Multiple first-line therapies as part of the response to antimalarial drug resistance

An implementation guide

World Health Organization

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Abbreviations

ACT	artemisinin-based combination therapy
AL	artemether–lumefantrine
ALAQ	artemether–lumefantrine–amodiaquine
AQ	amodiaquine
ASAQ	artesunate–amodiaquine
ASMQ	artesunate–mefloquine
ASPY	artesunate–pyronaridine
AWaRe	Access, Watch, Reserve (WHO classification of antibiotics)
DHA-PPQ	dihydroartemisinin–piperaquine
EML	essential medicines list
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMS	Greater Mekong Subregion
MFT	multiple first-line therapies
NMCP	national malaria control programme
PPQ	piperaquine
PQ	primaquine
RDT	rapid diagnostic test
SMC	seasonal malaria chemoprevention
SP	sulfadoxine–pyrimethamine
SPAQ	sulfadoxine–pyrimethamine plus amodiaquine
TES	therapeutic efficacy studies
WHO	World Health Organization

Executive summary

Malaria case management with prompt access to effective diagnostics and antimalarial therapies is essential to reduce morbidity and mortality due to malaria. Since 2001, artemisinin-based combination therapy (ACT) has been central to effective malaria treatment, as it combines artemisinin for rapid reduction of the parasite number with a longer-acting partner drug to ensure clinical and parasitological cure. The emergence and spread of resistance to antimalarial drugs, which allows the parasite to survive and multiply despite administration of standard drug dosages, poses a significant threat to malaria control and elimination.

Partial resistance to artemisinins, defined by the presence of *Pfkelch13* mutations and delayed parasite clearance, has emerged in several African countries. While such partial resistance alone does not lead to failure of ACT treatment, additional resistance to partner drugs would jeopardize the overall effectiveness of ACTs. In response to this growing threat, in 2022, the World Health Organization (WHO) launched the *Strategy for the response to antimalarial drug resistance in Africa (1)*. This strategy comprises 20 interventions grouped into four pillars:

- strengthening surveillance of drug efficacy and resistance;
- optimizing use of diagnostics and therapeutics to reduce drug pressure;
- limiting the spread of resistant parasites; and
- stimulating research and innovation to develop new and leverage existing tools.

The aim of the strategy is to improve detection of resistance, ensure timely responses and minimize the impact of drug resistance through evidence-based interventions. Although the focus of the strategy is on Africa, it is relevant to all malaria-endemic countries.

The fourth pillar calls for innovative approaches to prolong the lifespan of ACTs by using currently available drugs in ways that minimize the risk of resistance. One such approach is use of multiple first-line therapies (MFT).

The purpose of the WHO technical consultation on use of MFT was to develop evidence-based guidance for countries on use of this intervention to address the growing challenge of antimalarial drug resistance. The objectives and expected outcomes were to:

- provide an operational definition of MFT;
- review the evidence on the impact of MFT on antimalarial drug resistance;
- review the implications for policy and implementation of MFT;
- generate guidance on use of MFT by national malaria programmes and partners; and
- identify gaps in the evidence and the necessary research.

Malaria case management

Updates to national malaria treatment guidelines reflect a concerted effort by NMCPs in Africa to combat malaria effectively and improve case management. As most African countries are strongly dependent on artemether–lumefantrine (AL), however, they are vulnerable to any decrease in the therapeutic efficacy of this drug.

Other challenges include the role of the private sector in malaria case management, inadequate diagnostic testing, suboptimal availability and quality of drugs, and non-compliance with treatment protocols. These require enhanced coordination and quality assurance in all sectors.

In countries such as Nigeria, the private sector plays a significant role in malaria treatment, and most consultations occur outside the public health system. Coordination between the public and private sectors must therefore be improved to ensure adherence to treatment guidelines and rational prescribing practices. Similar situations are seen in other countries, such as Uganda and the United Republic of Tanzania, where a large proportion of antimalarials are used in the private sector, often without adherence to established treatment guidelines.

Improvement of malaria case management must include not only available, effective antimalarial drugs but also adherence to diagnostic testing practices and treatment guidelines. Use of digital solutions presents an opportunity to enhance health care operations and reporting. Such innovations, if they can be used off line, offer promising means for strengthening malaria case management and bridging gaps in data collection and reporting.

Summary of evidence for use of multiple first-line therapies

Mathematical modelling provides valuable insights into the selection and spread of antimalarial resistance and can contribute to predict the effectiveness of different MFT deployment strategies in various contexts.

Preliminary results suggest that, to reduce selection for drug resistance, rapid cycling between AL and artesunate–amodiaquine (ASAQ) is more effective than AL alone. To delay and slow the evolution of resistance, however, simultaneous use of several ACTs is more consistently effective than cycling strategies, especially if the cycling period is long. Caution should be exercised in including dihydroartemisinin–piperaquine (DHA-PPQ) in MFT strategies, as resistance to piperaquine (PPQ) developed in South-East Asia and spread rapidly in a strain with partial resistance to artemisinin, leading to high levels of treatment failure. Wide-scale use of DHA-PPQ at population level should be monitored and surveyed carefully to detect any emergence of PPQ resistance. More diagnostic testing for malaria should be conducted to avoid prescription of antimalarials for non-malarial fevers and thus delay the emergence and spread of resistance, particularly in high transmission settings.

Successful implementation of MFT requires consideration of details such as drug efficacy, rotation schedules, geographical or health-system distribution of all the drugs and the current level of antimalarial resistance . National analyses show the importance of timely policy changes and tailored approaches to use of MFT. Delaying action can increase treatment failure and limit the effectiveness of interventions to prevent resistance.

