Regional stakeholder meeting on the response to antimalarial drug resistance in Africa

Meeting report, Kampala, Uganda,
7–8 November 2023

World Health Organization

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Contents

Abbreviations

AL	artemether–lumefantrine
ASAQ	artesunate–amodiaquine
ASPY	artesunate–pyronaridine
DP	dihydroartemisinin–piperaquine
GMS	Greater Mekong Subregion
IRS	indoor residual spraying
*Pf*HRP2	*Plasmodium falciparum* histidine-rich protein 2
PfK13	*Plasmodium falciparum Kelch-13*
PMI	U.S. President's Malaria Initiative
TES	therapeutic efficiency studies
WHO	World Health Organization

Executive summary

A Regional Stakeholder Meeting on Antimalarial Drug Resistance in Africa was convened in Kampala, Uganda, on 7–8 November 2023, with the participation of country representatives, research partners, regional technical and economic organizations, funding and multilateral partners, civil society and other stakeholders. This purpose of this hybrid event, with both in-person and virtual attendance, was to align priorities, coordinate efforts and share information on combating antimalarial drug resistance. Expert-led discussions covered challenges, data findings and potential mitigation strategies.

The meeting provided a comprehensive update on the spread of artemisinin resistance across Africa. The countries affected include Eritrea, Rwanda, Uganda and the United Republic of Tanzania. The discussions addressed the presence of validated markers of partial resistance to artemisinin but recognized that there are limited data and knowledge gaps, such as the geographical spread of mutations and lack of markers of artemisinin-based combination therapy (ACT) partner drugs, such as lumefantrine. The participants emphasized the need for high-quality therapeutic efficacy studies (TES) in more regions to better understand and address drug resistance.

The meeting identified priorities for countries to prevent the spread of antimalarial drug resistance and to manage it where it has emerged. The priorities included targeted national response strategies and a framework for increasing coordination, sharing information and collaboration among regions.

Key next steps include establishing and supporting subregional networks to generate data for drug policy decisions. The first network meeting was scheduled to follow the workshop. National consultations will support the development and implementation of tailored national action plans against resistance. A coordinated platform should be created to align efforts across stakeholders involved in combating resistance. Resource mobilization was highlighted to finance national action plans for surveillance and response. Sustained collaboration and political commitment are essential to address the resistance challenge in Africa.

1. Introduction

1.1 Organization of the meeting

WHO launched a *Strategy to respond to antimalarial resistance in Africa* in 2022 *(1)*. As part of implementation of the strategy, WHO organized a regional stakeholder meeting to provide countries and partners with a platform to share information, align priorities and coordinate their work.

1.2 Objectives

The objectives of the meeting were to:

- review ongoing and planned activities;
- identify gaps and priorities for countries in which partial resistance to artemisinin has been confirmed (pillar III of the strategy);
- identify gaps and priorities for countries in which partial resistance to artemisinin has not been identified but which are at high risk (pillar II of the strategy);
- discuss the potential roles of stakeholders; and
- establish a framework for future coordination and information-sharing.

2. Opening session

The meeting was opened by representatives of the Global Malaria Programme, WHO headquarters, the regional offices for Africa and for the Eastern Mediterranean and the Uganda WHO Country Office. Later, a representative of the Ministry of Health of Uganda welcomed the participants to Uganda.

Dr Daniel Ngamije, Director of the WHO Global Malaria Programme, emphasized the continued significance of malaria as a global health issue. He said that the main topics at the meeting were the urgent challenge of the spread of partial resistance of artemisinin in the Horn of Africa and eastern Africa and worrying reports of a decrease in the efficacy of artemether–lumefantrine (AL) against malaria. Although the full scope and implications of the resistance were not yet known, lessons from previous devastation due to resistance to drugs such as chloroquine and sulfadoxine–pyrimethamine indicate that decisive action is required. The WHO Strategy proposes a multifaceted approach, with enhanced surveillance, reduced drug pressure and international collaboration, recognizing the unique obstacles faced by each country and region.

Dr Dorothy Achu, WHO Regional Office for Africa, stressed the role of the meeting in addressing the threat of antimalarial drug resistance in the African Region. Africa bears the greatest burden of malaria in the world, due to its climate, ecology, limited access to health care, inadequate housing and other risk factors that facilitate vector proliferation and expose communities to high-intensity malaria transmission. Compounding the challenge are resistance of vectors to insecticides and of parasites to antimalarial agents. It is essential to engage communities, strengthen Member State leadership and foster effective partnerships to assist countries in assessing their situations and taking timely action to prevent the spread of antimalarial resistance.

Dr Mariam Adam, WHO Regional Office for the Eastern Mediterranean, described the challenge of malaria in that Region, where prevention of malaria-related mortality remains a challenge, especially in view of the continuing humanitarian emergencies and instability in the Region. Environmental factors such as urbanization, deforestation and climate change, resource scarcity and weak health systems contribute to changing patterns of malaria transmission. Despite the challenges, the Regional Office has maintained a subregional network for monitoring antimalarial resistance to collect evidence, guide changes in treatment policies and address other threats, including *Plasmodium falciparum* histidine-rich protein 2 (*PfHRP2*) gene deletion and invasion by the *Anopheles stephensi* mosquito.

Dr Yonas Tegegn, WHO Representative in Uganda, described the work necessary to achieve the targets for 2030 outlined in the Glo*bal technical strategy for malaria 2006–2030* and the Sustainable Development Goals *(2, 3)*. Strong surveillance, including entomological surveillance – an area in which Uganda has worked consistently – and research are crucial to combatting threats such as resistance to insecticides and antimalarial drugs. The ongoing malaria burden continues to strain healthcare systems and resource allocations and contributes to misdiagnosis of other diseases, as evidenced during the outbreak of Ebola virus disease. Research remains pivotal to shaping strategies and supporting malaria control and elimination.

Dr Rosemary Byanyima, Ministry of Health, Uganda, welcomed participants and described Uganda's historical struggle with malaria. In the past, cases of malaria comprised half of all hospital outpatients, 20–30% of admissions and 20% of registered deaths. Although a reduction in the malaria burden was achieved between 2002 and 2019, there had been a resurgence since 2019, potentially due to factors such as resistance to insecticide and drugs. The Ministry of Health's strategies to combat drug resistance include routine efficacy studies, monitoring for resistance markers, preserving the effectiveness of available medicines and navigating the complexities of introducing new tools. Strengthening strategies for management of antimalarial drug resistance is crucial.

3. Session 1: malaria and the status of antimalarial drug resistance

3.1 Malaria and the status of antimalarial drug resistance

The efficacy of ACT depends on the parasite's sensitivity to artemisinin and the ACT partner compound. Partial artemisinin resistance is characterized by delayed parasite clearance and has been associated with specific *PfKelch-13* mutations. Delayed clearance alone does not lead to treatment failure but can result in high treatment failure rates if combined with resistance to the ACT partner drug.

In Africa, evidence of partial resistance to artemisinins and scattered reports from TES of high treatment failure rates have led to development of the strategy to respond to antimalarial drug resistance in Africa.[1] At that time, partial resistance to artemisinins had been confirmed in Eritrea, Rwanda and Uganda. Despite scattered findings in TES of high treatment failure rates, no resistance to the commonly used ACT partner drug has been confirmed in Africa. Since the launch of the strategy, however, partial resistance to artemisinins has also been confirmed in United Republic of Tanzania.

3.2 Overview of the malaria situation in the WHO African Region

The Africa Region is currently behind in achieving the targets set in the global technical strategy due to factors such as insecticide resistance, limited access to health care and inadequate coverage of essential malaria interventions. The threat of antimalarial resistance risks further undermining progress towards these goals.

AL is the ACT used in over 70% of countries, while other ACT options, such as dihydroartemisinin–piperaquine and artesunate–pyronaridine (ASPY), are less widely used. Reducing the disparities in access to high-quality treatment and care remains a major challenge, compounded by insufficient vector control coverage, variable standards of care and increasing numbers of *PfHRP2* gene deletions, which affect diagnostic accuracy.

Sustained support to countries is critical to overcome these barriers, including conducting TES, validating data and finding actionable plans to address resistance. Enhanced collaboration is also essential, by engaging sub-regional networks, fostering partnerships and strengthening regulations on medicines and diagnostics. Capacity-building and innovation are required to address the growing threat of antimalarial drug resistance effectively.

