Global status and the response to antimalarial drug resistance

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Topics covered

- Background on antimalarial drug resistance
- Global status of antimalarial drug resistance
- Strategy to respond to antimalarial drug resistance in Africa

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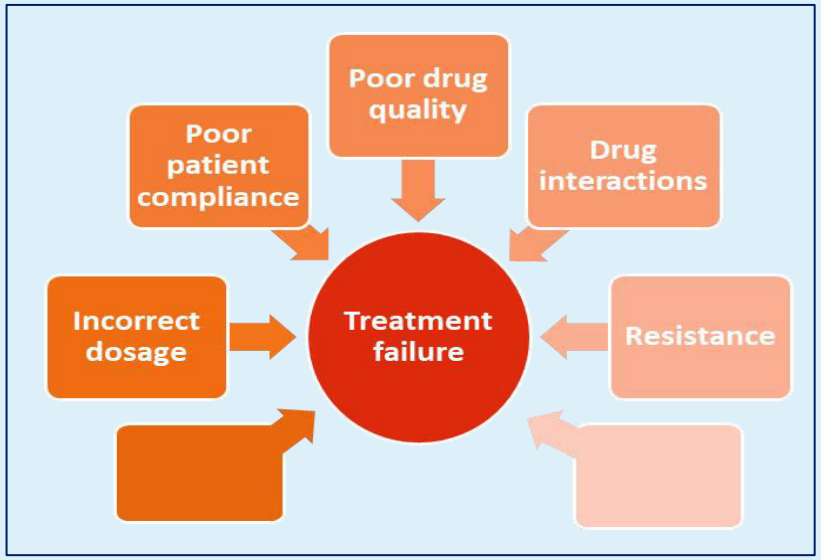
Some definitions

- **Antimalarial resistance:** 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.

- **Multidrug resistance (MDR):** resistance to more than 2 antimalarial compounds of different chemical classes. This term usually refers to *P. falciparum* resistance to chloroquine, sulfadoxine-pyrimethamine, and a third antimalarial compound

- **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.