While partial resistance to artemisinin has been detected in Africa, the mechanism of resistance to lumefantrine remains unclear, and validated molecular markers

are necessary. Possible competing mechanisms that decrease susceptibility to lumefantrine and amodiaquine (AQ) could delay the emergence of resistance to both drugs when used as MFT. Overall, modelling indicates proactive adoption of MFT to limit drug resistance while addressing the challenges specific to each context.

Definition of multiple first-line therapies

Aim: to reduce potential emergence and spread of resistance to antimalarial drug

Rationale: to expose a specific parasite population to several antimalarial molecules to prevent or delay the emergence or spread of drug resistance

Definition: MFT consists of use of two or more effective ACTs in a population for treatment of uncomplicated malaria; can be used either together or in rotation (cycling)

Deployment strategies:

- Simultaneous use: modelling suggests that a minimum consumption of each drug is necessary to effectively delay selection for resistance:
  - > 35% if two drugs are used;
  - > 25% if three drugs are used; and
  - > 15% if four drugs are used.
- Rotation: more effective for deterring resistance as the duration between rotated therapies decreases:
  - benefit of 1 year of rotation similar to that of simultaneous use;
  - 2 years appears to be the longest duration that provides a significant benefit.

Context

- MFT must be a deliberate, managed intervention at all levels of the health system, including the private sector.
- MFT requires that all the antimalarial drugs used are effective. Therefore, treatment policies must be changed before drug resistance undermines the clinical efficacy of any of the drugs used in MFT.

Key concepts

- All MFT strategies used in Africa require a relative decrease in use of AL.
- As lumefantrine and AQ have competing resistance mechanisms, concurrent use is likely to inhibit development of resistance to either drug.
- Preservation of the efficacy of lumefantrine is critical, as it is a component of both the triple ACT (ALAQ) and ganaplacide–lumefantrine, which are likely to be the next antimalarial products that will become available.
- The consequences and costs of non-action are likely to be significant.

Implementation of multiple first-line therapies

MFT approaches require meticulous planning and coordination among various sectors. An effective transition to MFT involves revision of national EMLs and treatment guidelines, securing a budget and developing allocation strategies, with procurement, distribution, logistics, and monitoring and evaluation of activities from the outset. Local solutions should be developed to address contextual challenges to effective implementation, such as:

- the dynamics of the private and public sectors;
- the availability and affordability of drugs;
- the preferences of health-care providers and patients;
- transmission dynamics, geography and seasonality;
- human displacement, cross-border movement and migration;
- the structure and capacity of the health-care system;
- the structure and capacity of the procurement system; and
- funding structures.

National implementation of MFT strategies presents both opportunities and challenges. In Nigeria, plans are under way to pilot-test MFT according to criteria such as eligibility for seasonal malaria chemoprevention (SMC) and private sector involvement in case management, The test will include enhancing health-care worker training and ensuring adherence to the protocol. Rwanda is planning to introduce MFT in six pilot districts, with robust logistics and supply infrastructure. As Sudan is facing challenges in supply and logistics, resources will be reallocated for use of additional ACTs. Uganda and the United Republic of Tanzania are confirming funding and the scope for implementation, while ensuring comprehensive planning and stakeholder consultation.

In all these countries, common themes are ensuring adherence to treatment guidelines, strengthening supply chains and addressing funding constraints. Innovative approaches, such as use of drugs in rotation in Rwanda and the pilot initiatives in Nigeria, offer promising strategies for optimizing malaria case management. Nevertheless, sustained work is necessary to overcome logistical challenges, enhance private sector and community engagement and ensure effective monitoring and evaluation of MFT.

Summary conclusions on multiple first-line therapies implementation

- **Alignment of guidelines with national policy:** Ensure alignment between the national EML, treatment guidelines, NMCP policy and regulatory approval. Minimize the time between policy changes and implementation, including procurement and training.
- **MFT deployment strategy:** Base the strategy on the country context and the feasibility of the approach. Conduct modelling to evaluate the potential impact of different options. Ensure the effectiveness, accessibility, affordability and acceptability of the antimalarial therapy.
  - Specify an ACT for rescue therapy (second-line) for treatment failures.
  - Consider patient preferences for access, convenience, price and tolerability.
  - Discourage preferences for inappropriate drugs (e.g. injectable artesunate for uncomplicated malaria).
  - Limit use of SMC to areas of seasonal transmission, and reduce overall drug pressure for AQ.
- **Pilot studies and implementation plans:** Conduct pilot studies in selected regions before broad implementation to collect evidence for nationwide scaling up, implementation and funding applications.
- **Cost and funding:** Estimate the full cost of implementation, including for capacity-building and training. Secure sustainable funding, and reduce costs through strategic planning and forecasting demand by modelling.
- **Procurement:** Ensure that manufacturers can supply the required volumes by weight band of the ACTs, preferably WHO pre-qualified medicines. Explore national and regional manufacture and approvals. Monitor the quality of antimalarial drugs to ensure effectiveness and affordability.
- **Capacity-building:** Strengthen health system capacity for MFT implementation. Improve malaria case management by training health-care staff and providing supportive supervision, with effective supply and logistics systems.
- **Supply chain and logistics:** Ensure effective supply chain management. Coordinate drug rotation, and manage stock. Consider digitizing supply chain management.
- **Social and behaviour change communication:** Engage communities, social and civil society as well as the peripheral health system to prepare for introduction of new antimalarial drug treatment, with continuous engagement during deployment.
- **Efficacy and resistance:** Ensure the efficacy of all the ACTs used. Conduct therapeutic efficacy studies (TES) and molecular marker surveillance of all drugs used in the country.
- **Monitoring and evaluation:** Use a robust monitoring and evaluation framework to ensure the effectiveness of MFT and no unintended consequences. Extend and strengthen existing reporting and supervision systems for malaria case management and supply chain management.
- **Private sector involvement:** Consider the role of the private sector in MFT deployment. Influence private sector involvement by price manipulation, subsidies, co-payments and regulation. Improve the quality of ACTs, diagnostic testing rates and adherence to guidelines without reducing access.