3.3 Overview of the malaria situation in the WHO Eastern Mediterranean Region

In the Eastern Mediterranean Region, continuous monitoring of the therapeutic efficacy of antimalarial medicines by countries has been effective. The Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT), supported by the WHO Regional Office, facilitates discussions for updating national treatment guidelines according to TES results.

The Region's health systems also face broader challenges, and addressing antimalarial resistance requires collaboration beyond the malaria community. Regulatory authorities are essential in this work, given the ongoing challenge of enforcing bans on the influx of counterfeit drugs. The persistence of oral artemisinin-based monotherapy – despite clear policies against its use – indicates that there are gaps in regulation that affect all health sectors, including malaria control.

Humanitarian crises and limited access to health care create environments in which counterfeit medicines can proliferate. Collaboration is necessary to foster the development of new medicines and ensure that healthcare providers adhere to established guidelines. Consistent treatment practices in both the public and private sectors are critical, as the private sector often provides care in areas or situations in which the public sector has limited reach. Advocacy should actively involve all stakeholders – regulatory bodies, healthcare providers, and the private sector – to ensure that policies are adhered to and that treatment is aligned with national protocols.

Discussion points

- **Access to diagnosis:** Participants emphasized the importance of accessible diagnostic services in both the private sector and the community. Engagement with and full understanding of the role of the private sector was considered crucial for effective malaria control.

- **ACT resistance:** Participants discussed use of the term "ACT resistance" and suggesting that it be avoided to avoid oversimplification of the current situation. Even in South-East Asia, where certain ACTs have high failure rates, other ACTs remain highly effective.

- **Training for microscopists:** Training and competency assessments for certification of microscopists have been conducted in several African countries. WHO reiterated its commitment to such efforts and expressed readiness to continue training and assessments in collaboration with countries according to their needs.

3.4 Country presentations (part 1)

Eritrea

Eritrea continues to face substantial challenges with respect to malaria, especially in rural areas, where approximately 70% of the population remains at risk. Malaria cases are due predominantly to *P. falciparum* (70–80%) and *P. vivax* (20–30%), with transmission patterns that vary across the country. Although Eritrea has achieved a significant reduction in the number of malaria cases since 2006, the country experienced increases in the numbers in 2021 and 2022.

The first-line treatment is artesunate–amodiaquine (ASAQ), with a single low dose of primaquine for *P. falciparum* and ASAQ and a 14-day course of primaquine course for *P. vivax*, *P. ovale* and mixed infections. AL is used as second-line treatment. Severe cases receive artesunate injections. The private sector plays a minimal role in malaria treatment. Unfortunately, early treatment-seeking behaviour remains low in the general population.

Eritrea's drug regulatory authority is robust, and there is minimal use of oral artemisinin-based monotherapy. Since 2017, antimalarial drug efficacy and resistance have been monitored every 2 years at four sites. In 2022, the day 3 positivity rate in TES in four sites ranged from 1–24%, with an observed increase in the *Pfkelch13 R622I* mutation associated with artemisinin partial resistance at all study sites. Additionally, deletions in *hrp2/hrp3* genes were noted in parasites with the *Pfkelch13 R622I* mutation. Both ASAQ and AL continue to show high efficacy.

Eritrea requires technical support for developing a national strategy to mitigate biological threats, including vector resistance, emergence of *An. stephensi* as a new malaria vector, *PfHRP2* deletions and partial artemisinin resistance. The country currently relies on external laboratories for molecular analysis, and local capacity should be built for molecular diagnostics and resistance monitoring.

Rwanda

In Rwanda, where 12.9 million people are at risk, the rates of malaria transmission, predominantly due to *P. falciparum*, vary among districts. In 2022–2023, the malaria incidence was approximately 47 cases per 1000 population – a 76% reduction from 2019–2020.

Rwanda's 2020 malaria treatment guidelines provide a framework for case management at all healthcare levels, from community centres to hospitals. Community health workers use rapid diagnostic tests, while health centres and hospitals use microscopy for diagnosis. AL is used as first-line treatment, dihydroartemisinin–piperaquine (DP) as second-line and quinine as the third-line option for uncomplicated malaria. Severe malaria is treated mainly with injectable artesunate and parenteral quinine as a secondary option. Over 55% of malaria cases are managed by community health workers, easing the load on health facilities, particularly for uncomplicated malaria. The private sector has limited involvement in malaria treatment. Challenges include refugee displacement and cross-border movement.

TES have been conducted since 2004, although recruitment for such studies was difficult in 2018 due to a lower malaria incidence. Previous studies indicated that AL was highly effective, although the *PfK13 R561H* mutation, linked to delayed parasite clearance, was detected in 2018.

Uganda

In Uganda, malaria transmission is perennial, with seasonal variations and some epidemic-prone areas. AL is the first-line treatment for uncomplicated malaria, and ASAQ is listed as an alternative. Severe malaria is treated mainly with parenteral artesunate, and chemoprevention consists of intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine.

In studies in 2022–2023, the efficacy of AL was < 90% in Arua and Busia, and that of ASAQ and DP was > 95%. The efficacy of ASPY was < 90% at the Arua site on day 42. Partial resistance to artemisinin was confirmed in 2019.

Uganda's response to artemisinin resistance includes multiple ACT options and a diversified drug portfolio. Challenges nevertheless persist, including a reliance on AL, reluctance among physicians to use ASAQ, lack of compliance with national treatment guidelines by the private sector and regulation of alternative antimalarials. Initiatives to address these challenges include drug registration, large-scale procurement, vector control, chemoprevention and cross-border collaboration. With effective partnerships, Uganda is also conducting research on triple therapy and plans to introduce a malaria vaccine in some regions.

United Republic of Tanzania

With funding from the Bill & Melinda Gates Foundation, 7782 samples were collected from over 100 facilities in a molecular surveillance initiative launched in 13 regions. Of these, 6000 samples were analysed for *PfK13* mutations. The highest prevalence of the *R561H* mutation was found in Kagera (7.7%), followed by Tabora (0.5%) and Manyara (0.5%). Notably, the mutations in Kagera were similar to those observed in Rwanda.

To examine the effect of the *R561H* mutation on treatment outcomes, a TES on the efficacy of AL and ASAQ, supported by WHO, was conducted near the Rwandan border. Both ACTs showed high cure rates on day 28, validated by polymerase chain reaction, with an adequate clinical response; however, 9.0–11.4% of patients with the *R561H* mutation had persistent parasites on day 3. These findings confirm the presence of partial resistance to artemisinins in United Republic of Tanzania, indicating that proactive measures are essential to prevent the spread of partial resistance to other regions.

Discussion points

- **Patient recruitment for TES.** Concern was expressed about the representativeness of TES in Rwanda, as most malaria cases are managed in the community, while cases are often enrolled into TES at facilities. It was noted that United Republic of Tanzania had adapted the WHO protocol to address TES recruitment challenges in 2010, with adjustments that included altering the requirements for age range and parasitaemia density. The representative of Nigeria also noted difficulty in recruiting patients for TES due to low parasitaemia levels and requested WHO guidance on adjusting the criteria. WHO confirmed that protocol adjustments are permissible according to local transmission levels; the site could be changed when difficulties in recruitment are met though this needs to be approved by the ethical committee.

3.5 Country presentations (part 2)

Democratic Republic of the Congo

In the Democratic Republic of the Congo, 120 million people are at risk of malaria, and 27 million cases and 2500 deaths were reported in 2022. The main malaria parasite species are *P. falciparum*, *P. ovale* and *P. malariae*. The recommended treatments for uncomplicated malaria are ASAQ, AL and ASPY. Parenteral artesunate, quinine and artemether are advised for severe malaria management, while quinine and clindamycin are used for malaria in the first trimester of pregnancy. During epidemic outbreaks, DP is provided by mass drug administration.

The Democratic Republic of the Congo conducts a TES every 2 years at five sites. Data for 2017–2018 and 2020–2021 showed reduced efficacy of AL at three sites and low efficacy of ASAQ at one site. The country faces several challenges, including few sentinel sites, delays in sample analysis, poor laboratory capacity, a shortage of molecular scientists, insufficient funding, inadequate private sector surveillance and security issues. The technical assistance required includes training in molecular surveillance, laboratory capacity-building, support for a national laboratory network and advocacy for collaboration with neighbouring countries.

Ethiopia

Transmission rates vary in the country, the highest burden being along its western border. *An. arabiensisis* and *An. stephensi* are the main vectors responsible for transmission of *P. falciparum* (70–80% of cases) and *P. vivax* (20–30%).