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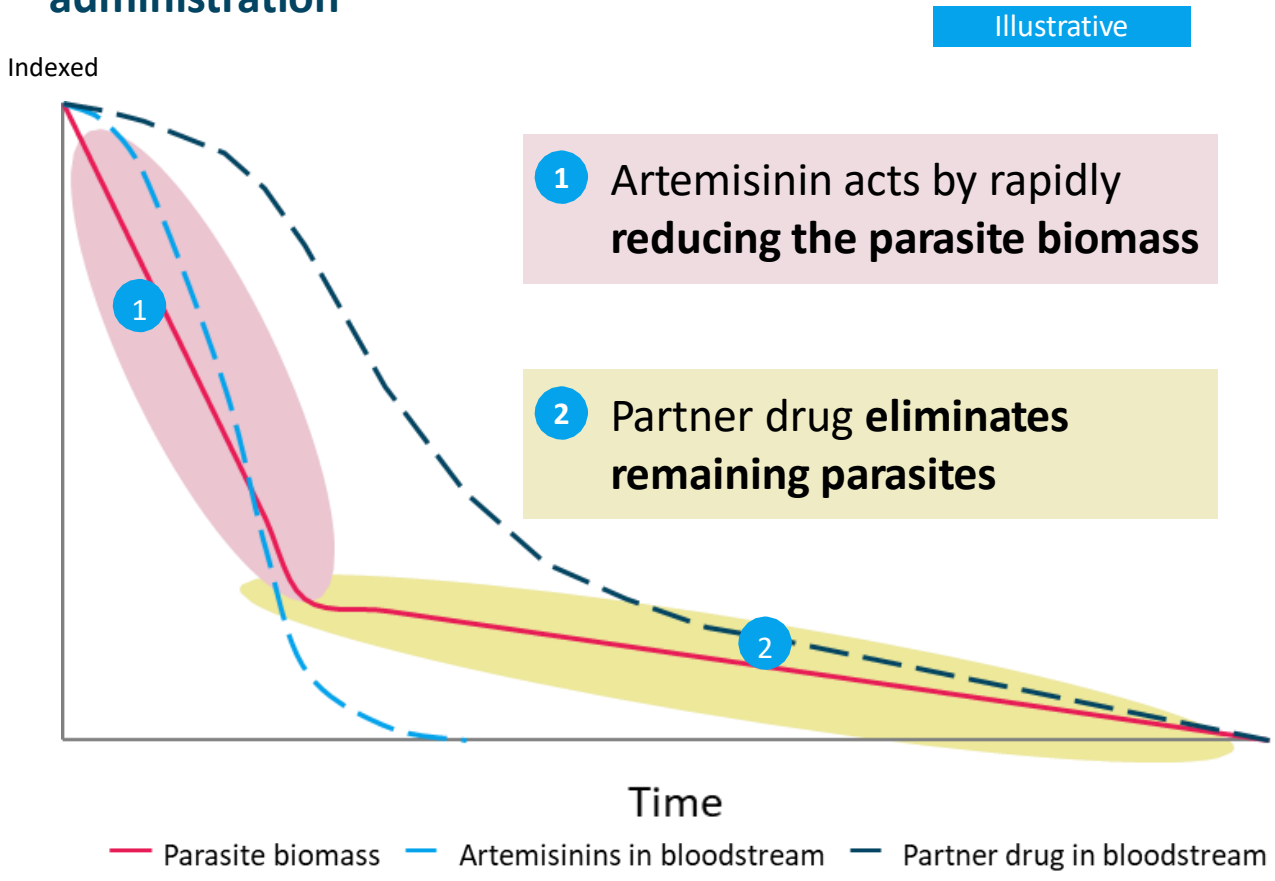
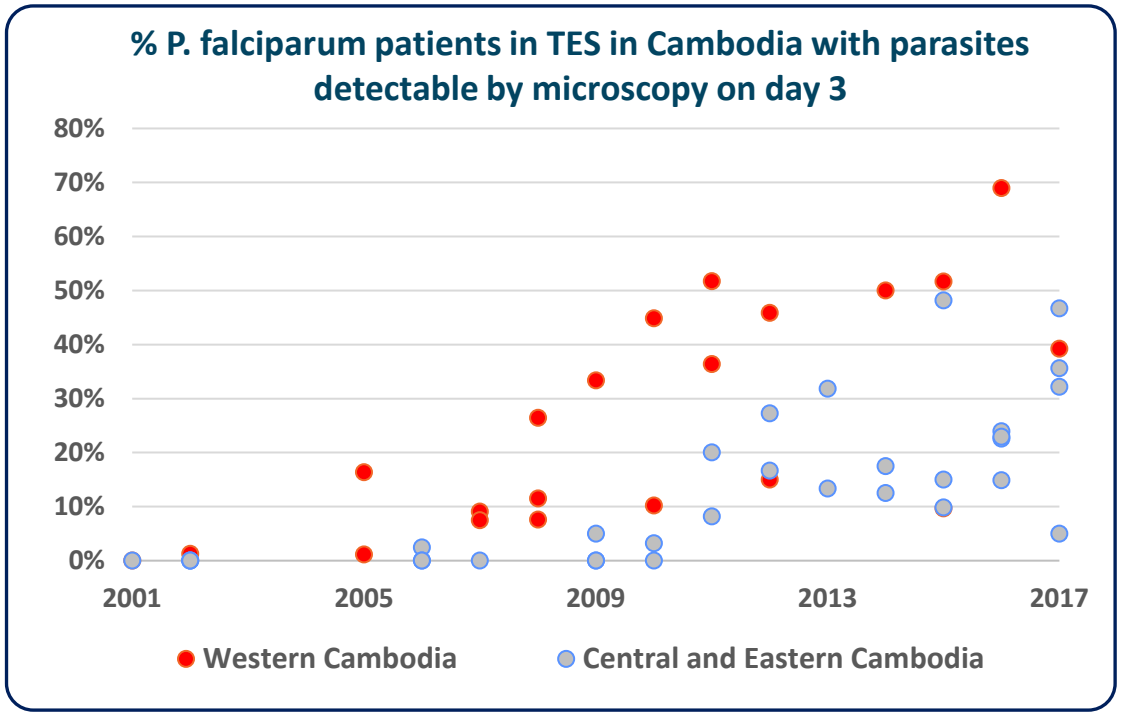
Artemisinin-based combination therapies at the heart of the response

- After the spread of chloroquine and SP resistance, artemisinin-based combination therapies (ACTs) became the main tool for malaria treatment
- ACT combines 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
- We don’t use the term “ACT resistance”. Instead, we talk of:
  - Artemisinin partial resistance
  - Resistance to an ACT partner drug, or
  - High failure rate with a specific ACT