1. Background

Management of malaria cases, from prompt access to effective diagnostics and antimalarial therapies, is critical for reducing morbidity and mortality. Since 2001, ACT has been the mainstay of effective malaria case management *(2)*, and its continued efficacy is essential for treatment of malaria. ACTs combine artemisinin derivatives, which rapidly reduce the biomass of parasites, with a longer-acting partner drug that completes parasite elimination. The efficacy of ACTs relies on the effectiveness of both components.

Resistance to antimalarial drugs is manifested as the ability of a parasite strain to survive and/or multiply despite administration and absorption of the drug given at doses equal to or higher than those usually recommended but that are tolerated by the subject. The emergence and spread of drug resistance threatens malaria control and elimination, and rigorous measures are required to protect the efficacy of antimalarial drugs.

Partial resistance to artemisinin is defined as delayed clearance after treatment with a drug containing an artemisinin derivative by a parasite strain carrying a particular mutation or set of mutations that have been validated as associated with delayed clearance. At present, only *PfKelch13* mutations have been validated as markers of partial resistance. Partial resistance to artemisinins is confirmed in a quality-controlled study with an ACT or with artesunate monotherapy when ≥ 5% of patients carrying validated *PfKelch13* resistance mutations and with delayed clearance are shown either as persistent parasitaemia detected by microscopy at 72 h (± 2 h, i.e. day 3) or a parasite clearance half-life ≥ 5 h *(1)*. Although partial resistance to artemisinin is still uncommon in most of Africa, it has emerged independently in several countries in East Africa and the Horn of Africa. Delayed parasite clearance due to partial resistance does not result in treatment failure; however, the emergence and spread of resistance to partner drugs threatens to undermine the efficacy of antimalarial treatment in Africa.

In 2022, the WHO launched the *Strategy for the response to antimalarial drug resistance in Africa (1)*. The strategy involves 20 interventions grouped into four pillars:

- strengthening surveillance of drug efficacy and resistance;
- optimizing the use of diagnostics and therapeutics to reduce drug pressure;
- limiting the spread of resistant parasites; and
- stimulating research and innovation to leverage existing tools and develop new ones.

The aims of the strategy are to improve detection of resistance, ensure a timely response, and minimize the impact of drug resistance by promoting evidence-based interventions to reduce the emergence and spread of resistant parasites. Although the strategy focuses on Africa, it is relevant to all malaria-endemic countries.

The fourth pillar includes consideration of innovative approaches to prolong the lifespan of existing ACTs by using available drugs in such a way as to reduce the risk of emergence and spread of resistance. The purpose of the WHO technical consultation on use of MFT was to develop evidence-based recommendations for countries on potential use of this intervention to address the growing challenge of antimalarial drug resistance.

The WHO Global Malaria Programme convened an independent group of technical experts on 14–16 May 2024 to review the evidence for MFT and strategies for implementation, with input and feedback from the NMCPs of Eritrea, Nigeria, Rwanda, Sudan, Uganda and the United Republic of Tanzania. Resource people in Burkina Faso and Kenya were also consulted. The participants also included representatives of stakeholder organizations and funding partners, i.e. the Medicines for Malaria Venture, the Bill & Melinda Gates Foundation, the President's Malaria Initiative, the Roll Back Malaria Partnership to End Malaria, Population Services International, Unitaid, the Malaria Control and Elimination Partnership (PATH), the Clinton Health Access Initiative, Maisha Meds, Jhpiego, and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) who served as observers.

The objective of the technical consultation was to provide evidence-based guidance on MFT as a potential intervention for reducing antimalarial drug resistance. The meeting was chaired by Professor Olugbenga Mokuolu (University of Ilorin, Nigeria). The objectives and expected outcomes were to:

- provide an operational definition of MFT;
- review evidence on the impact of MFTs on antimalarial drug resistance;
- review the implications for policy of implementation of MFT;
- provide guidance on MFT for NMCPs and partners; and
- identify gaps in the evidence and the necessary research.

1.1 Update on the status of resistance and the *WHO strategy to respond to antimalarial resistance in Africa*

Partial resistance to artemisinins was first observed on the Cambodia–Thailand border area in 2008 and spread rapidly throughout the Greater Mekong Subregion (GMS). Subsequently, resistance to partner drugs emerged, with reports of clinical failure rates of four ACTs > 10% *(3)*. As there were few remaining effective treatment options, MFT could not be used, and the treatment policy was changed sequentially in response to reduced drug efficacy identified by strong surveillance. The policy changes were made by countries and were not part of a proactive resistance management plan. Since 2015, the objective has been to eliminate malaria in the GMS, and significant progress has been made towards that goal.