AL is the first-line treatment for uncomplicated *P. falciparum* malaria, and chloroquine plus primaquine is used for *P. vivax*. Severe malaria is managed with parenteral and rectal artesunate for pre-referral treatment. DP is the recommended second-line treatment but is not used in the country.

Since 2007, Ethiopia has conducted TES, molecular surveillance and drug resistance studies in collaboration with the Ethiopian Public Health Institute and the Armauer Hansen Research Institute. The country has 25 sentinel sites, and studies have been conducted at five selected sites. TES in 2020–2021 and 2022–2023 showed > 90% efficacy for all tested ACTs (AL, DP and ASPY). When AL was tested at four sites in 2022–2023, efficacy > 96% was reported at all sites.

Drug resistance and cross-border population movement by one million refugees and seasonal migrant workers add to the complexity. Biological threats, including diagnostic resistance, gene deletion and invasive vector species, are concentrated along border areas and in the north of the country. Challenges include a lack of standardized training, budget limitations and long pre-referral treatment delays.

Sudan

Malaria in Sudan is due predominantly to *P. falciparum* (89%) and *P. vivax* (11%). War-affected states contribute significantly to the malaria burden, and children, internally displaced people and pregnant women have the highest burden. AL is the first-line treatment for uncomplicated malaria, including for pregnant women. DP is the second-line treatment but it is not used in the country. Severe malaria is treated with intravenous artesunate.

Since 2004, Sudan has conducted annual TES, the most recent having been completed in 2022–2023. Although K13 mutations have been detected in certain regions, TES in 2019–2022 showed a 100% adequate clinical and parasitological response to both

AL and DP. Key challenges include poor adherence to protocols, lack of availability of second-line drugs, spread of counterfeit medicines, inadequate enforcement of regulations and recent political instability.

Discussion points

In response to a question about a potential link between circulating substandard medicines and delayed parasite clearance or partial resistance, the representative of Sudan said that, while no current work was under way in that area, it was important to consider the complexity of conflict zones for operational environments.

A broader question was raised about how countries address the factors that contribute to resistance, as TES findings showing efficacy < 90% at certain sites. The participants highlighted the importance of tailored strategies and funding to better understand the dynamics of malaria in challenging contexts, such as conflict-affected areas.

The representative of the Democratic Republic of the Congo outlined its strategy of using three different ACTs in different settings, such as rural versus urban, to optimize the effectiveness of malaria treatment.

3.6 Known and unknown aspects of partial resistance to artemisinins

In South-East Asia, delayed parasite clearance was observed after treatment with artemisinin. Standard IC50 assays did not reveal this phenotype; however, decreased activity was identified in the ring stage survival assay, which was associated with specific mutations in the *Pfkelch* gene.

A number of validated markers of partial resistance to artemisinins have emerged and spread in eastern Africa. Data from Rwanda and Eritrea show that ACT are efficacious despite the presence of *PfK13* mutations, and, overall, associations between these mutations and clinical and in-vitro outcomes are modest. It is likely that factors other than *PfK13* mutations contribute to resistance. Indications of potential loss of ACT efficacy, particularly for AL, are found in the absence of *PfK13* mutations. Currently, five validated *PfK13* mutations have been identified in Uganda, which may have occurred due to high malaria transmission in a region previously characterized by low transmission intensity.

With respect to resistance to ACT partner drugs, modest decreases in the activity of lumefantrine have been observed in Uganda, but there is minimal evidence of true resistance. Amodiaquine has shown improved activity with the loss of chloroquine resistance, but heavy use might again lead to selection of resistance. Resistance to piperaquine has been common in Cambodia, but markers of resistance (amplification of *pmp2/3* and novel *PfCRT* mutations) have probably not been observed in Africa. There are currently no known instances of resistance to the partner drug, pyronaridine. Resistance to mefloquine has been documented in South-East Asia, but markers of resistance (amplification of *pfmdr1*) are generally not observed in Africa.

In summary, there has been rapid emergence and spread of validated artemisinin partial resistance mutations, with several independent emergences and significant geographical heterogeneity. Multiple therapeutic efficacy studies (TESs) have demonstrated sub-optimal efficacy for artemether-lumefantrine (AL), but these have not been conducted in settings with a high prevalence of relevant *PfK13* mutations. Many unknowns and uncertainties remain, including what additional mutations are required to achieve stable artemisinin partial resistance while maintaining parasite fitness, the likelihood of resistance to key partner drugs, and the best options to slow the emergence and spread of artemisinin partial resistance.

Discussion points

Participants emphasized the importance of standardized TES and of sharing methods and results. A proposed link between withdrawal of indoor residual spraying (IRS) and the spread of drug resistance was discussed. While it is not clear whether there is a causal association, interruption of IRS may facilitate the spread of less-fit parasites in populations with low immunity.

Mutations in the *PfK13* gene or other parasite mutations may increase gametocyte production. Additional data are required.

4. Session 2: responding to antimalarial drug resistance

4.1 Progress in malaria elimination in the Greater Mekong Subregion

The emergence of chloroquine resistance in the Greater Mekong Subregion (GMS) and its subsequent spread to Africa was followed by the emergence and spread of resistance to sulfadoxine–pyrimethamine from the GMS to Africa. This, with the finding of partial resistance to artemisinin in the GMS, raised concern about the potential global threat posed by the spread of resistance to another antimalarial drug.

Despite this threat, a notable decrease in the numbers of reported cases and deaths in the GMS was observed between 2013 and 2023, with clear heterogeneity in the burden between the eastern and western parts of the GMS. Cambodia, Lao People's Democratic Republic and Viet Nam have experienced significant decreases in the numbers of cases. Recent political unrest in Myanmar has resulted in an increase in transmission in that country and in areas of Thailand that border Myanmar, undermining substantial gains in the fight against malaria.

The Greater Mekong Therapeutic Efficacy Network, established in 2001, has facilitated consistent monitoring and exchange of data on efficacy and resistance. Data on the efficacy of ACTs in the Subregion indicate several effective treatments in each country. A significant challenge remains the absence of molecular markers for lumefantrine and pyronaridine.

Elimination continues to encounter challenges, such as supply chain disruptions, procurement delays, integration of healthcare workers, decreasing political interest, difficulty in reaching hard-to-reach populations and lack of sustained collaboration. The importance of sustained malaria surveillance, diagnosis and treatment and cross-border collaboration cannot be overstated. Basic tools have played a substantial role in reducing the malaria burden.

4.2 Cambodia's response to antimalarial drug resistance

Malaria elimination in Cambodia has faced significant challenges, including a high incidence of malaria among non-immune migrants and forest workers. Issues such as irrational use of anti-malarial drugs in the private sector, emergence of partial resistance to artemisinins reported in 2008 and limited access to vulnerable populations in remote areas have added to the complexity of the situation.

Cambodia has struggled with a decline in efficacy for may ACTs; however, strategic adjustments to drug policies, including shifts from artesunate–mefloquine to dihydroartemisinin-piperaquine in 2014 and later back to artesunate–mefloquine,

demonstrate Cambodia's adaptability in managing resistance. Notable achievements include a substantial reduction in the number of malaria cases since 2018, with fewer than 25 *P. falciparum* cases reported in the first half of 2023.

The malaria intensification plan launched in 2018 is based on targeted interventions, including early treatment, distribution of long-lasting insecticidal nets, focus interventions, targeted mass drug administration for certain populations and surveillance with digital technology. The interventions have high-level commitment, with the malaria elimination strategy endorsed by the Prime Minister. Partnerships with WHO and other organizations have provided technical and financial support. The Government has enforced a ban on oral monotherapies and has limited malaria treatment in the private sector. A robust surveillance system and continuous monitoring and evaluation address cross-border challenges. Sustained commitment and collaboration are necessary to secure Cambodia's progress in eliminating malaria.

4.3 Overview of a strategy to respond to antimalaria drug resistance in Africa

Artemisinin partial resistance can be defined as delayed parasite clearance after treatment with a drug containing an artemisinin derivative. No significant reduction in treatment efficacy has been observed in association with delayed parasite clearance after treatment with a drug containing an artemisinin derivative; however, increased proportions of parasites carrying *PfK13* mutations indicate that they have an advantage in current treatment strategies and transmission dynamics.

Given the heavy reliance on ACTs in Africa, the threat of artemisinin partial resistance and partner drug resistance must be monitored and addressed urgently. The apparent rapid spread of some mutations associated with artemisinin partial resistance indicates that vigorous measures must be taken before ACTs start to fail in Africa. As no alternative drugs are likely to become available in the near future, it is essential to preserve the therapeutic lifespan of ACTs.

