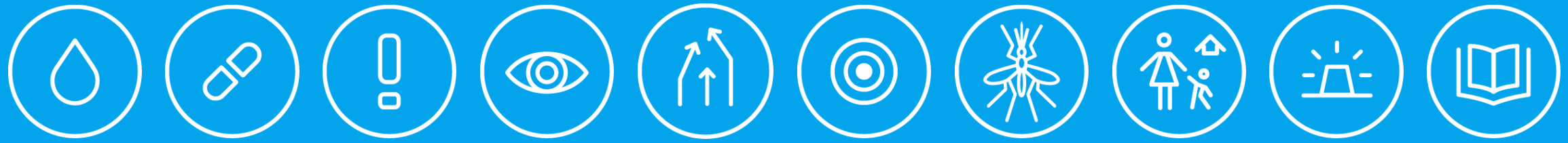
Antimalarial drug resistance in Africa



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Outline of the presentation

- **Background on antimalarial drug resistance**
- **Resistance situation in Africa**
- **Strategy to respond to antimalarial drug resistance in Africa**

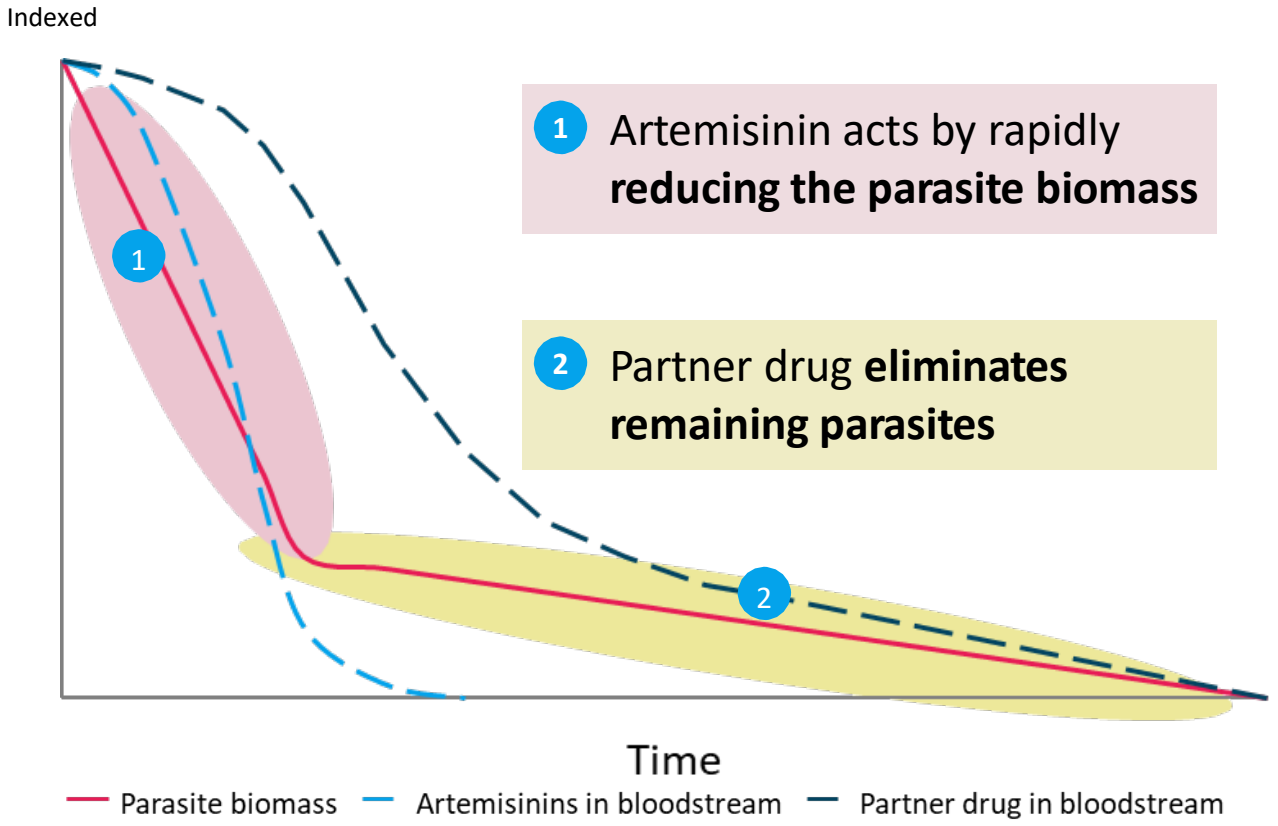
World Health Organization

Artemisinin-based combination therapies at the heart of the response

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

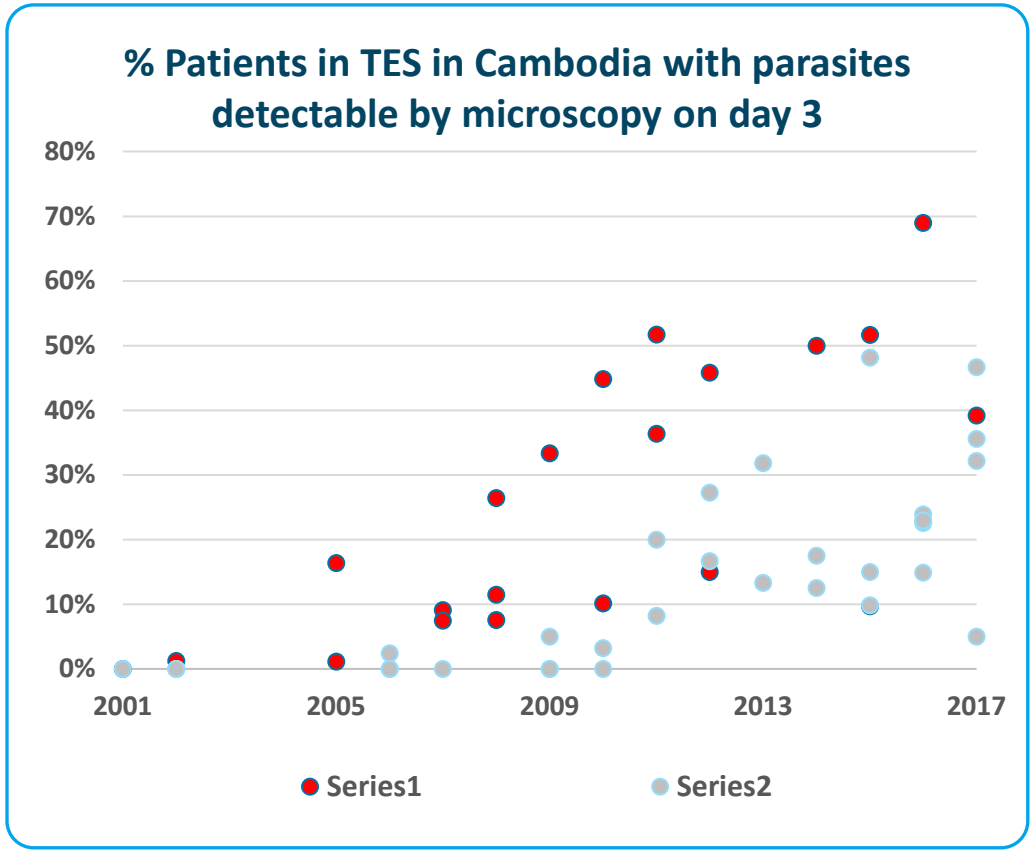
Evolution of parasite biomass in the body following ACTs administration