Evolution of parasite biomass in the body following ACTs administration



Artemisinin partial resistance



- **Artemisinin partial resistance** seen as delayed parasite clearance following treatment of *P. falciparum* 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*)
- For artemisinin partial resistance to be confirmed in a site, quality evidence is needed on:
  - Presence of validated marker (≥5%) (PfK13 mutations)
  - Evidence of delayed clearance (Day 3 + or parasites clearance half-life)

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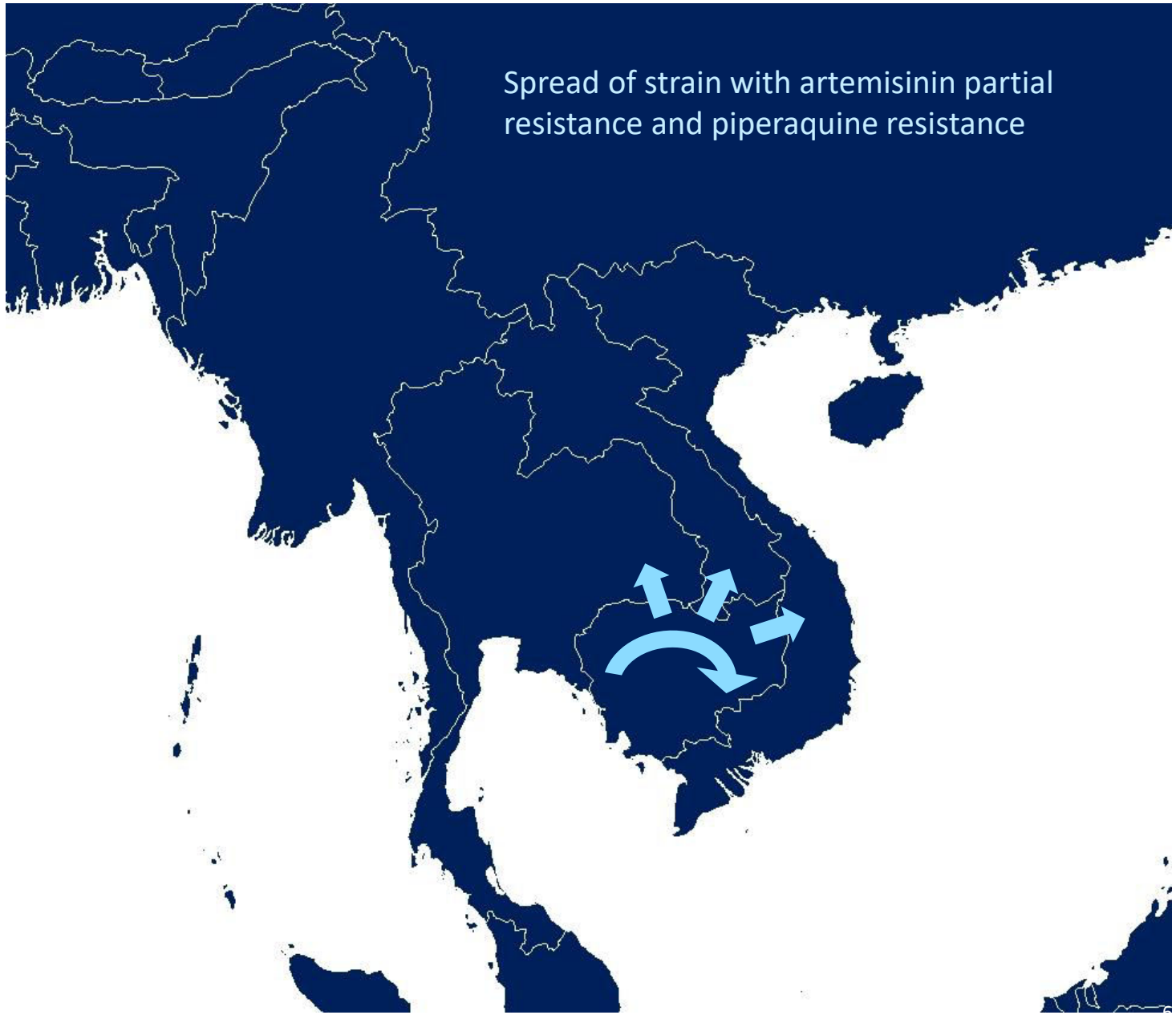
Risk of partner drug resistance