Development of the strategy to respond to antimalarial drug resistance in Africa began with identification of the factors that could drive resistance, including background drivers such as immunity and treatment-related drivers affecting drug exposure frequency, dosage and duration of exposure to a drug. The strategy identifies practical interventions to address treatment-related drivers of resistance and calls for more research on background drivers.

The strategy proposes 20 interventions under four pillars to mitigate the risk of drug resistance and considers the evolving understanding of strategies that are effective against each driver. The four pillars are: strengthening surveillance of antimalarial drug efficacy and resistance, optimizing and better regulating the use of diagnostics and therapeutics to limit drug pressure through pre-emptive measures, reacting to resistance by limiting the spread of drug-resistant parasites, and stimulating research and innovation to better leverage existing tools and develop new tools against resistance. Operationalization of the strategy will require national assessments and plans to address the most important drivers of resistance in the local context, global and regional support mechanisms and research prioritization.

4.4 WHO process for changing drug policies

The goal of antimalarial drug policies is to use available antimalarial drugs and other resources efficiently to maximize reductions in morbidity and mortality (severity, duration of illness and adverse outcome) due to malaria disease, while minimizing the development and spread of resistance. WHO generates evidence-based

recommendations and clear guidance for decision-makers, who develop national policies to guide health workers.

Efficacy, safety, potential for widespread use, consumer compliance, cost-effectiveness and alignment with the country's broader drug policy are important criteria for policy change. Considerations in developing treatment policies include analysing the technical, social and economic aspects of malaria control, building consensus among stakeholders and assessing the decision-making environment.

Indicators for changing policy include increased malaria-associated morbidity and mortality, dissatisfaction of consumers and providers with the current policy, evidence of therapeutic efficacy and evidence from trials of new drugs, strategies and approaches to improve the effectiveness of the current policy.

Challenges to implementing new policies include political endorsement, deployment strategies, resource allocation, national treatment guidelines, product registration and regulation, health worker training, communication strategies and procurement and distribution. As delays between policy adoption and implementation may be up to 6–18 months, proactive planning is necessary.

The most effective malaria treatments must be chosen to reduce morbidity, mortality and development of resistance. Affordable, accessible antimalarial therapies, simplified regimens and better quality of care are crucial for effective policy implementation.

4.5 Antimalarial drug resistance in Africa: perspective of the U.S. President's Malaria Initiative

PMI provides support for monitoring therapeutic efficacy in 27 countries in sub-Saharan Africa and three countries in the GMS and has conducted TES at 75 sites in 20 countries in the past 3 years. The Initiative collaborates with national malaria programmes and other partners in line with national malaria strategies.

Adapting to the changing scenario of drug resistance, potential actions includes diversifying treatment options. Diversifying carries risks such as increased costs and supply chain complexity while delaying diversification can result in higher morbidity and mortality rates. Countries face challenges in gauging this balance.

Discussion points

Policy changes are necessary when the efficacy of an antimalarial is < 90% at one or more study sites. While nationwide policy changes are usual, heterogeneous efficacy might require subnational revisions of treatment policy rather than a nationwide switch.

Mitigation strategies should be based on assessment of specific local challenges before solutions are defined and implemented. The role of changes to drug policies in a broader mitigation strategy was discussed, as was the importance of government ownership and partner investment during policy change.

4.6 Assessment of country-specific situations for prioritizing interventions: example of Rwanda

The objectives of this assessment were to respond to resistance and prevent its emergence and spread. In phase 1 of the assessment, lasting 1 month, a situation analysis was conducted with data from the health system, consultations, data analysis

and review in collaboration with many stakeholders. Phase 2 will consist of development of the strategy. WHO guidance, as outlined in the *Strategy to respond to antimalarial drug resistance (1)*, was used throughout the assessment.

The results for TES in 2018 and 2020 showed delayed parasite clearance and an increasing prevalence of *K13* resistance markers such as *R561H* at some sites, although first-line (AL) and second-line (DAP) ACTs remained fully efficacious.

Access to health services in Rwanda is good, supported by an extensive community health worker network, high coverage with high-quality malaria care and a shift toward testing in the community. Some weaknesses were, however, observed in adherence to guidelines and the quality of care at health centres. These included delayed referral and overuse of injectable artesunate, indicating that more data on case management in health facilities and timely dissemination of data are necessary. Rwanda has a strong commitment to adapting national policies to align them with the latest WHO recommendations. The next steps involve translating the results of the assessment into a strategy, setting clear goals and addressing emerging issues to improve resistance management.

Discussion points

The representative of Rwanda described its approach to including the results of assessments, including from genomic surveillance, in their national malaria strategy and policy document. The results will also be included in the national strategic plan, with a 5-year timeline.

Proposed use of three ACTs as first-line treatments prompted questions about whether the approach would be geographically specific or whether all prescribers would be able to choose among the three options. The approach will be outlined in the final strategy.

WHO recommends that each country conduct an assessment as a basis for local activities, even if there is currently no evidence of emerging drug resistance.

5. Session 3: prioritizing intervention in countries: group work on drivers of and responses to antimalarial drug resistance

Four groups were created:

- Group 1: Eritrea, Rwanda, Uganda and United Republic of Tanzania
- Group 2: Ethiopia, Kenya, Somalia, South Sudan and Sudan
- Group 3: Burundi, Democratic Republic of the Congo and Senegal
- Group 4: Ghana, Nigeria and South Africa

In preparation for the meeting, the WHO Global Malaria Programme sent a questionnaire to countries for a rapid self-assessment of the drivers of drug resistance (Annex 3). The group work was divided into two phases: discussion of the results of the country self-assessments on drivers of resistance (Annex 4) and discussion on common challenges, solution, data requirements and country-specific issues.

Group 1. Issues discussed

- **Misuse and overuse of malaria therapies**. Over-reliance on a limited number of ACTs was identified as a key driver of resistance. The challenges include securing funding, managing supply chains for second-line therapies and establishing policies for alternative first-line therapies. Proposed interventions included reviewing country-specific issues in first- and second-line therapies, revising guidelines for managing treatment failure and increasing funding for procurement and distribution of second-line therapies.

- **Provider-related challenges**. Inadequate treatment due to provider practices was included as a driver of resistance. The challenges include limited information on managing treatment failure and a shortage of skilled healthcare workers who follow guidelines. The suggested interventions included updating the guidelines and providing targeted training for healthcare workers.

- **Substandard and falsified drugs**. The availability of low-quality drugs was another concern. The challenges include enforcement of regulations and adherence to policy, particularly in the private sector. Recommended actions included partnerships with regulatory authorities, intensifying monitoring and enforcing strict quality standards for medications.

- **Inadequate vector control**. Barriers to effective control of malaria transmission were noted, including the sustainability of resource allocation. The cost-effectiveness of IRS was stressed, as was the importance of data for decision-making. Suggested actions include resource mobilization, multisectoral collaboration and optimal vector control deployment.

- **Resource constraints**. Limited resources were highlighted as a challenge for implementing the malaria strategic plan, which could be mitigated by mobilizing domestic and international resources and fostering multisectoral collaboration.

Group 2. Issues discussed

- **Interventions to combat drug resistance**: include extending vector control coverage, more alternative ACTs, use of several first-line treatments, available second-line treatment and engaging the private sector in improving case management;

- **Priorities**: include conducting TES, enforcing bans on monotherapy, improving the quality of care, extending diagnostics, conducting post-market surveillance of medicines and diagnostics, educating patients and engaging diverse stakeholders;

- **Common challenges**: include the feasibility of conducting TES for many ACTs, timelines for policy updates, prescriber training, supply management, security in complex emergencies and molecular analysis for TES and *HRP2* gene deletions; and

- **Data and research priorities**: include data on prescriber behaviour, caregiver practices, inaccessible population health data (e.g. for refugees, internally displaced people, migrants) and sharing cross-border data.

Group 3. Issues discussed

- **Shared challenges**: include quality control of medicines (both internally and cross-border), extending antimalarial drug monitoring sites and establishing cross-border monitoring of resistance;

- **Country-specific challenges and plans**:
  - *Burundi*: poor drug quality and insufficient funding to conduct studies at all sites;
  - *Democratic Republic of the Congo*: to conduct efficacy studies for all first-line treatments and strengthen quality control of circulating antimalarial drugs; and
  - *Senegal*: to maintain three types of ACTs to help prevent resistance, and develop a comprehensive resistance management plan.