In Africa, partial resistance to artemisinins is emerging. Several *PfK13* mutations have been identified in the Horn of Africa, Rwanda, Uganda and the United Republic of Tanzania. The R622I mutation is associated with delayed parasite clearance has been detected in Eritrea, Ethiopia, Somalia and Sudan in the Horn of Africa. In Uganda, various mutations (primarily C469Y and A675V but also R561H and C469F) are spreading rapidly, at a rate of spread comparable to that observed in the GMS. In Rwanda and the United Republic of Tanzania, the *R561H* mutation predominates *(1)*.

No widespread resistance to partner drugs has been confirmed in Africa, but some falciparum genotypes have been associated weakly or moderately with reduced sensitivity to partner drugs. Isolated reports of relatively high treatment failure rates with AL and DHA-PPQ indicate potential resistance. Failure is often associated with molecular markers of resistance to artemisinin and PPQ similar to those seen in Asia.

There are, however, no validated molecular markers of resistance to amodiaquine, lumefantrine or pyronaridine.

The WHO strategy *(1)* proposes dynamic deployment of diverse antimalarial treatments to prolong the effectiveness of existing ACTs. One option is MFT; the feasibility of MFT, including logistics, costs and national acceptability, affect the effectiveness of this intervention and should be assessed before deployment. Additionally, modelling and research can be used to predict the impact of MFT on drug resistance. To build a healthy market, deliberate, proactive interventions are necessary, and comprehensive studies should be conducted on market challenges and market interventions, such as volume guarantees and co-pay mechanisms. The goal is to increase the diversity, availability and affordability of antimalarial products.

The WHO strategy calls for a proactive, adaptive approach, with regular updating when new evidence becomes available. The strategy includes strengthened surveillance of resistance, monitoring implementation of interventions and ensuring that policies and practices respond to evolving resistance.

Comments

- In the GMS, changes in treatment policy led to selection of various molecular markers for partial resistance to artemisinins and resistance to partner drugs. For example, DHA-PPQ selected for a strain with the *PfK13* C580Y mutation and increased *Pf plasmepsin* copy numbers, and a change to artesunate-mefloquine (ASMQ) in Cambodia included replacement of this strain.

- Data from TES are captured promptly on the WHO Malaria Threats Map. Other data, however, may not be reported. An annual TES meeting was held in the GMS to share and discuss data and responses. TES meetings have also been held in the African and Eastern Mediterranean regions, and further meetings are planned, pending funding.

Although the reports of drug resistance are alarming, few patients experience recrudescence, as shown in TES. In some areas, however, there is evidence of selection of strains with a changed response to the drugs being used, and the cost of a delay in policy change may be unacceptably high.

1.2 WHO recommendation and guidance on national antimalarial policies and treatment guidelines

A policy for use of antimalarial drugs is designed to provide evidence-based guidelines for decision makers and health workers to ensure early diagnosis and prompt, effective treatment, tailored to the local contexts The goal is to use available antimalarial drugs and other resources efficiently to maximize reductions in morbidity and mortality due to malaria while minimizing the development and spread of drug resistance.

Developing and updating national antimalarial drug policies involve analysing technical, social and economic issues in malaria control and drug resistance, including assessing the magnitude and risk of resistance and potential interventions. Consensus-building among policymakers, researchers and other stakeholders is essential. The potential environment of decision-making and implementation should be analysed

and a national supervisory body established to oversee policy development and implementation *(2)*.

Indicators for policy change include increases in malaria morbidity and mortality, dissatisfaction of prescribers or consumers with current policies, evidence of reduced therapeutic efficacy, and the availability of new, more effective treatments. A treatment failure rate > 10% (corrected by polymerase chain reaction) and a cure rate > 5% in clinical trials are critical thresholds for decision-making. Treatments with failure rates > 10% should be replaced with more effective treatment, which should have a cure rate > 95%. Important factors in selecting drug combinations include therapeutic efficacy, safety, potential for widespread use, consumer compliance, cost-effectiveness, prevention of the emergence and/or spread of resistance, availability and national guidelines.

Policy implementation requires technical and political endorsement and decisions on the most appropriate deployment strategy. Implementation involves several steps, including resource mobilization, guideline development, product registration, health worker training, communication strategies, procurement, distribution and post-marketing surveillance, including pharmacovigilance and establishment of systems for monitoring and evaluation. Thus, there may be a significant delay between adoption and implementation of a new policy, which is typically 18 months. This shows the importance of responding to resistance promptly.

WHO guidelines for malaria treatment recommend six ACTs for treatment of uncomplicated malaria: AL, ASAQ, ASMQ, DHA-PPQ, artesunate–pyronaridine (ASPY) and artesunate plus sulfadoxine–pyrimethamine (SP), if the partner drug is not known to be resistant (e.g. artesunate–SP should not be recommended in areas with SP resistance). Recurrence of *P. falciparum* malaria can result from re-infection or recrudescence due to drug resistance, inadequate dosing, poor adherence, individual differences in drug metabolism or use of a substandard medicine. Failure within 28 days should prompt a switch to an effective alternative (second-line) ACT. Failures after 28 days are presumed to be new infections and should be re-treated with the same first-line ACT. Training of health-care workers should emphasize the importance of asking each malaria patient when they were last treated for malaria.

Use of the most effective drug for malaria is likely to reduce mortality and minimize the risk of development of resistance. Effective antimalarial therapies must therefore be affordable to communities, be applicable in simplified regimens, and also be available in the private sector.

