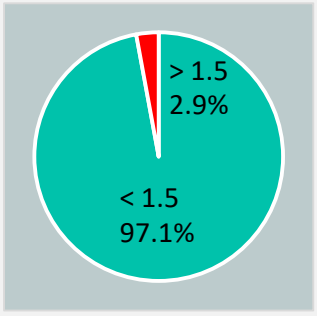
Prevalence of molecular markers in Cambodia

	Pfkelch13	*PfPlasmepsin 2/3*	*Pfmdr1*
2016 (n = 238)			
Policy change: DP to ASMQ and ASPY = MFLT	P553L 0.4% R539T 0.4%		
2019 (n = 115)			
2020 (n = 43)			

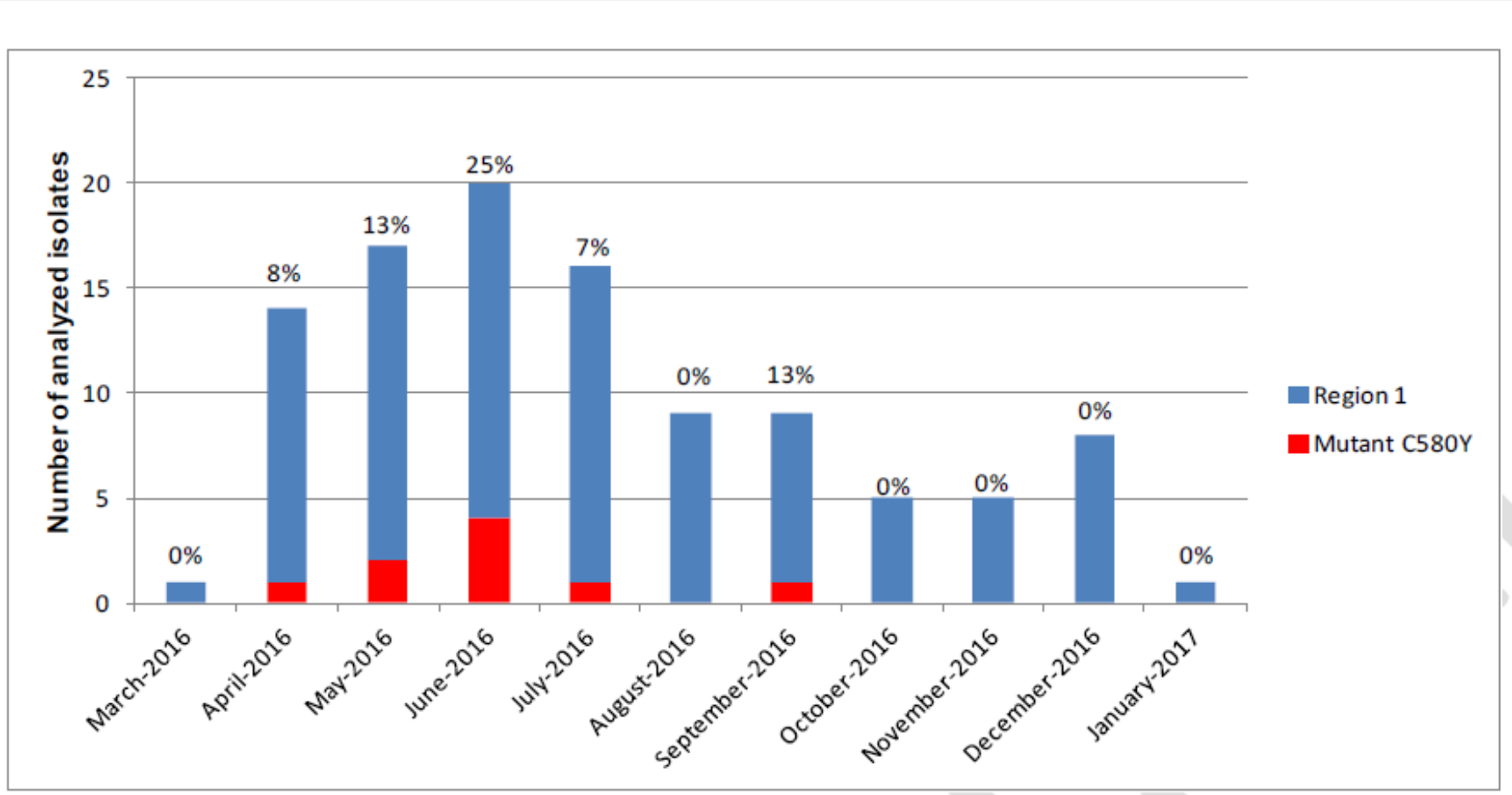
Prevalence of molecular markers in Lao PDR