Illustrative



Artemisinin partial resistance

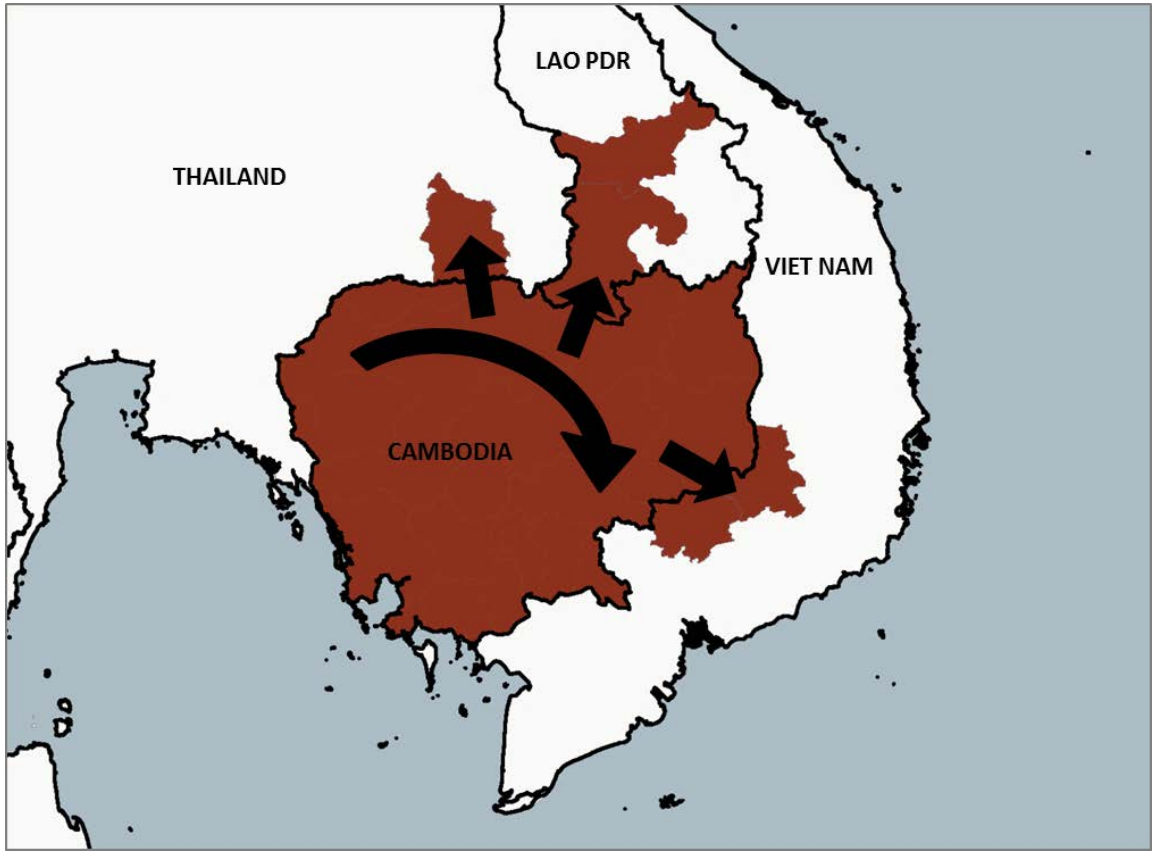
- **Artemisinin partial resistance** seen as delayed parasite clearance following treatment with artemisinin-based monotherapy or with an ACT



- Delayed clearance alone does not lead to ACT treatment failure
- In combination with partner drug resistance, very high failure rates have been seen
- Artemisinin partial resistance have been associated with different mutations of *Pfkelch13.* List of validated and candidate markers available on GMP website (*https://www.who.int/news-room/questions-and-answers/item/artemisinin-resistance*)
- 7-day artesunate treatment showed > 90% efficacy even in areas of high prevalence of mutant *Pfkelch13*
- For artemisinin partial resistance to be confirmed in a site, quality evidence is needed on:
  - Presence of validated marker (≥5%)
  - Evidence of delayed clearance

Risk of partner drug resistance

- In Southeast Asia, artemisinin partial resistance has not been seen to cause the emergence of partner drug resistance
- However, artemisinin partial resistance 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 by DHA-piperaquine
- However, change in first-line treatment in Cambodia does appear to select against this strain