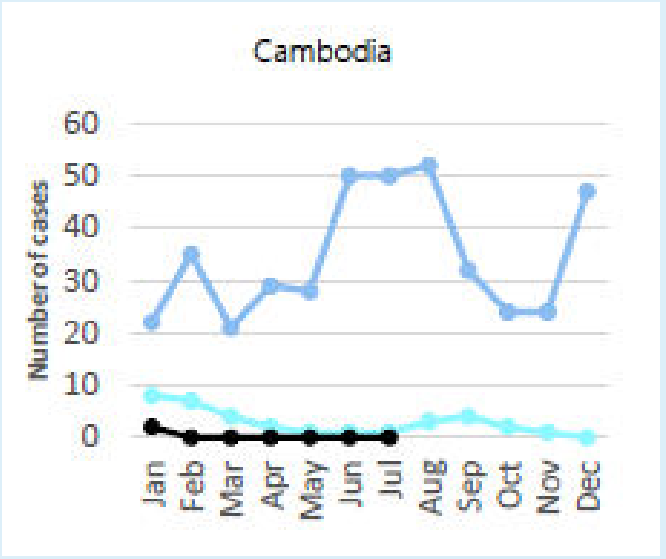
- In Southeast Asia, artemisinin partial resistance has not been seen to cause the emergence of partner drug resistance
- However, artemisinin partial resistance may have helped spread piperaquine resistance through a strain with artemisinin partial resistance and piperaquine resistance
- The spread 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



Adapted from Imwong et al. 2017 Lancet Inf Dis.

Status of resistance

Number of *P. falciparum* + mixed cases by month and country (2022–2024)*



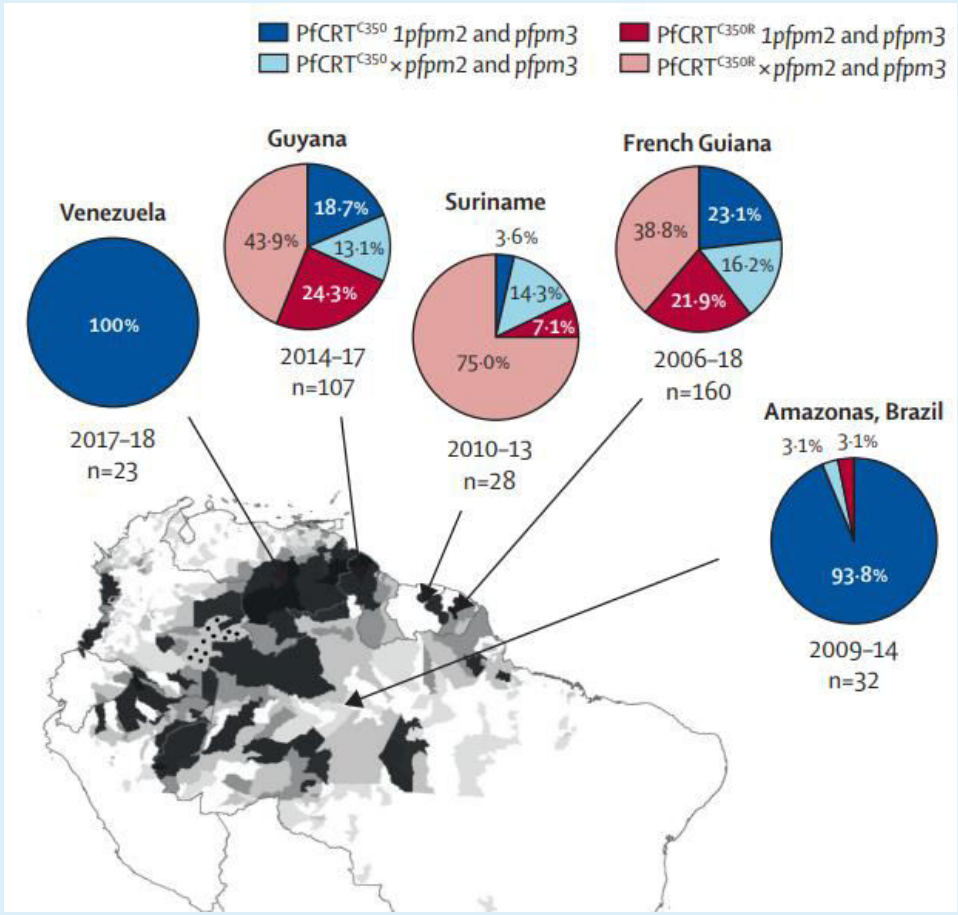
Source: Mekong Malaria Elimination Programme epidemiology summary