	Pfkelch13	*PfPlasmepsin 2/3*	*Pfmdr1*
2016-2017 (n = 70) * Champassak	 R539T 1.4%		
Policy change: PQ single dose			
2018-2019 (n = 41) * Champassak	 C447R 2.5%		
2019-2020 (n = 105)			

Prevalence of molecular markers in Viet Nam

	Pfkelch13	*PfPlasmepsin 2/3**	*Pfmdr1**
2017 (n = 262) * 2 double mutants	 K503N 0.4%		
Policy change: DP to ASPY			
2019 (n = 208) * 3 double mutants			
2020 (n = 106) * 1 double mutant			

Artemisinin partial resistance: trends in Guyana



Delayed parasite clearance after treatment with artemisinins found to be associated with *PfKelch13* (K13) mutations

***PfK13* markers of artemisinin partial resistance**

Validated markers

- F446I
- N458Y
- C469Y
- M476I
- Y493H
- R539T
- I543T
- P553L
- R561H
- P574L
- C580Y
- R622I
- A675V

Candidate markers

- P441L
- G449A
- C469F
- A481V
- R515K
- P527H
- N537I/D
- G538V
- V568G

Resistance situation in Africa

Key messages from Technical workstream on drug resistance | Situation still under control, but measures should be implemented to avoid ACT treatment failure

- Artemisinin partial resistance confirmed in Rwanda, Uganda, Horn of Africa
- Lack of geographical coverage of data

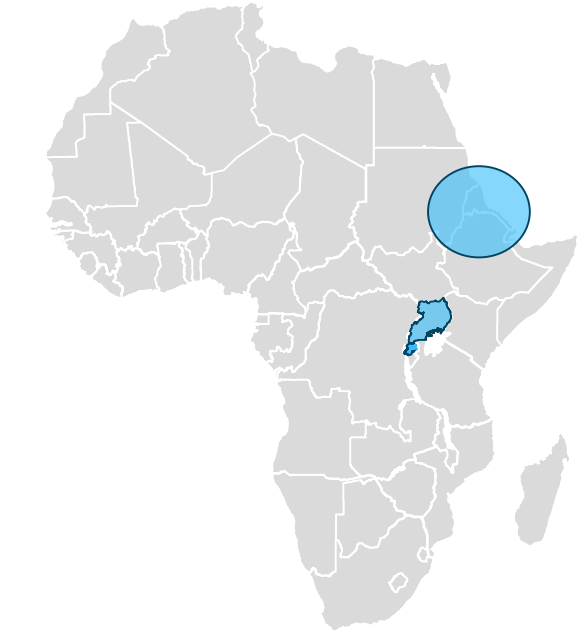
- Fitness cost and parasite genetic background expected to play a key role in resistance's ability to spread
- Spread potential likely to differ from the Greater Mekong Subregion

- For partner drugs, scattered reports of treatment failure but no resistance confirmed (*in vitro,* molecular markers or blood levels)

- Potential risk of issue underestimation by local stakeholders (≠ GMS)
- Communication and advocacy will play a key role

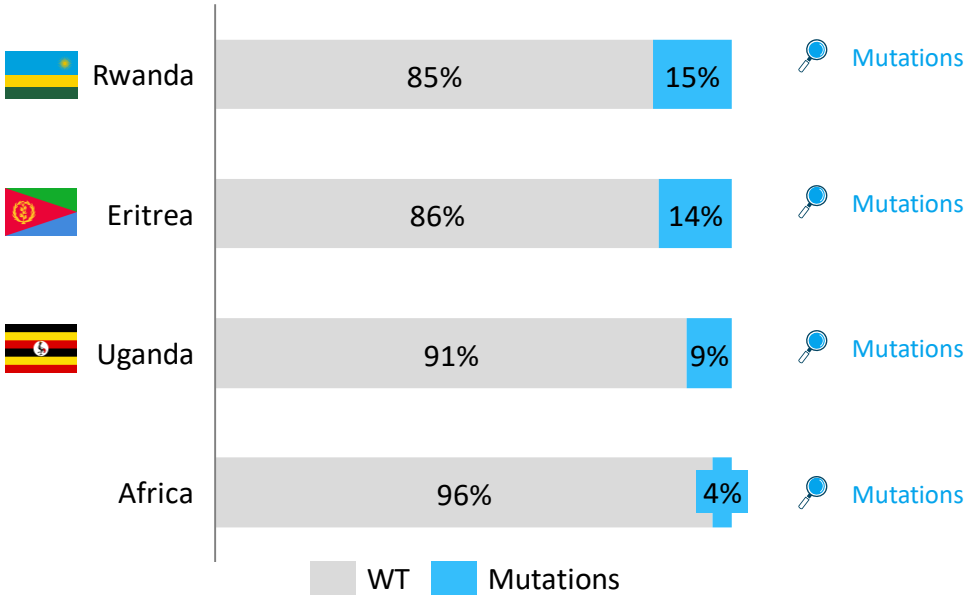
K13 Wild Type still dominant in Africa, but presence >5% of mutants already identified in 3 countries