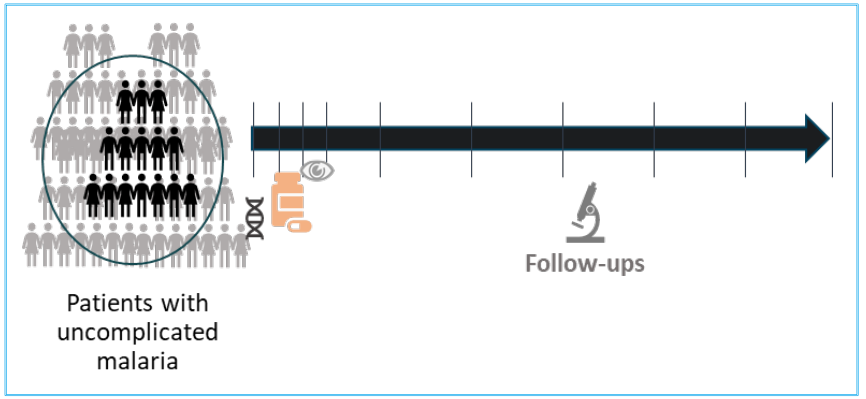


Imwong et al. 2017 Lancet Inf Dis.

Sources of information on drug efficacy and resistance

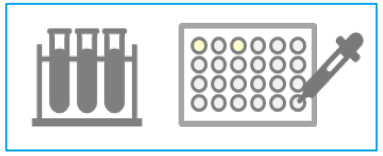
Therapeutic Efficacy Studies (TES)

- 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.

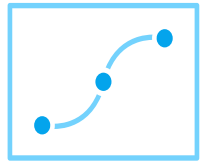


Molecular markers

- 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 situation in Africa

In early 2022, experts on drug resistance reviewed the data on antimalarial drug resistance in Africa | Situation still under control, but measures should be implemented to avoid ACT treatment failure

- Artemisinin partial resistance confirmed in Rwanda, Uganda, and Eritrea
- Lack of geographical coverage of data

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

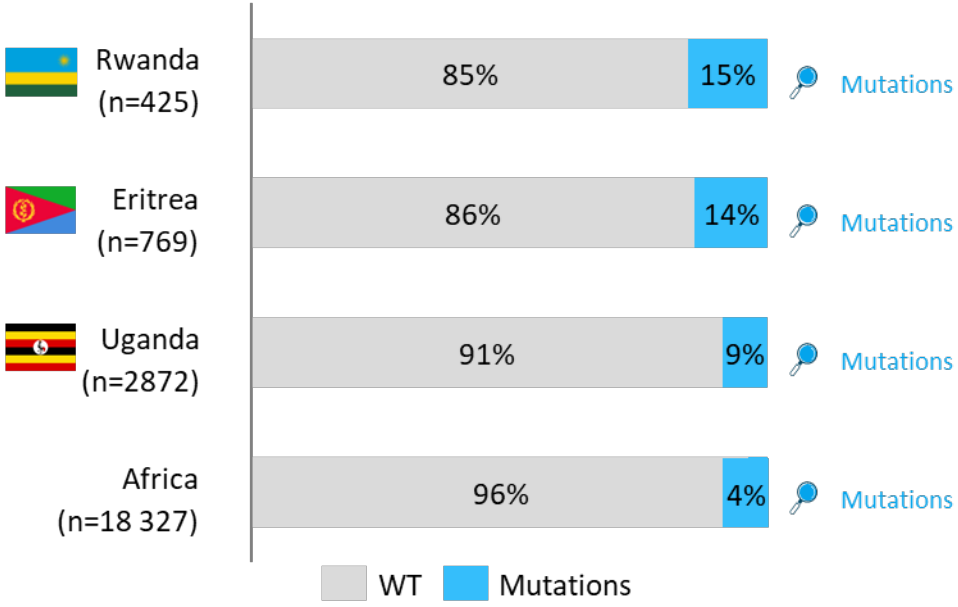
- For partner drugs, scattered reports of treatment failure but no resistance confirmed (*in vitro,* molecular markers or blood levels)

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

Conclusion of review in 2022: Molecular markers of artemisinin partial resistance found at high prevalence in 3 African countries