Comments

- DHA-PPQ and ASPY are more expensive than AL; however, if MFT increases demand for these drugs, their prices are expected to fall.
    - Policy decisions in Nigeria significantly impact demand, given the large market.
    - Work should be undertaken to reduce the cost of manufacturing ASPY and DP, and manufacturers of generic products should be engaged to increase their affordability within 3–5 years.
- Loss of the efficacy of AL entails significant costs due to frequent repeated treatment, an increased risk of poor treatment outcomes and purchase of more expensive medicines. Thus, inaction or delay in taking measures to prevent and respond to antimalarial drug resistance has a cost.

- Ensuring that diagnostics are used to identify malaria cases correctly is a key part of managing ACT consumption and thus drug pressure. Quality-assured, sensitive, specific diagnostic testing should be promoted at all levels of the health system, including in the private sector.

1.3 Overview of case management at national level

1.3.1 Eritrea

The Eritrean Ministry of Health recently updated its guidelines for malaria diagnosis and treatment, which now include both curative and preventive strategies. The private sector is not active in Eritrea, and most health care is provided through public and military services. Malaria case management, including diagnosis and treatment, is provided mainly in communities.

Malaria is defined by parasitaemia confirmed with a rapid diagnostic tests (RDT) or microscopy. First-line treatment for uncomplicated *P. falciparum* malaria is ASAQ plus single-dose primaquine (PQ), at all levels of the health service. Pregnant women can receive AL in their first trimester, but PQ is not recommended during pregnancy or for women who are breastfeeding infants aged < 6 months. AL is recommended if ASAQ treatment fails. Uncomplicated *P. vivax* malaria is treated with ASAQ, followed by 14 days of PQ.

To reduce the risk of extrapyramidal symptoms due to high doses of ASAQ, a weight-based dosing regimen is used. If patients cannot be weighed, dosing according to age is recommended.

A TES conducted in 2022–2023 showed that ASAQ was highly effective (98.8%), but with a rate of parasitaemia on day 3 of 9.8%. The prevalence of *PfK13* mutations (R622I) was greater in 2019 than in 2017 at all sites studied.[1]

1.3.2 Nigeria

The national malaria treatment guidelines in Nigeria were last updated in 2020. Malaria diagnosis requires confirmation with an RDT or microscopy, and about 95% of suspected cases in the public sector and 74% in the formal private sector are tested. Four ACTs are recommended for treating uncomplicated *P. falciparum* malaria: AL, ASAQ, DHA-PPQ and ASPY. Pregnant women are treated with AL during their first trimester. The TES in 2021 indicated that all four registered ACTs were highly efficacious, although, in clinical practice, the effectiveness of AL appeared to be suboptimal. AL is the most widely used ACT in the public sector, although there are plans to increase the availability of other ACTs in some states. All four ACTs are available in the private sector. Patient acceptability of ASAQ is low because of potential adverse drug reactions. The national EML is being revised to include all relevant antimalarial medicines.

SMC with SP and AQ (SPAQ) reached approximately 28 million children in 2023. In a few states, training of health-care providers included promotion of rational prescribing, such as using ASPY or DHA-PPQ rather than ASAQ for the treatment of uncomplicated malaria in areas in which SPAQ is used.

The diverse private sector plays a significant role in malaria case management in Nigeria, where it manages 66% of consultations. An ACT is prescribed to > 95% of

1 National Malaria Control Programme, Ministry of Health, Eritrea (Personal Communication).

confirmed malaria cases in the public health sector and about 80% in the formal private sector. Data collection from the private sector is, however, insufficient. Interventions to improve case management in the informal private sector have been undertaken in some states.

Malaria is managed primarily at community level. Challenges in malaria case management include an inadequate number of health workers, shortages of commodities, deficits in infrastructure, poor coordination, weak monitoring and supervision and non-adherence to guidelines. Despite these challenges, progress has been made towards better adherence to diagnosis and treatment guidelines.[2]

1.3.3 Rwanda

The national malaria treatment guidelines were updated in 2024. Malaria is diagnosed with an RDT in communities and by microscopy at higher-level health centres and private clinics. About 60% of malaria cases are treated at community level. AL, DHA-PPQ and ASPY are all recommended as alternative first-line options, while cases of treatment failure are given an ACT different from that used initially. Currently, uncomplicated malaria is treated mainly with AL. Procurement of AL (80%), DHA-PPQ (15%) and ASPY (5%) has been secured for 2024. ASAQ was removed from the treatment guidelines > 15 years ago because of concern about adverse drug reactions.

Workshops will be conducted for health facility leads to disseminate the new treatment guidelines. Once the drugs are available, national implementation will be undertaken, with cascade training down to community level, including development of job aids.

Drugs are supplied through the Rwanda Medical Supply, a central facility for both the public and the private sectors. There is an active distribution plan from the central to the district level and a coordinated supply chain for managing drug stocks and avoiding stock outs.[3]

1.3.4 Sudan

Sudan's national malaria case management protocol was updated in 2023. AL is the first-line treatment for uncomplicated malaria, including for pregnant women during the first trimester. Second-line treatment is DHA-PPQ. Uncomplicated *P. vivax* malaria is treated with AL followed by PQ. The latest TES, conducted during the 2022–2023 transmission season, showed 100% efficacy of both AL and DHA-PPQ.