3 countries with more than 5% K13 mutations (2015-2020)

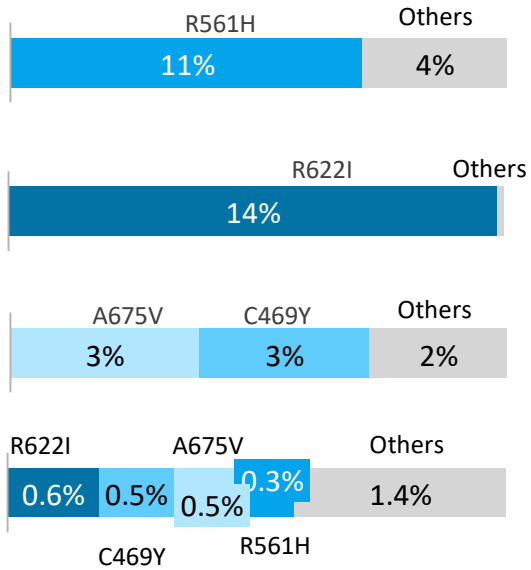


Countries with >5% K13 mutations

Wild Type still significantly dominant



Various K13 mutants identified in different countries



- Mutations not spread from Asia
- Mutations have been found to be associated with increased proportion of patients with detectable parasites on day 3 but tested ACTs still efficacious

So far, no confirmed partner drug resistance in Africa[1]

Partner drug	Current evidence	Molecular markers of resistance	Comments
Amodiaquine	• Treatment failure rates > 10% identified in two TES in Liberia in 2017-2018	To be validated in Africa	• IC_{50} affected in vitro by *Pfcrt* and *Pfmdr1* mutations but shift of IC_{50}s less significant than for chloroquine, and *Pfcrt* and *Pfmdr1* mutations cannot be considered amodiaquine resistance markers at present
Lumefantrine	• Treatment failure rates > 10% reported in 4 countries (Angola, Burkina Faso, Democratic Republic of Congo and Uganda) between 2009 and 2019 • Increased IC_{50} in Uganda	To be validated	• Short half-life → potential misclassification of reinfections as recrudescences • Studies have used PCR-correction method based on microsatellites and a Bayesian algorithm (Angola, DRC, Uganda) • Concerns on quality of microscopy (Burkina Faso) • In Burkina Faso, Uganda and DR Congo, AL treatment failures in sites where DP treatment failures were also found
Piperaquine	• Treatment failure rates > 10% reported in 3 countries (Burkina Faso, Uganda and Democratic Republic of Congo)	To be validated in Africa (*Pfpm2/3* increased copy number and *Pfcrt* mutations validated in GMS and South America)	• Studies have used PCR-correction method based on microsatellites and a Bayesian algorithm (DRC, Uganda) • Concerns on quality of microscopy (Burkina Faso) • In Burkina Faso, Uganda and DR Congo, AL treatment failures in sites where DP treatment failures were also found