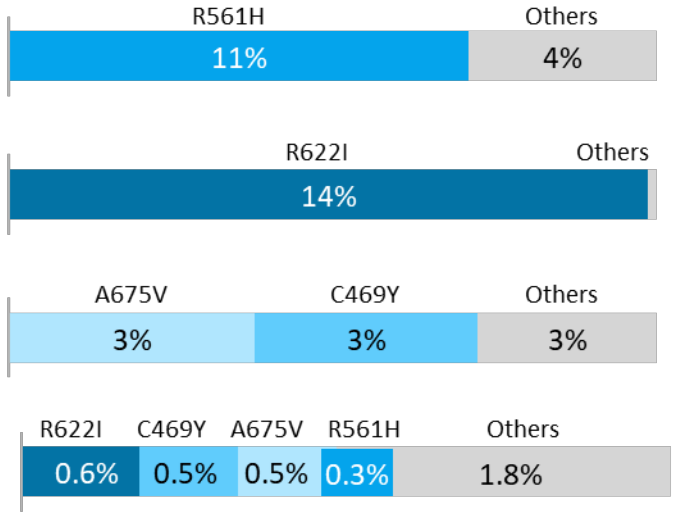
Countries with >5% K13 mutations

Wild Type still significantly dominant



n = number of samples collected

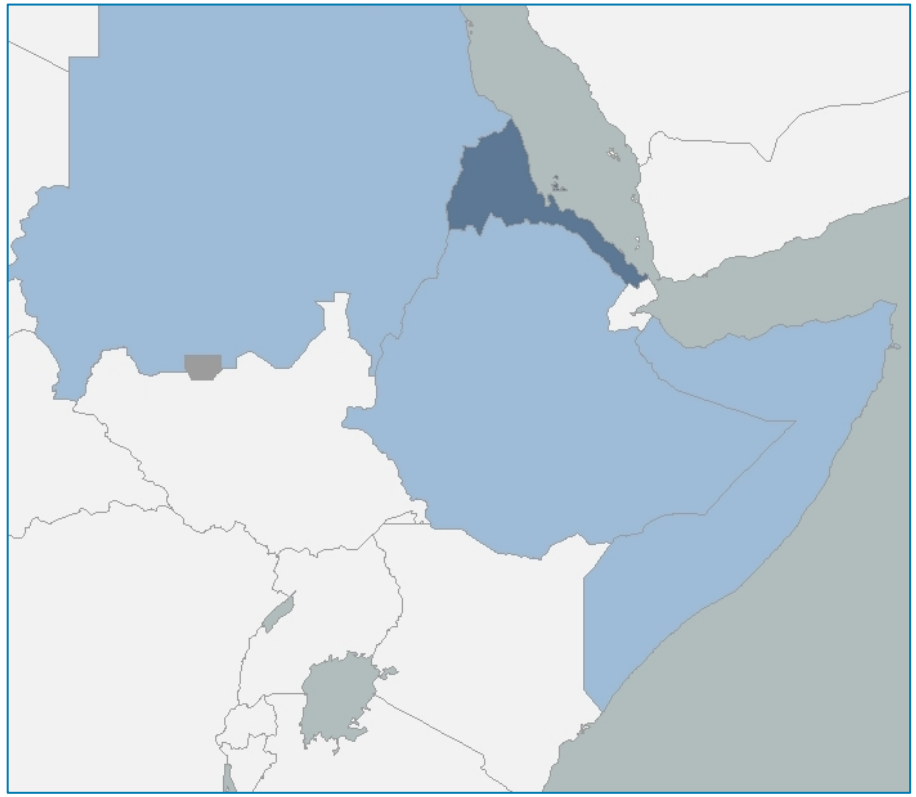
Various K13 mutants identified in different countries



Note: Wild Type refers to a phenotype, genotype, or gene that predominates in a natural population of parasites