Greater Mekong Subregion (GMS)

- Artemisinin partial resistance and resistance to key partner drugs was first detected in the Greater Mekong Subregion
- Response to resistance was in the GMS supported through a regional hub to help coordinate the response, strong sub-regional network on surveillance of drug efficacy and resistance, and a regional Global Fund grant (the Regional Artemisinin Initiative)
- Now countries where resistance posed the greatest challenge are close to elimination of *P. falciparum* (Cambodia, Lao PDR and Viet Nam)

Status of resistance

Distribution of piperaquine resistance markers from isolates collected between 1997 and 2018 and spatial distribution of Plasmodium falciparum malaria infections in 2017

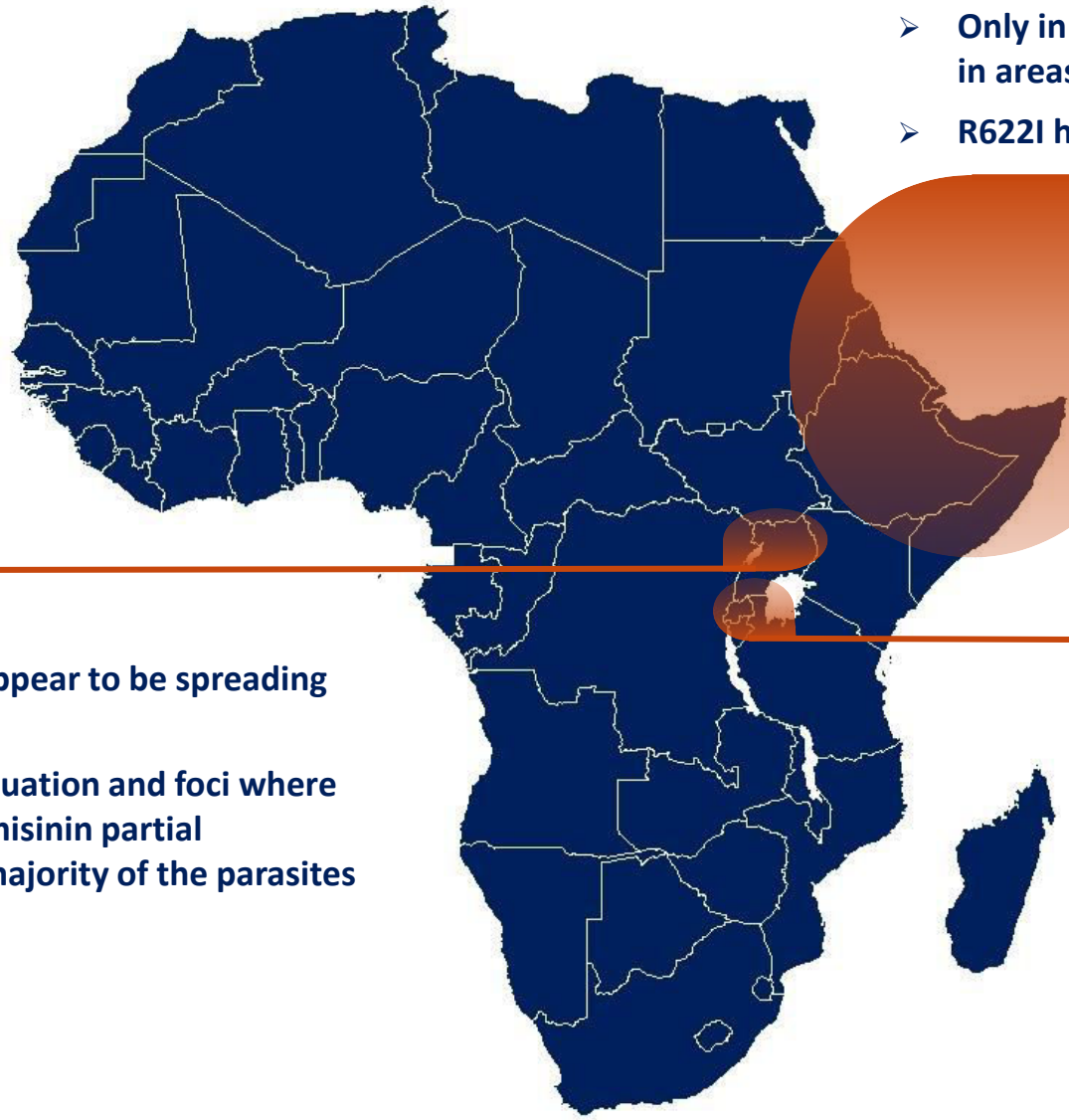


Source: Florimond et al. Lancet Infect Dis 2024; 24: 161–71

Guiana shield countries

- Artemisinin partial resistance was detected in Guyana. Appears to have disappeared
- However, now piperaquine resistance have developed and DHA-piperaquine can’t be used in some countries.

Africa: Partial resistance to artemisinin has been confirmed with several independent emergences



Horn of Africa

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

Uganda

- Different K13 mutations appear to be spreading in Uganda
- Data shows an evolving situation and foci where validated markers of artemisinin partial resistance are found in a majority of the parasites sampled

Rwanda & Tanzania

- K13 mutation R561H had been found at high prevalence in studies with evidence of delayed clearance in Rwanda
- R561H has now also been detected in Tanzania in a study with a high proportion of patients with delayed clearance indicating the presence of artemisinin partial resistance in Tanzania

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Status and challenges in interpretation of data from therapeutic efficacy studies

Studies showing treatment failure rates > 10% or ≈ 10% for:

- **Artesunate - amodiaquine**
- **Artemether - lumefantrine**
- **DHA - piperaquine**
- **Artesunate-pyronaridine**

TES with high reported failure rates from 2015 - 2024

Scientific challenges include:

- Molecular markers for resistance missing for key ACT partner drugs. Markers would facilitate confirmation of resistance and monitoring of spread.