[1] Excluding sulfadoxine-pyrimethamine

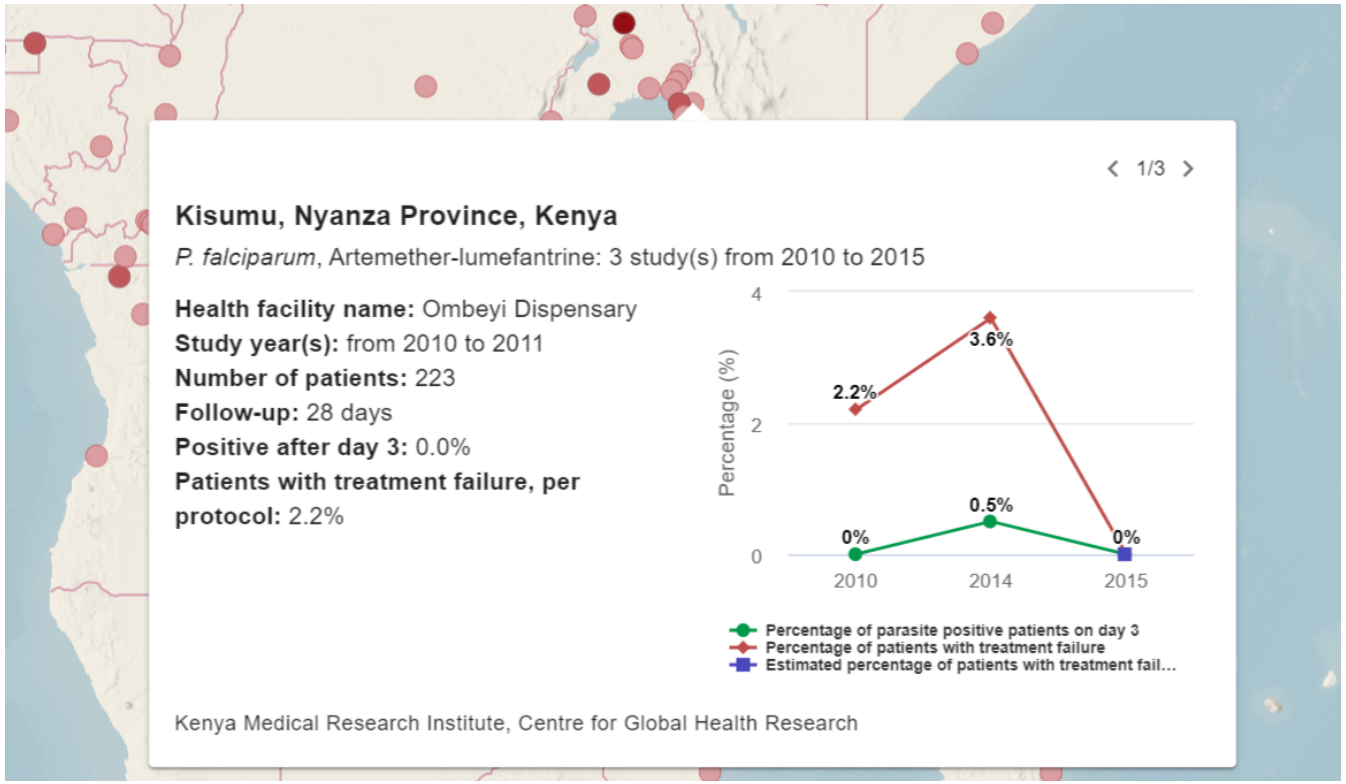
Is there lumefantrine resistance in Africa?

- TES have highlighted signals of high treatment failure rates, but sometimes studies deviated from WHO protocols
- Many confounders of AL treatment failure are possible during a TES:
  - poor drug absorption,
  - non-adherence as the second daily dose is often unsupervised,
  - short half-life of lumefantrine leads to higher reinfection rates, with some reinfections potentially misclassified as recrudescence
- Reports of AL treatment failures in travellers returning from Africa to the UK, Sweden and Portugal: information on lumefantrine blood levels was often missing
- AL treatment failures in travellers successfully cured with a second treatment of AL in Turkey and Sri Lanka after treatment failure with a prior full treatment of AL.
- A few reports have shown increases in in vitro inhibitory concentrations 50%
- High treatment failure rates for AL have not been reported in Lao PDR and Myanmar, despite high prevalence of artemisinin partial resistance.

Additional information and data

Malaria threat maps

http://apps.who.int/malaria/maps/threats/



Strategy development

Why a strategy for antimalarial drug resistance in Africa is needed

Context

- **Artemisinin-based combination therapies** (ACTs) as main medicine to fight malaria.
- There is **heavy reliance on artemether-lumefantrine** (85% of courses procured by GF).
- ACT treatment failures due to artemisinin partial resistance and partner drug resistance appeared in **GMS.**
- High number of cases (>90% of global malaria cases) and reliance on few treatments put Africa particularly at risk **if resistance emerges and spreads.**