The NMCP works with the National Medicines and Poisons Board to ensure registration and quality control of antimalarials, and policies prohibit use of medicines that have been removed from the national treatment guidelines. Both the public and the private sector are required to adhere to the case management protocol, and there is continuous monitoring of antimalarial efficacy, training and supervision to promote adherence. Currently registered antimalarials in Sudan include AL, artesunate for injection, DHA-PPQ, quinine, PQ and SP. The NMCP, through the Global Fund, provides 100% of medicines for the public sector free of charge. About 30% of patients seek care in the private sector. Three local manufacturers produce first-line antimalarials, and one also produces artesunate injections.

2 National Malaria Elimination Programme, Ministry of Health, Nigeria (Personal Communication).

3 Malaria Division, Ministry of Health, Rwanda (Personal Communication).

Challenges in implementing malaria treatment policies include the ongoing conflict, which has disrupted TES implementation, allowed the spread of counterfeit medicines and resulted in a high turnover of trained care providers. Problems are also faced in adherence to protocols, the quality of diagnosis, policy enforcement and the capacity of the programme and the supply chain to provide new medicines promptly.[4]

1.3.5 Uganda

The national malaria treatment guidelines recommend that all suspected cases of malaria undergo parasitological testing with quality-assured diagnostics, either RDT or microscopy, and that positive cases be treated with ACT and be properly documented. RDTs are used at all levels of service delivery, although microscopy is the gold standard. The ACTs registered in Uganda are AL, ASAQ, DHA-PPQ and ASPY. Malaria treatment guidelines specify AL as the first-line treatment for uncomplicated malaria, ASAQ as an alternative first-line treatment and DHA-PPQ as second-line treatment. SMC is conducted in only one region.

The challenges include an increasing prevalence of non-falciparum malaria species and drug resistance and non-compliance with treatment guidelines, especially in the private sector. The priorities are to develop a strategy for managing antimalarial resistance, reducing malaria mortality through better case management and improving adherence to test-and-treat guidelines through training, external quality assurance and supply chain management.[5]

1.3.6 United Republic of Tanzania

The United Republic of Tanzania is working within the National Strategic Plan for 2020–2025; national treatment guidelines were updated in 2020. The definition of a malaria case now includes any person with confirmed infection, regardless of symptoms, particularly in low-transmission areas targeted for local elimination. RDTs are widely used, and microscopy is available at higher-level centres. If a patient does not respond to treatment within 3–14 days, follow-up testing is recommended.

AL is the first-line treatment for uncomplicated malaria, including for women in the first trimester of pregnancy. In low-transmission areas, a single low dose of PQ is recommended. DHA-PPQ and ASAQ are recommended as second-line treatment if there is no response to AL or if AL is contraindicated. In practice, however, DHA-PPQ is given as second-line treatment in the public sector. ASAQ is not on the national EML and is used mainly in the private sector, which is not covered by the co-payment system. TES showed reduced efficacy of AL in Pwani (89.9%) and evidence of day-3 slide positivity in some regions after use of AL or ASAQ.

A new formulation of AL is now available in the private sector, and introduction of ASPY in the private sector requires enhanced pharmacovigilance. Various preventive approaches are being explored, and DHA-PPQ is being procured for preventive use and focal mass drug administration.

Most cases of uncomplicated malaria are treated in the community. Operational issues include nationwide use of AL for uncomplicated malaria in the public and private sectors and challenges in maintaining supplies of alternative ACTs. The quality of care and adherence to protocols, with particular attention to potential drug resistance, are priorities.[6]

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4 National Malaria Control Programme, Ministry of Health, Sudan (Personal Communication).

5 National Malaria Control Programme, Ministry of Health, Uganda (Personal Communication).

6 National Malaria Control Programme, Ministry of Health, United Republic of Tanzania (Personal Communication).

1.3.7 Comments on the availability of ACTs in the public sector

- AL is the ACT used predominantly in Africa. Although some countries have registered other ACTs, they are used in the public sector sequentially as first- or second-line treatment, rather than as MFT. All the ACTs that are registered in a country could potentially be used as first-line therapy.
- Parasitological confirmation of a malaria diagnosis is crucial.
  - Tests based on plasmodium lactate dehydrogenase are preferable in areas in which *hrp2/3* deletions are prevalent.
  - Multiplex diagnostics for febrile conditions are being developed, which may improve differential diagnosis and rational prescribing of antimalarials.
- Second-line therapy should be available, with clear guidance and training. In the absence of documented patient follow-up or clear guidance, second-line drugs may be reserved and expire.
- A recurrence may not be a treatment failure and should be confirmed by microscopy. In areas of high transmission, such as much of sub-Saharan Africa, it is difficult to distinguish recurrences from treatment failure or reinfection.
- Delivery systems and contextual issues must be addressed for each country, including the involvement of the private sector.

1.4 Availability of antimalarials in the private sector

1.4.1 ACTwatch Lite – private sector survey (Benin and Cameroon)

The private sector plays a key role in malaria treatment in sub-Saharan Africa, and early engagement is essential to combat antimalarial drug resistance. The ACTwatch Lite project, funded by the Bill & Melinda Gates Foundation, collects data on malaria treatment and diagnostics from private sector sources to inform strategic decisions *(4)*.

In Benin, the private market for antimalarials has shifted significantly since 2016, with near disappearance of informal sector outlets. Non-ACTs have been largely replaced by ACTs, particularly AL (74%) and DHA-PPQ (10%), most of which are not prequalified by WHO. Pharmacies are the main distributors of antimalarials but provide minimal diagnostic testing.