Group 4. Issues discussed

- **Challenges in vector control**: include altered vector behaviour (more outdoor biting), insecticide resistance, insufficient IRS coverage and inadequate funding. Suggested solutions include prevention of outdoor biting, larval source management, entomological research, selecting effective insecticides, increased funding and enhancing collaboration and workforce capacity.

- **Treatment without testing**: notably in the private sector, including medical errors and inadequate surveillance systems. Proposed solutions include better training, supervision and availability of rapid diagnostic tests. Little is known about overuse of monotherapy. Recommendations include further research and policy changes to ensure alternative first-line treatments and multiple first-line therapies.

- **Drug storage and transport**: common challenges with storage facilities and ACT transport require better facilities. Suggested incentives include subsidies for the private sector and incentives for patient adherence.

- **Country-specific challenges***:* Ghana and Nigeria reported invasion by *An. stephensi* and low coverage of insecticide-treated bednets, while South Africa reported that preferential use of injectable artesunate was a problem. The recommendations included targeted mosquito interventions, training and revision of medication policy.

- **Research priorities**: priorities include surveillance of *HRP2* deletion, research on the private sector, drivers of adherence to treatment, motivation to report and the effect of multiple first-line therapies. Additional topics include research on single-dose primaquine, reaching remote and mobile populations in South Africa and improving pharmacokinetics studies in Ghana.

6. Session 4: coordination among countries

Panel discussions were held on ensuring closer collaboration among countries and models of coordination among countries. The panel explored current gaps, collaboration needs, and ideal models for cross-country coordination in tackling antimalarial drug resistance. Key points from each country and organization were as follows:

The Democratic Republic of the Congo transitioned from academia-centred to country-driven resistance monitoring with technical and financial partners (PMI, the Global Fund to Fight AIDS, Tuberculosis and Malaria [the Global Fund], WHO) but identified funding gaps. Collaboration with universities, particularly in the eastern regions, is essential for comprehensive data collection, especially in refugee camps. Support is required for better data sharing.

Ethiopia emphasized the collaborative nature of its malaria programme, which involves national research institutions such as the Armauer Hansen Research Institute for

identifying challenges such as drug resistance. The benefits include capacity-building and sharing of expertise, with international coordination through a technical advisory committee.

Sudan highlighted effective coordination platforms (the Horn of Africa Network for Monitoring Antimalarial Treatment) for monitoring antimalarial resistance with neighbouring countries. The network also serve as a platform for discussing issues such as *HRP2* gene deletion and invasion by *An. stephensi*. Partners such as the Institute of Entomology in Sudan contribute to the national malaria control programme. Coordination could be improved by involving more partners and audiences.

Uganda presented a structured approach to collaboration and emphasized the importance of clear problem definition, urgency and alignment to set focused goals. Effective stakeholder engagement modelled on global efforts should extend to national level, supported by a robust communication framework. Uganda stressed the importance of an evidence-driven approach to persuade stakeholders and assign leaders to ensure mobilization, and clear procedural roles to facilitate coordination and impact.

The Worldwide Antimalaria Resistance Network collects and standardizes data from many studies and plays a role in identification of markers of resistance by pooling data from many studies to draw meaningful conclusions. Standardized data collection and analysis can indicate the necessary formats and analytical approaches.

PMI supports TES in 27 African countries and collaborates with the Global Fund in site selection and filling gaps. The Partnership for Anti-malarial Resistance Monitoring in Africa provides training, capacity-building and centralized sample analysis in Africa, creating a collaborative network among African investigators for sharing data and resolving challenges.

The Global Fund emphasized the importance of cohesive coordination and regional mechanisms to harmonize evidence and guide national policies. The Global Fund has no staff in countries, and its role is primarily in strategy development and regional coordination. A structured, costed plan, timely data access and sustainable resource are essential, with coordination of work with partners such as WHO, PMI and other funding partners to avoid duplication.

Discussion

The importance of the East African Network for Malaria Drug Resistance in regional policy changes since its formation in 1997–1998 was emphasized. EANMAT's was closed following the end of funding, emphasizing the importance of long-term support. Participants proposed establishment of a dedicated secretariat for coordination, which would include members from national malaria control programmes and institutions that conduct TES to promote sustainable network initiatives.

Participants noted the variation in genotyping protocols in the region and called for standardized methods to ensure data comparability, given the current limitations of sequencing. Use of certified commercial firms for genomic sequencing was mentioned as a potential solution.

Reflecting on previous collaborative efforts in West Africa, the attendees proposed that sub-regional networks be revived to increase information-sharing among West African countries. It was suggested that an Africa Anti-malaria Resistance Network be initiated to support collaboration across the continent.

The importance of political will for the success of interventions was underscored, and a recommendation was made to form subcommittees that would engage regularly with national governments to strengthen support for initiatives.

7. Closing session

7.1 Statements by delegations

Eritrea called for active follow-up and monitoring by all partners, especially WHO, to address gaps in prevention of resistance and proposed follow-up meetings until resistance is definitively eliminated. Senegal emphasized the value of the workshop's approach and looked forward to its practical application at country level.

The Global Fund said that the workshop had shaped a coherent regional strategy and highlighted the urgency of coordinated action, especially for new therapeutics such as ACTs, while addressing challenges of access to the next generation of drugs through their market-shaping initiative. Duplication should be avoided, coordination with funders should be enhanced and costs for emerging treatments such as vaccines should be managed.

The Bill & Melinda Gates Foundation outlined its commitment to reducing the burden of malaria, accelerating eradication with innovative tools and "staying ahead" of resistance. Its interests include improving diagnostics, drug development and digital health tools to improve surveillance across Africa.

The Clinton Health Access Initiative described its collaborative approach, with country programmes to implement global guidance. It will share information from the meeting with their national teams.

PMI highlighted the importance of monitoring therapeutic efficacy and revitalizing regional networks for cross-border coordination. Data from TES should be translated into actionable policies through evidence-based decision-making and political will.

The Medicines Management Venture reaffirmed its role in the development of new antimalarials with partners such as WHO and in promoting diversification of ACTs in Burkina Faso and Kenya, with plans to include other countries.

UNITAID reiterated its focus on catalysing access to new tools. Recent proposals were designed to address drug resistance in Africa by promoting diverse ACTs and conducting operational research to improve delivery.

The University of Cape Town, representing the Mitigating Antimalarial Resistance Consortium in Southern and East Africa, thanked the organizers for the workshop and affirmed their commitment to support regional action plans and updated treatment guidelines.

7.2 Conclusions and recommendations

The meeting underscored the urgency of coordinated collaboration among countries to address the escalating challenge of antimalarial drug resistance in Africa. In-depth discussions had been held on the drivers of resistance, and rapidly evolving resistance

patterns in parts of Africa had been described in country presentations and in the responses to the WHO questionnaire. Priorities had been identified to help countries in preventing emergence and in limiting the spread of resistance through systematic coordination, information-sharing and collaborative responses.

The proposed next steps include establishment of subregional networks to generate essential data for evidence-based drug policy decisions. Additionally, national consultations should be held on development and implementation of national action plans against drug resistance.

To support this work, a platform should be established to coordinate the work of stakeholders involved in combating antimalarial resistance. Resources should be mobilized to improve national action plans for surveillance and response. Success will require sustained partnerships, active information exchange and firm political commitment, which are essential to counteract the growing threat of antimalarial drug resistance across the continent.

7.3 Closing remarks

Daniel Ngamije, Director of the WHO Global Malaria Programme, said that the workshop had re-emphasized the importance of addressing the spread of partial resistance to artemisinins in Africa, with discussions on emerging data, drivers of resistance and response strategies. Since the launch of WHO's strategy, resistance has continued to expand, making it crucial for countries to develop national work plans to strengthen surveillance, update treatment policies and improve case management in both the public and the private sectors. WHO remains committed to supporting national malaria programmes in addressing these challenges while advocating for continued investment in primary health care, early diagnosis and treatment, robust supply chains and regulatory systems.

References[1]

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2. Global technical strategy for malaria 2016–2030, 2021 update. Geneva: World Health Organization; 2021. https://iris.who.int/handle/10665/342995. Licence: CC BY-NC-SA 3.0 IGO.