- There is a need to have improved methods available to distinguish recrudescence and reinfection.

Challenges related to adherence to standard protocol and quality of implementation:

- Some studies does not follow the standard protocol making comparison difficult.
- Challenges with the quality of the implementation of some studies including the quality of microscopy.
- Reporting using different methods to distinguish recrudescence and reinfection.

Contributing to the solution

WHO is establishing a roster of consultants to support training and TES site visits.

Has been improvements in coordination and discussion ongoing with partners on how to improve TES quality.

Process of the development of the Strategy to respond to Antimalarial drug resistance in Africa

Launched November 2022

Development process

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

Starting point for the Strategy

Background drivers

Environmental factors as well as intrinsic factors linked to the parasite, the host, and the drugs used

Treatment related drivers

Affecting how often, at what doses, and for what length of time a parasite population is exposed to drugs

Focus of this strategy: identifying practical interventions to these drivers

Strategy to respond to antimalarial drug resistance in Africa

20 interventions across 4 pillars aiming to mitigate risks and respond to

Preliminary assessment to prioritize interventions

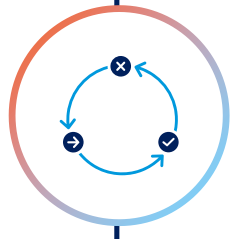
- **Countries' baseline with respect to the status and drivers of resistance**
- **Assessment of strengths and weaknesses of the health and the regulatory systems**

I — **Strengthen surveillance of antimalarial drug efficacy and resistance**

II — **Optimise and better regulate the use of diagnostics and therapeutics to limit drug pressure through pre-emptive measure**

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

IV — **Stimulate research and innovation to better leverage existing tools and to develop new tools against antimalarial drug resistance**



Living strategy

- Monitor the implementation and update based on new evidence and learnings

Key enabling mechanisms

- **Country ownership**
- **Financing**
- **Advocacy effort**
- **Regional coordination**
- **Routine surveillance system**