In Cameroon, preliminary data showed a diverse market dominated by general retailers (in the informal private sector), and formal sector outlets such as for-profit facilities and pharmacies. 74% of private sector outlets had at least one antimalarial in stock on the day of the study, but only 33% had any test available. 6% of pharmacies were found to stock oral artemisinin monotherapy. The market share of antimalarials varied considerably by region, Litttoral (excluding Douala) showing a predominance of parenteral artemisinins (making up 17% of antimalarial volumes distributed in the previous week. ACTs were more commonly distributed through pharmacies and general retailers (representing 33% and 24% of all antimalarials distributed, respectively). AL was the most common treatment distributed in the private sector (62% overall), followed by DHA-PPQ (11%). In both Benin and Cameroon, diagnosis is evenly divided between microscopy and RDTs, most testing being done by for-profit facilities. About one third of private sector providers reported that they would recommend antimalarial treatment after a negative test for malaria.

The project will create a comprehensive toolkit for monitoring and improving malaria case management in the private sector, and the results and tools will be publicly available. Results are available for Benin and Cameroon, and a study is under way in Nigeria.

Comments

- The quality of care in the private sector should be improved, particularly for diagnostic testing, and coordination with the public sector is necessary for efficient deployment of MFT.
- Samples of antimalarials are not controlled for quality control, but this could be included if required.

1.4.2 Maisha Med – ACT consumption in the private sector

Maisha Meds, founded in Kenya in 2017, provides digital solutions to improve health-care operations and reporting in settings with low connectivity. Their software digitizes operations for pharmacies in several countries on over 1.5 million patient visits each month.

In Kenya, the private sector is estimated to account for 65% of ACT consumption, while, in Uganda, the proportion could exceed 50% or be as low as 30%. In the United Republic of Tanzania, Maisha Meds has estimated that the private sector accounts for 75% of ACT consumption, which is much higher than current estimates of 10–35%. This does not directly contradict previous research such as the district health surveys but highlights the difference in testing and presumptive treatment rates between the public and private sectors, that has been previously overlooked in commodity consumption estimates.

AL is the primary choice of ACT. Kenya and Uganda favour DHA-PPQ as the second option. In Uganda, use of injectable artesunate is about 9%. Patients in the United Republic of Tanzania are still given SP, while, in Nigeria, artemether monotherapy and AS-AQ are preferred. Non-prequalified AL and DHA-PPQ are widely used in all countries because of their lower prices, though there is evidence of an impact of the Global Fund co-payment mechanism in Uganda and, to a lesser extent, in the United Republic of Tanzania.

Overall, the analysis showed that the private sector in sub-Saharan Africa is significantly larger and less consistent with clinical guidelines than previously found by modelling. Estimates of ACT consumption vary widely, private sector consumption being 40–70%, which is far higher than the previous assumption of 10–15%. The quality of ACTs in the private sector is uncertain, and there is evidence both supporting and questioning their quality. Diagnostic testing rates are generally low in the private sector but could be improved with appropriate incentives.

Maisha Meds proposes to analyse antimalarial consumption in the private sector throughout sub-Saharan Africa to better understand uptake and quality, address the lack of funding and provide data on the role of the private sector in antimalarial resistance. They will create a comprehensive database, disseminate access to aggregate data, disseminate findings and validate their methods against existing data sources.

Comments

- Use of artesunate monotherapy for treatment of uncomplicated malaria in Uganda is a concern in view of the prevalence of *PfK13* mutations in the country.
- Data on the volume and nature of cross-border transactions should be made available, including for China, the Republic of Korea and Türkiye.
- Data on patient characteristics and the quality of antimalarial drugs in private health care outlets would allow better targeting for education and health-care provision.

2. Multiple first-line therapies

2.1 Evidence from mathematical modelling

2.1.1 Modeling – a tool in evaluating drug policies and antimalarial resistance containment strategies

Modelling can indicate the factors that drive selection for antimalarial resistance, predict the spread of resistance in the absence of containment and be used to evaluate policies for containing resistance. The outputs of antimalarial resistance modelling can be combined with commodity forecasts to determine the long-term demand for multiple ACTs to support country strategies. A key limitation is the contribution of the private sector to selection of antimalarial resistance. Further work is required to determine the impact of combining MFT with other strategies, such as single low-dose PQ or triple ACTs.

Preliminary results indicate that MFT (50% AL, 50% ASAQ) performs better than continuing to use AL alone in reducing the prevalence of partial resistance to artemisinin and consequently reducing treatment failure. A cycling strategy, such as switching between AL and ASAQ every 5 years or when the treatment failure rate reaches 10%, is also better than use of AL alone. MFT performs better than the cycling strategies, unless cycling is conducted every year, when the outcomes are similar *(5)*.

Inclusion of DHA-PPQ in MFT (equal use of AL, ASAQ and DHA-PPQ) reduces the impact of MFT and of cycling strategies because of rapid selection of PPQ resistance. In settings with very high treatment coverage, MFT with DHA-PPQ performs less well than continuing with AL because of the predicted rapid selection of parasites with PPQ resistance. As shown in Asia, resistance to antimalarials leads to higher rates of treatment failure with DHA-PPQ than with AL. If DHA-PPQ is used, continuous monitoring of drug efficacy, molecular surveillance and rapid cycling of ACTs in response to treatment failure are required.

Reducing presumptive treatment of non-malarial fevers with antimalarials by increasing diagnostic testing for malaria also reduces the impact of antimalarial resistance, particularly in higher transmission settings. This is because populations are more likely to have lower concentrations of partner drugs when they are reinfected, increasing the potential for resistance selection, whereas in low transmission settings the drug is probably eliminated before reinfection.