Evidence from the Horn of Africa countries – K13 mutation R622I

- K13 mutation R622I now detected in several countries in the Horn of Africa including Ethiopia, Eritrea, Sudan and Somalia.
- R622I has been detected in parasites with *Pfhrp2/3* deletions
- Only in Eritrea is there evidence of delayed parasite clearance in areas of high prevalence of R622I



TES of artesunate-amodiaquine in Eritrea 2019 (PCR corrected, 28 days of follow-up)

	n	Day 3+ %	Treatment failure %	R622I %
Agordat	88	0	0	28.3
Tokombia	71	10.2	4.7	32.1
Shambuko	83	5.7	3.6	9.5
Guluj	94	1.1	2.2	24.4

Uganda

- **Extensive molecular surveillance ongoing**
- **Data shows an evolving situation and foci where validated markers of artemisinin partial resistance are found in a majority of the parasites sampled***

- Four main mutations detected:
  - C469Y and A675V mutations increasing prevalence in northern Uganda since 2016, with gradual spread around the country by 2021-22
  - Additionally, C469F and R561H have been detected at high prevalence in a specific region of southwestern Uganda

*Conrad et al. *Evolution of artemisinin partial resistance in Ugandan malaria parasites.* Forthcoming article

Evidence from Rwanda and Tanzania - K13 mutation R561H

Rwanda

- TES from 2018 showed evidence of delayed clearance and R561H as most prevalent K13 mutation

TES of artemether-lumefantrine in Rwanda 2018 (PCR corrected, 28 days of follow-up)

	n	Day 3+ %	Treatment failure %	R561H%
Rukara	66	13.6	5.8	19.5
Masaka	50	15.4	4	17.3
Muganza	76	0	2.6	1.2

Tanzania

- A TES was done in 2022 in Kagera close to Rwanda
- Study was initiated in this area based on molecular surveillance identifying R561H
- The study found evidence of artemisinin partial resistance in Tanzania
  - high proportion of parasites with R561H
  - high number of patients being day 3+ and slow parasite clearance time

TES in Kagera 2022 (PCR corrected, 28 days of follow-up)

	n	Day 3+ %	Treatment failure %	R561H%
AL	59	12.5	3.4	24.1 (28/116)
ASAQ	86	19.3	0	20.5 (18/88)

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 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	• Studies show that lumefantrine selects for *Pfmdr1* mutations (N86) • Short half-life → potential misclassification of reinfections as recrudescences • Studies have used PCR-correction method based on microsatellites and a Bayesian algorithm rather than WHO recommended method • Concerns on quality of microscopy • 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 • Concerns on quality of microscopy • In Burkina Faso, Uganda and DR Congo, AL treatment failures in sites where DP treatment failures were also found

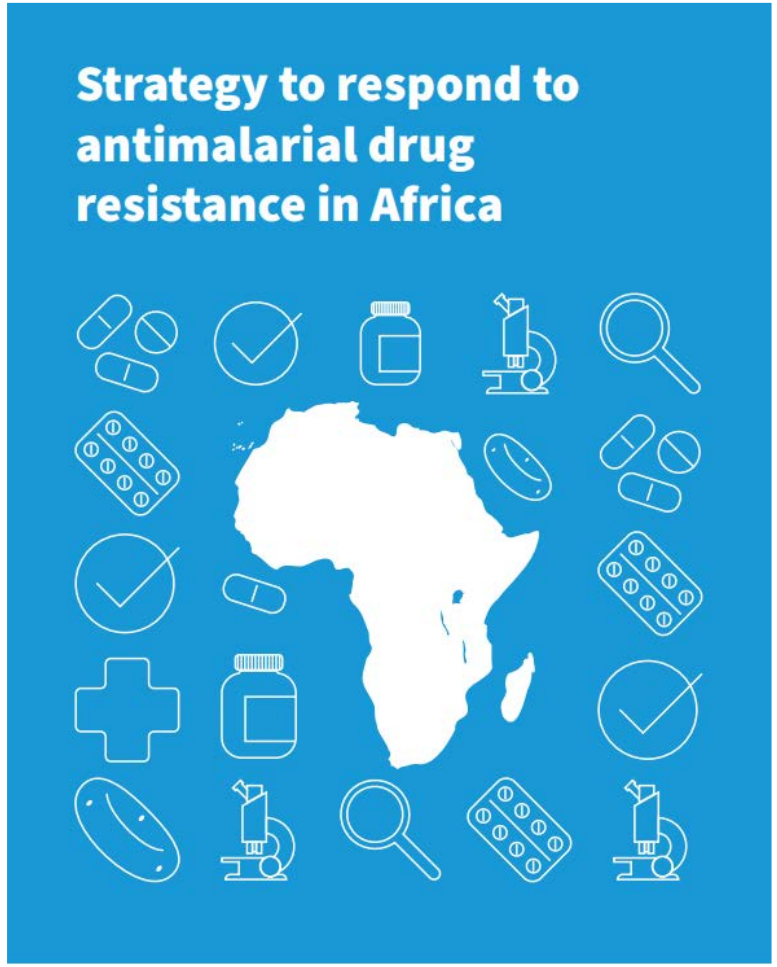
[1] Excluding sulfadoxine-pyrimethamine. Mefloquine and pyronaridine have not been widely used for treatment in Africa