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

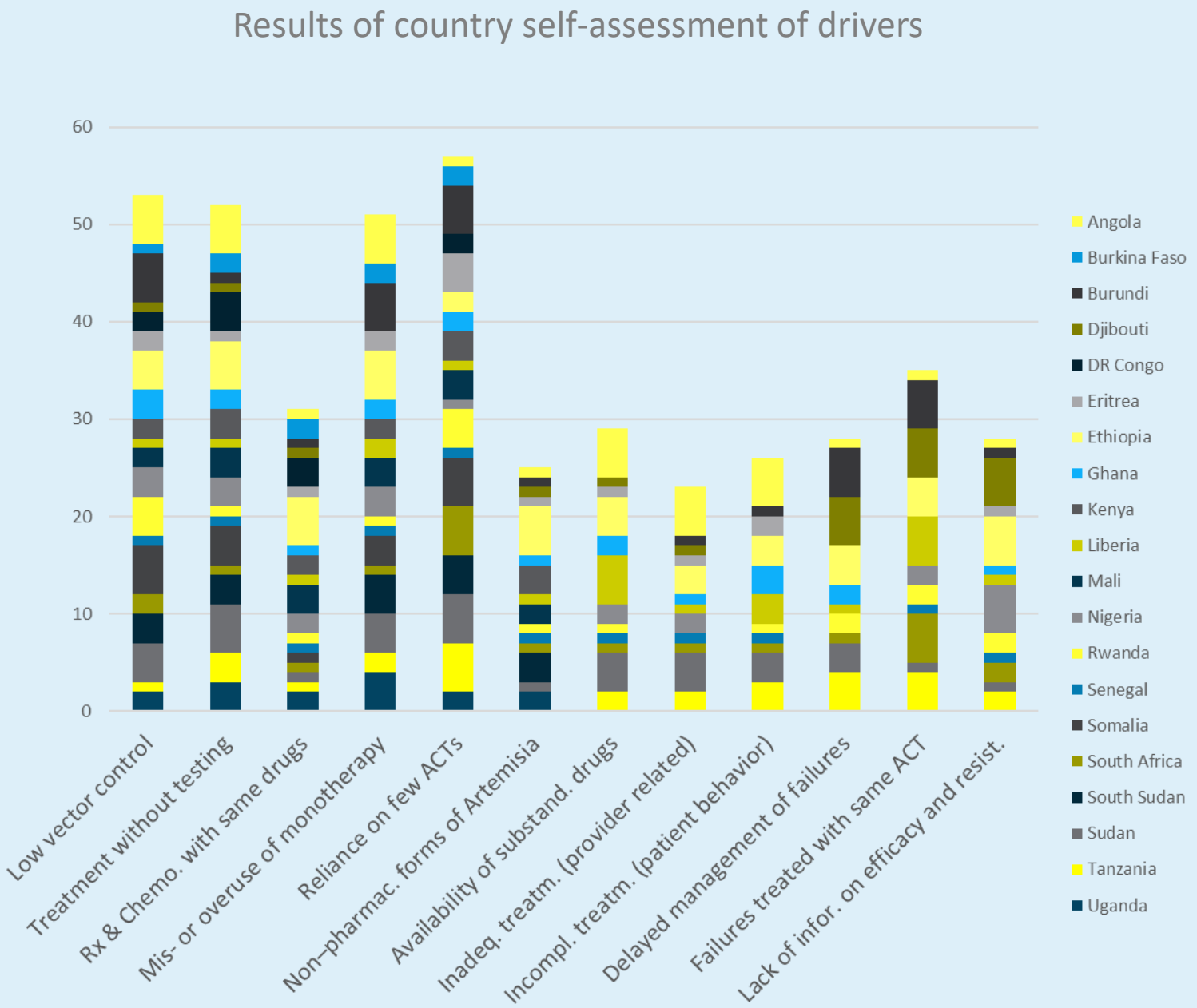
1. Ensure optimal malaria vector control intervention coverage in priority areas
2. Leverage preventive measures to reduce transmission of antimalarial drug-resistant parasites
3. Limit the risk of increased transmission of resistant parasites
4. Strengthen cross-border collaboration on malaria activities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

Regional stakeholder meeting, November 2023

- Main aims were to present the strategy, discuss drives of drug resistance and activities needed in countries
- In preparation to the meeting, countries had been asked to rate different potential drivers in their country using a survey tool developed by WHO/GMP to help inform the discussion



Conclusions from regional stakeholder meeting

- Strengthen and support subregional networks to generate data for drug policy
- Support in-country consultations to develop and implement national plans of action to respond to the threat of drug resistance
- Develop a platform for coordinated action of all stakeholders in the fight against antimalarial drug resistance
- Mobilize resources to support the national action plans on antimalarial drug resistance

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Thank you

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