3. The 17 goals. New York: United Nations, Department of Economic and Social Affairs; 2024. https://sdgs.un.org/.

1 All references accessed on 29 January 2025.

Annex 1. Agenda of the meeting

Day 1 (7 November 2023)		
Opening session		
9:00–9:45	Opening remarks, introduction and objectives	
Session 1: Malaria and the status of antimalarial drug resistance		
10:15–10:45	Overview of the malaria situation in Africa	Regional Offices for Africa and for the Eastern Mediterranean
10:45–11:00	Global distribution of antimalarial drug resistance	Global Malaria Programme
11:00–11:40	Information on artemisinin partial resistance from countries (10 minutes each) • Eritrea • Rwanda • United Republic of Tanzania • Uganda	Country representatives and researchers
11:40–12:20	Country examples of therapeutic efficacy and molecular surveillance of resistance • Democratic Republic of the Congo • Ethiopia • Sudan	Country representatives and researchers
12:20–13:00	Known and unknowns of artemisinin partial resistance	Philip Rosenthal
Session 2: Responding to antimalarial resistance		
14:00–15:00	Responding to antimalarial drug resistance in the Greater Mekong Subregion • In countries • Across countries	Pascal Ringwald Cambodia National Malaria Programme Manager
15:00–15:30	Overview of strategy to respond to antimalarial drug resistance in Africa	Regional Offices for Africa and for the Eastern Mediterranean/Global Malaria Programme
15:30–15:45	Discussion	

Day 2 (8 November 2023)		
Session 3: Prioritizing intervention in countries		
09:00–09:35	Assessment of country specific situation to prioritize interventions: example of Rwanda	Jean Olivier Guintran and country team
09:35 –09:45	Discussion	
09:45 –09:55	Introduction to group work	Jackson Sillah (Regional Office for Africa)
09:55 –10:40	Group work on drivers and response to antimalaria drug resistance	Participants
11:00–12:00	Continuation of group work	Participants
12:00–13:00	Presentations and discussion of group work	Participants

Session 4: Coordination among countries		
14:00–15:00	Panel discussions on • Needs and gaps for closer collaboration. • Models for coordination across countries	Moderator: Dorothy Achu (Regional Office for Africa)
15:00–15:30	Discussion	
Session 5: Consensus statements and conclusions		
16:00–17:00	Statements by delegations attending the meeting	Country representatives, researchers, technical agencies and funding organizations
17:00–17:20	Conclusion and next steps	Regional offices for Africa and the Eastern Mediterranean, Global Malaria Programme
17:20–17:30	Closing remarks	Regional offices for Africa and the Eastern Mediterranean, Global Malaria Programme

Annex 2. List of participants

Country representatives

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Bosco Agaba, Infectious Diseases Research Collaboration, Uganda

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Simon Ijezie, National Malaria Elimination Programme, False-positive Malaria Diagnosis, Nigeria

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Rapporteur

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Jean-Olivier Guintran, WHO consultant, Technical adviser in Malaria Control, France

Daniel Ngamije, Director

Peter Olumese, Medical Officer, Diagnostics, Medicines and Resistance Unit

Charlotte Rasmussen, Technical Officer, Diagnostics, Medicines and Resistance Unit

Marian Warsame, WHO consultant, Gothenburg, Sweden

Annex 3. Country questionnaire on drivers of antimalarial drug resistance

The *Strategy to respond to antimalarial drug resistance in Africa* identifies factors that could be responsible for driving the emergence and spread of resistance in different settings. To develop plans and strategies relevant for individual countries, it is necessary to identify factors that are likely to be responsible for driving resistance spread in that specific country. Each country team should complete the template below. For more information, please consult the Strategy.

High proportion of parasites exposed to a drug			
	1 - Failure to limit malaria transmission by vector control		
	Explanation: High, effective coverage of interventions such as vector control interventions will help limit the overall number of parasites exposed to drugs, making emergence and spread of drug resistance less likely.		
	Rating 1 to 5	**Rate**	**Explanation (optional)**
	Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= High, effective coverage of vector control. 5= Generally low coverage and usage of vector control. NI= No information)		
	2 - Broad use of antimalarials for non-confirmed cases		
	Explanation: Providing treatment to patients without parasitological diagnosis of malaria, increases the number of people with low level of antimalarial drug in the blood. This can make selection of drug resistance more likely. Please consider treatment provided in both public and private sectors.		
	Rating 1 to 5	**Rate**	**Explanation (optional)**
	Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Provision of antimalarial treatment without prior parasitological diagnosis **uncommon**. 5= Provision of antimalarial treatment without prior parasitological diagnosis **very common**. NI= No information)		
	3 - Widescale use of same drugs for chemoprevention and treatment		
	Explanation: If a drug is used both for treatment and chemoprevention, emergence and spread of resistance to this drug is more likely.		
	Rating 1 to 5	**Rate**	**Explanation (optional)**
	Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Drugs used for treatment are **not used** for chemoprevention. 5= Drug used for treatment are **frequently used** for chemoprevention. NI= No information)		

Parasites exposed to one drug only

4 - Misuse or overuse of monotherapies

Explanation: Use of artemisinins or any of the partner medicine alone can compromise the value of ACTs by selecting for drug resistance. Overuse includes using an artemisinin-based injectables for non-severe patients. Misuse includes not providing a full 3-day ACT treatment after the administration of a parental (or rectal) artesunate to severe patients once they can take oral treatment.

Rating 1 to 5	**Rate**	**Explanation (optional)**
Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Misuse or overuse uncommon and unlikely to be a driver. 5=Misuse or overuse very common and likely to be a driver. NI= No information)		

5 - Reliance on a few ACT treatments

Explanation: If the same ACT is used on a very large scale as the main treatment of malaria, in both the public and private sector, this could make the spread of resistance to an ACT partner drugs more likely.

Rating 1 to 5	**Rate**	**Explanation (optional)**
Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1: Large number of different quality assured ACTs are widely used. 5: Only 1 quality assured ACT is widely used. NI= No information)		

Parasites exposed to subtherapeutic levels of a drug

6 - Broad use of non–pharmaceutical forms of *Artemisia*

Explanation: If non–pharmaceutical forms of *Artemisia* are widely used, for instance in the form of artemisia tea, this could lead to parasites being exposed to sub-therapeutic levels of artemisinins alone in the blood. This could make the selection and spread of parasites resistant to artemisinin more likely.

Rating 1 to 5	**Rate**	**Explanation (optional)**
Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1=Use of non–pharmaceutical forms of *Artemisia* **not common**. 5= Use of non–pharmaceutical forms of *Artemisia* **very common**. NI= No information)		

7 - Wide availability of substandard and falsified drugs

Explanation: Drugs can be substandard due to problems in production or inadequate transport or storage conditions. If substandard and falsified drug are widely available, this could increase the risk of the selection and spread of resistance by exposing parasites to sub-therapeutical levels of drugs. Please consider drugs provided both in public and private sector.

Rating 1 to 5	**Rate**	**Explanation (optional)**
Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Substandard and falsified drugs **not widely** available 5= Substandard and falsified drugs **widely** available. NI= No information)		

Parasites exposed to subtherapeutic levels of a drug (cont.)	**8 - Inadequate treatment [due to provider-related drivers]**		
	Explanation: Health care provider may not give the treatment as per the national treatment guidelines for different reasons including poor training. This could lead to underdosing or use of a monotherapy increasing the risk of selection and spread of resistant parasites.		
	Rating 1 to 5 Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Inadequate treatment provided to patients by provider rare. 5= Inadequate treatment provided to patients by provider very common. NI= No information)	**Rate**	**Explanation (optional)**
	9 - Incomplete treatment (due to patient behavioural drivers)		
	Explanation: Patients may not to take (or give their child) the correct treatment prescribed, for instance for financial reasons. This could lead to parasites being exposed to sub-therapeutic levels of drugs the blood making the selection and spread of parasites resistant to artemisinin more likely.		
	Rating 1 to 5 Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Incomplete treatment taken by the patient **rare**. 5= Incomplete treatment taken by the patient **very common**. NI= No information)	**Rate**	**Explanation (optional)**
Parasites not fully sensitive more likely to be transmitted	**10 - Recrudescent cases likely to transmit parasites less sensitive to a drug**		
	Explanation: If treatment fails due to drug resistance, in the absence of rapid treatment with second-line ACT, the parasites transmitted could be a potential source of transmission of drug resistance.		
	Rating 1 to 5 Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Recrudescent cases **likely to be treated rapidly** with 2nd-line ACT before any further transmission can happen. 5= Recrudescent cases **unlikely to be treated before any further transmission** can happen. NI= No information)	**Rate**	**Explanation (optional)**

Parasites exposed to drug to which they are not fully sensitive

11 - Treatment failure followed by treatment with same drug

Explanation: If a patient fails a treatment, and are then treated with the same treatment, emergence and spread of resistance is more likely.