Strategy

Need for a strategy

- Need **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 relies on **better use of existing tools** & **development of new tools & strategies**, with actions at global, regional and local level

Launched November 2022

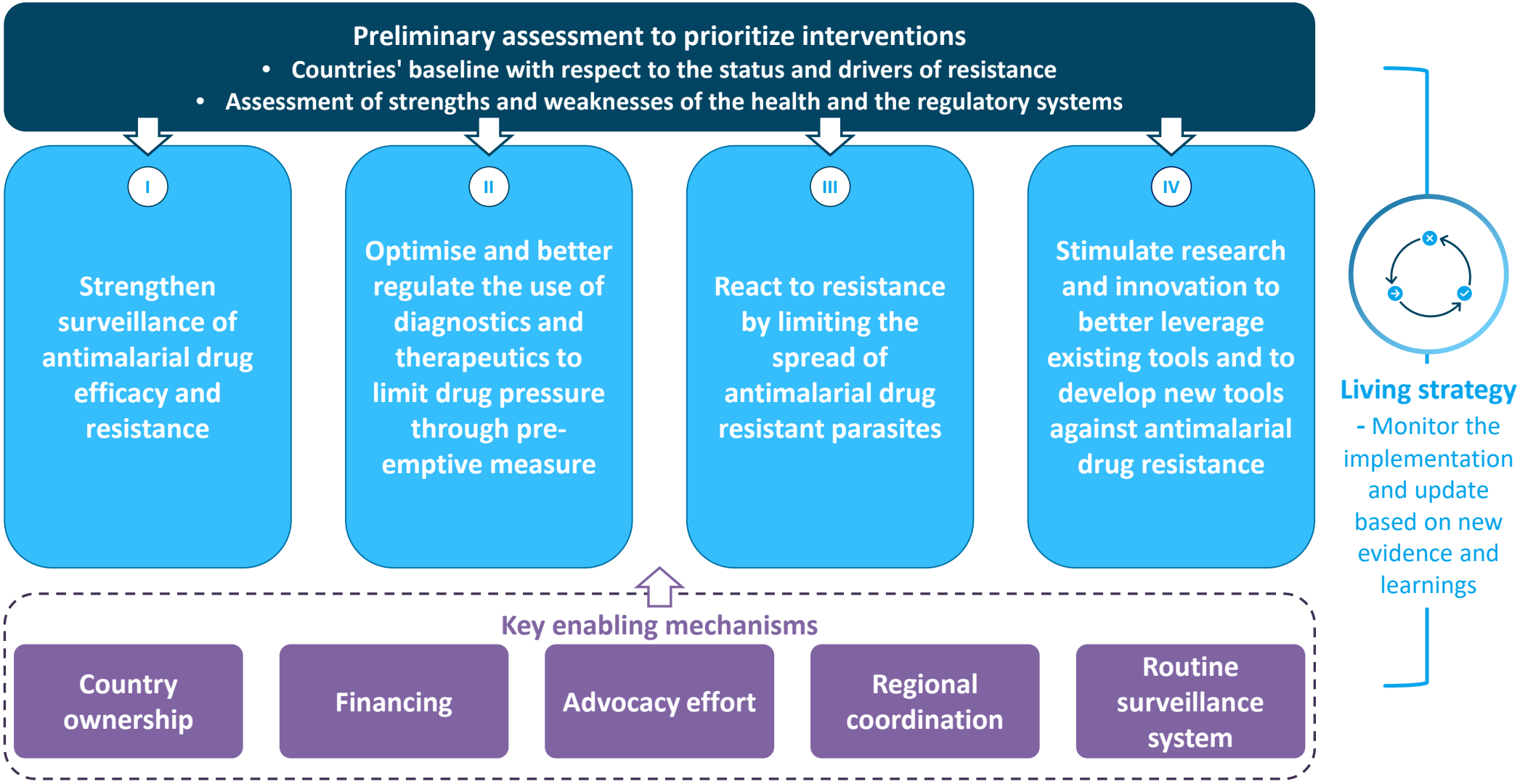


Development included

- 5 Working groups — 86 leading malaria experts
- 74 Additional individual contribution — Diversified panel of global and local stakeholders
- 100+ Scientific papers reviewed — Broad literature review to collect existing evidence
- 2 Consultations — Expert and public consultation

Strategy to respond to antimalarial drug resistance in Africa

Interventions to mitigate risks and respond to resistance



Interventions by pillar

I Strengthen surveillance of antimalarial drug efficacy and resistance

1. Enhance capacity and capabilities to generate better quality and standardized data on antimalarial drug efficacy and parasite resistance
2. Increase coverage of surveillance systems for efficacy and resistance
3. Increase collection of additional, more detailed data at select sites
4. Improve data dissemination systems to facilitate a reactive and coordinated response to resistance data

II Optimize and better regulate the use of diagnostics and therapeutics to limit drug pressure through pre-emptive measures

1. Develop national treatment policies that promote deliberate use of existing treatments to prevent and react to the emergence and spread of resistance
2. Promote the availability of a diversified drug portfolio in countries
3. Prevent exposure to subtherapeutic drug levels driven by substandard and falsified ACTs by promoting drug quality
4. Remove non-recommended monotherapies and ensure that other monotherapies are used in accordance with WHO guidelines
5. Promote equitable access to quality drugs
6. Promote equitable distribution of and access to high-quality diagnostics to reduce drug pressure