Problem statement

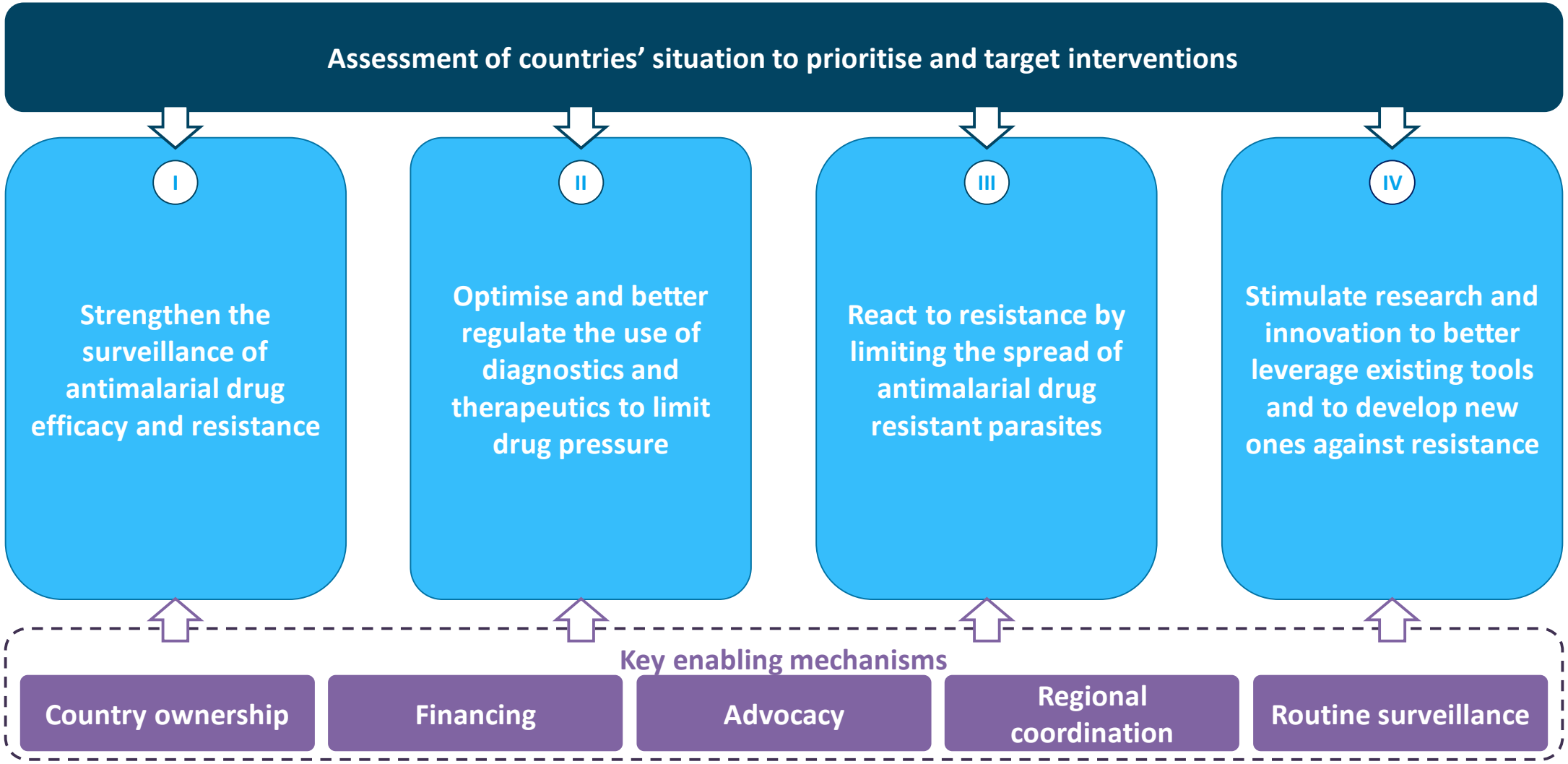
- **Artemisinin partial resistance** confirmed in Uganda, Rwanda and Horn of Africa.
- Artemisinin partial resistance **puts pressure on partner drug** and might trigger de novo emergence of resistance or selection of existing partner drug resistance.
- There are huge gaps in information and data that urgently needs to be addressed

Way forward

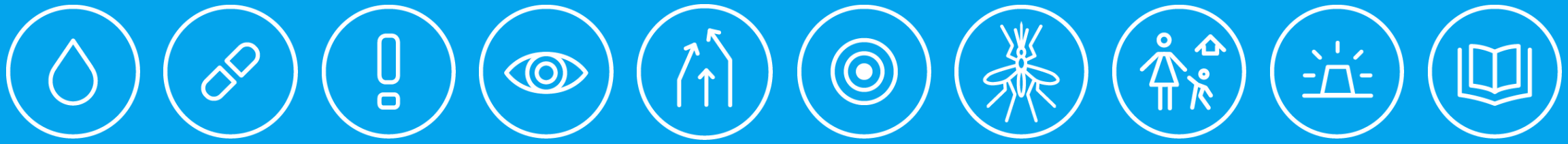
- **Need to define a strategy to respond to antimalarial drug resistance in Africa, and**
  1. **Prevent the emergence of resistance**
  2. **Tackle resistance once it has emerged**
- **Strategy will rely on a better use of existing tools & development of new tools & strategies, with actions at global, regional and local level**

Proposed interventions

Four proposed areas of interventions to be prioritised and targeted through country assessment



Thank You



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