Rating 1 to 5	**Rate**	**Explanation (optional)**
Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1= Patients that fails a treatment are very **unlikely** to be treated with the same medicine. 5= Patients that fails are treatment are very **likely** to be treated with the same treatment. NI= No information)		

12 - Lack of information on efficacy and resistance to inform treatment

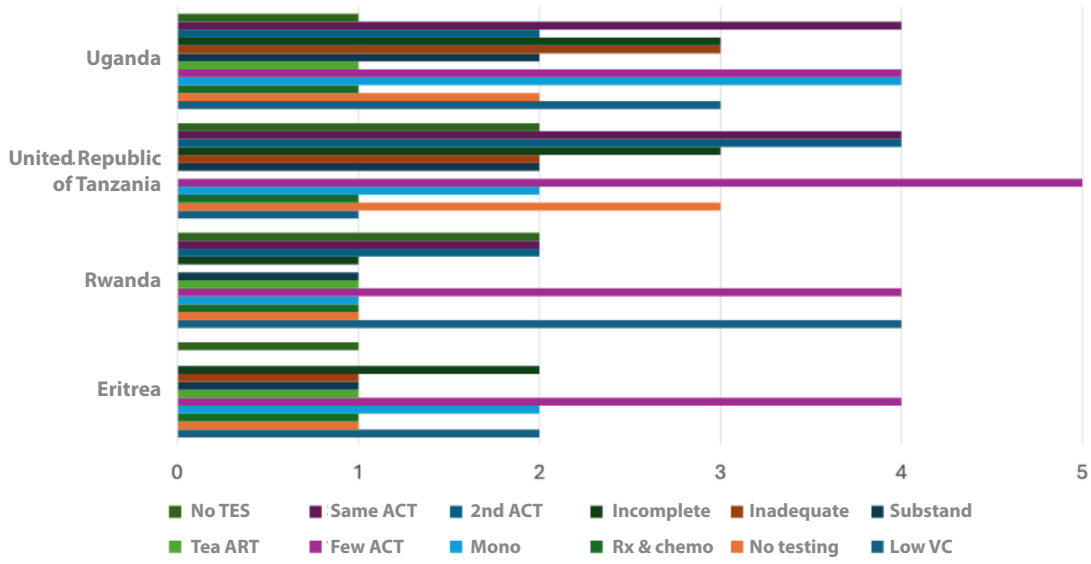
Explanation: If there is no up-to-date information on the efficacy and resistance to currently recommended treatment, the treatment policy may recommend a treatment to which some resistance may have evolved. Continued use of such a treatment would increase level and spread of drug resistance.

Rating 1 to 5	**Rate**	**Explanation (optional)**
Please rate the importance of this driver in your country with a rate from 1 to 5 based on current information. (1 = data on the efficacy of the first-line treatment is available from the last 2 years. 5= No recent data on the efficacy of the first-line treatment is available.)		

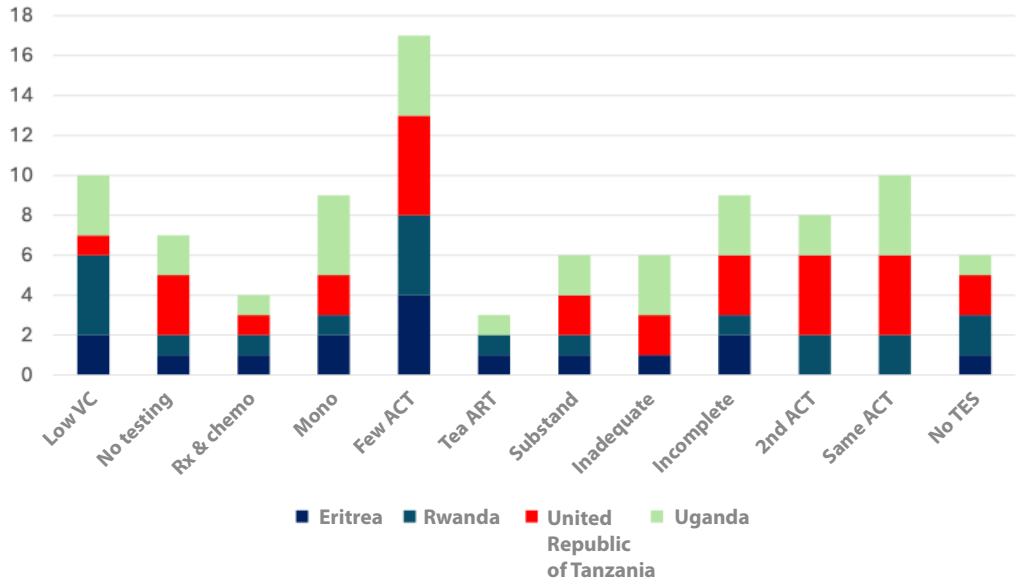
Annex 4. Responses to the questionnaire, by group

Group 1. Eritrea, Rwanda, Uganda, United Republic of Tanzania

Results of questionnaires on main drivers by country

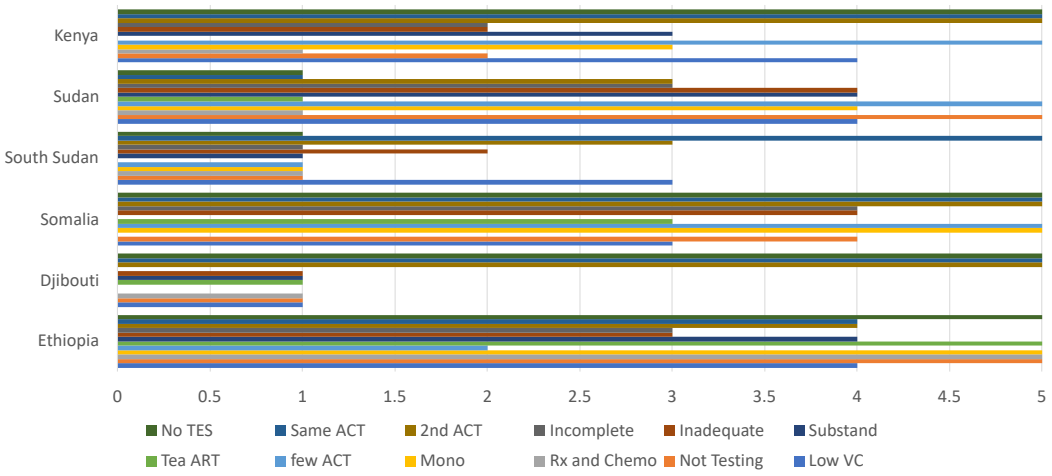


Results of questionnaires on main drivers (aggregated data)