7. Empower patients, HCWs and other stakeholders to make informed decisions, and provide appropriate treatment

III React to resistance by limiting the spread of antimalarial drug-resistant parasites

1. Ensure optimal malaria vector control intervention coverage in priority areas
2. Leverage preventive measures to reduce transmission of antimalarial drug-resistant parasites
3. Limit the risk of increased transmission of resistant parasites
4. Strengthen cross-border collaboration on malaria activities to ensure coordinated resistance management

IV Stimulate research and innovation to better leverage existing tools and develop new tools against resistance

1. Identify innovative approaches using currently available drugs to delay the development and spread of resistance
2. Identify areas and populations where drug resistance is deemed more likely to develop and spread
3. Develop new treatments and diagnostics with the objective of delaying the emergence and spread of resistance
4. Identify and develop innovative tools to limit malaria infection and transmission
5. Conduct modelling and research to better understand and track resistance

Strategy implementation | Selected WHO planned and ongoing activities

- **Collection and sharing of data in the Malaria Threat Maps**

Malaria threat maps

https://www.who.int/teams/global-malaria-programme/surveillance/malaria-threats-map

Finished and published data

Planned and ongoing studies

- Dashboard on studies of drug efficacy
- Dashboard on surveys of molecular markers of drug resistance

- **WHO plans to convene a regional stakeholder meeting to align on intervention priorities to support countries responding to resistance**
- **WHO plans to reconvene subregional networks of antimalarial drug resistance and efficacy surveillance**

Thank You

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