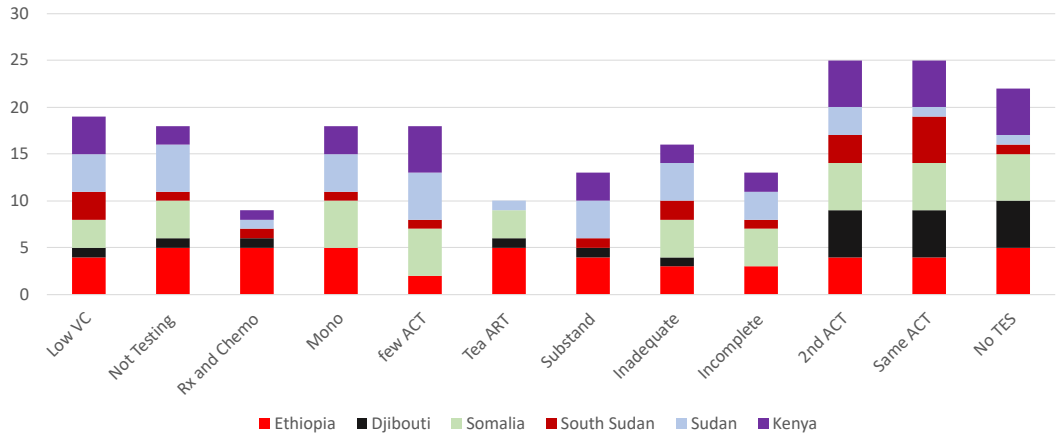


Group 2: Ethiopia, Kenya, Somalia, South Sudan and Sudan

Results of questionnaires on main drivers by country

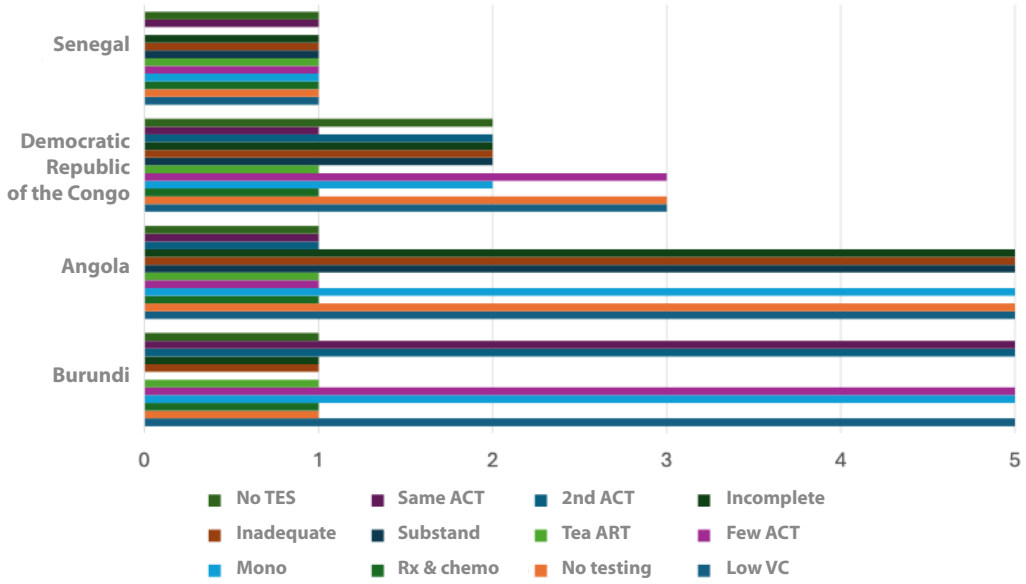


Results of questionnaires on main drivers (aggregated data)

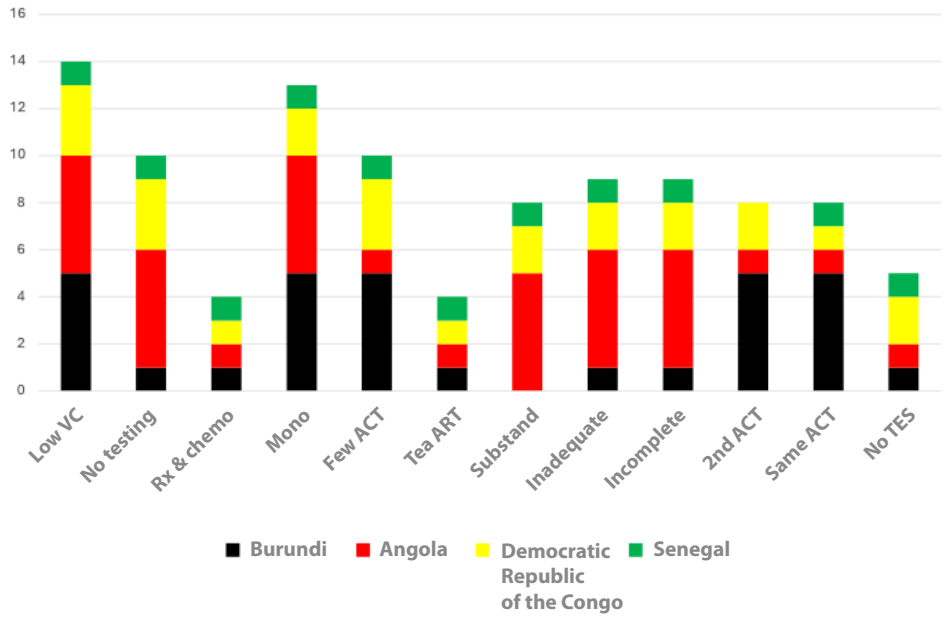


Group 3. Burundi, Democratic Republic of the Congo, Senegal

Results of questionnaires on main drivers by country

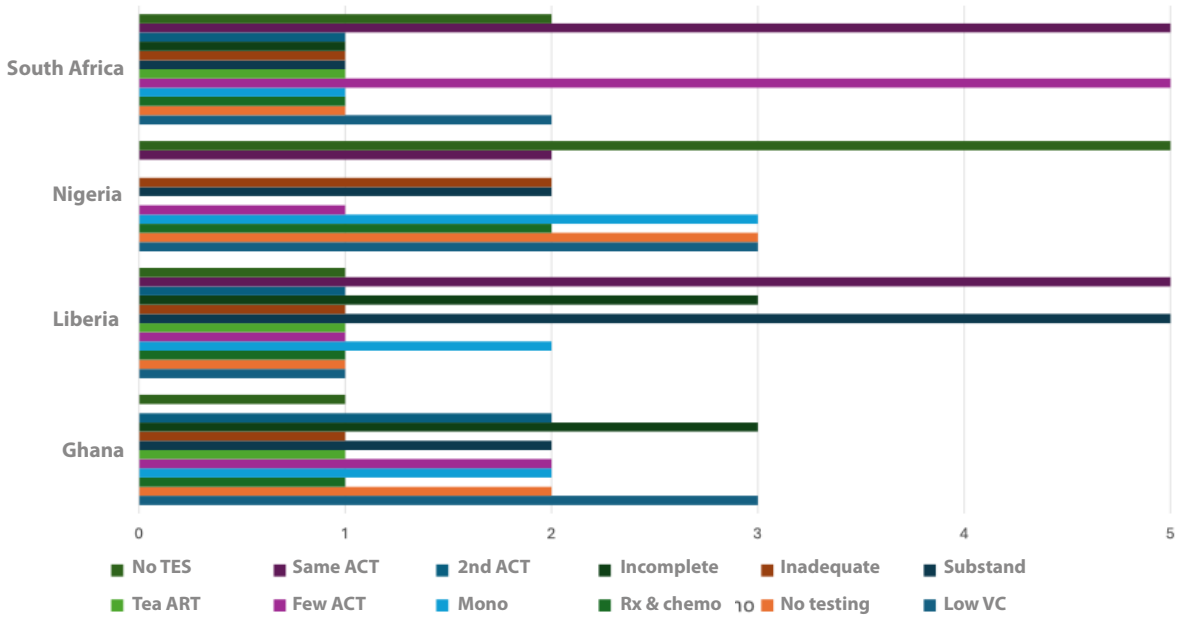


Results of questionnaires on main drivers (aggregated data)

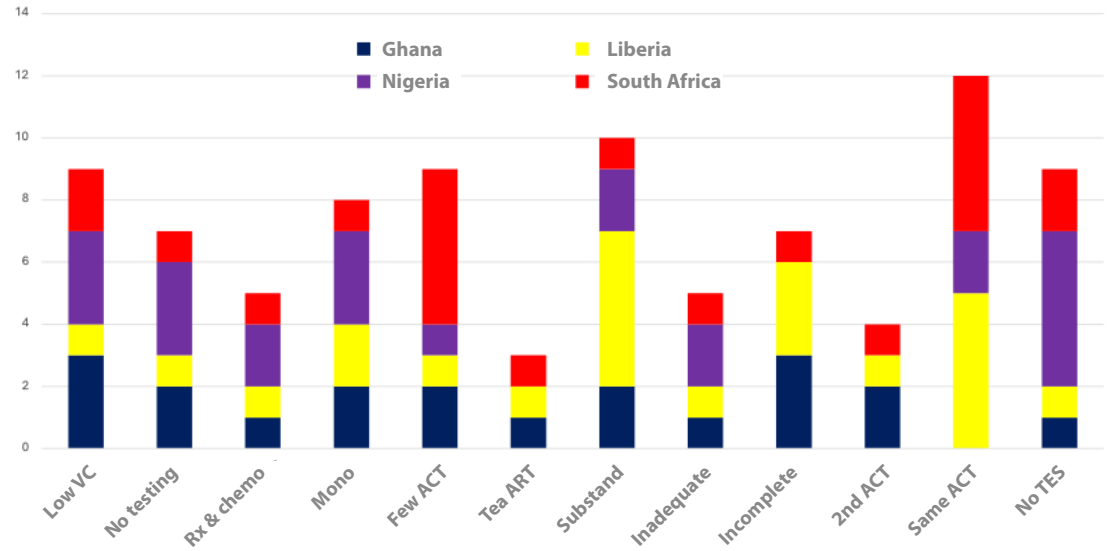


Group 4. Ghana, Liberia, Nigeria and South Africa

Results of questionnaires on main drivers by country



Results of questionnaires on main drivers (aggregated data)



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