Modelling of specific settings should be conducted to determine the feasibility of different approaches, such as the speed of cycling that can be achieved and whether

MFT can be used spatially or targeted by age, clinic or by patient. Making no change to current practices is predicted to result in rapid acquisition of resistance and an increased treatment failure rate in most settings.

Comments

- Lack of a validated molecular marker for lumefantrine resistance is a limitation.
- It is unclear whether the selection and spread of resistance to PPQ in Africa will be similar to that seen in the GMS.
- Changes in policy in response to an increase in the treatment failures rate may not be rapid enough in practice to ensure effective cycling. Annual cycling would be difficult to implement, and a plan would be required to manage residual drug stocks.

2.1.2 Modelling – the use of multiple first lines therapies to treat malaria

The goal of MFT is to treat and cure as many people as possible without increasing the rate of selection of drug resistance *(6)*. Field trials are impractical for evaluating drug resistance containment strategies, and therefore mathematical models are used. The Boni Lab individual-based model includes real-world information, such as genotype-specific treatment failure rates based on TES data *(7)*, multi-clonal patterns of infection and age-specific incidence *(8)*. The model does not include gametocyte development, vector species and some vector behaviour, multi-compartment pharmacokinetics and progression of severe disease. Two outcome measures that can be monitored with the model are the total number of treatment failures after 5 years and the time until significant resistance thresholds are reached. TES and genotype data are important to guide treatment strategies.

Three main strategies are generally evaluated with this and similar models: combination therapy, MFT and cycling. Combination therapy with triple ACTs such as ALAQ is generally the most effective of the three approaches, although DHA-PPQ-mefloquine could be used in some contexts *(9)*. MFT is preferred to cycling because it delays and slows the evolution of resistance more effectively; however, all drugs used in an MFT approach must be highly effective *(10,11)*. Cycling is better than "doing nothing" but should be rapid (6, 12 or 24 months), depending on seasonality. MFT also appears to delay the emergence of double- and triple-resistant parasites better than 5-year cycling or adaptive cycling *(12)*, in which a therapy is changed once it is shown to be failing.

Implementation of MFT or cycling approaches requires careful consideration of factors such as drug efficacy, geographical distribution and rotation schedules. Analyses in Rwanda, Uganda and the United Republic of Tanzania *(13)* show the importance of timely policy changes and tailored approaches to various predicted outcomes according to the drugs used, their sequencing and the period of rotation. In the United Republic of Tanzania, an immediate switch to ASAQ is suggested, while in Rwanda and Uganda, MFT or cycling is possible, mainly with ASAQ. There is, however, considerable uncertainty about the outcomes after a switch to DHA-PPQ because of lack of data from Africa on how PPQ resistance will emerge and spread on the continent. Thus, use of PPQ should be accompanied by rapid molecular surveillance for markers of PPQ resistance.

The analyses also underline the risks of doing nothing, as most MFT or cycling strategies perform better than the status quo. Importantly, delaying action limits the effectiveness of the intervention in preventing resistance and leads to more treatment failures in the future. Overall, all the strategies evaluated in 2024 suggest that switching away from AL is the best way to reduce the treatment failure rate over the next 5 years.

In terms of implementation, numerous approaches or combinations of approaches are possible and can be modelled. For example, in Rwanda, stratifying drug use by district between AL and DHA-PPQ is predicted to be of limited effectiveness in preventing resistance, as most of the population does not move between districts often enough. Thus, rotation of first-line ACTs within each district is also required. Overall, modelling suggests that immediate action and precise implementation of MFT can improve malaria treatment outcomes and manage drug resistance effectively.

Comments

- As only certain regions of the United Republic of Tanzania were modelled, a model for the entire country is being developed to guide decisions on MFT implementation.
- Addition of ASPY was also modelled and was shown to be beneficial in deterring resistance.

2.2 Empirical evidence

The selection pressure exerted by multiple antimalarial drugs is complex. Selection for resistance is most effectively prevented when the number of drugs used increases and the time between exposures to different drugs is reduced. Combination therapies such as SP and ACT have been used, and triple ACTs are being evaluated. MFT and multi-drug combinations are commonly used in treating other infectious diseases such as tuberculosis, HIV infection and complex bacterial infections.

Suboptimal therapy or use of substandard drugs promote resistance by exposing parasites to non-lethal concentrations of the drug, thereby selecting parasites with reduced susceptibility to the drug. Drug resistance leads to treatment failure, and treatment failures allow transmission of resistant parasites.

Partial resistance to artemisinin has been detected in Africa. Where there is evidence of reduced susceptibility to lumefantrine, resistance to chloroquine and AQ has almost disappeared, with no evidence of PPQ or PY resistance. Certain mutations in drug transporters, such as *Pfmdr1* Y500N, are linked to reduced susceptibility to lumefantrine; however, there are no validated molecular markers for lumefantrine resistance. Notably, the resistance mechanism for AQ opposes that for lumefantrine. This can be observed in TES results for Uganda, where the relative efficacy of ASAQ over AL has improved over time.

Resistance monitoring involves testing for drug susceptibility in vitro, identifying polymorphisms associated with resistance, and TES. The associations between molecular, parasitological and clinical measures of resistance are not, however, as clear in Africa as in the GMS. TES in Africa have found an efficacy < 90% (adjusted by polymerase chain reaction) in Angola, Burkina Faso, the Democratic Republic of the Congo, Uganda and the United Republic of Tanzania, generally, however, not at sites with a high prevalence of *PfK13* mutations associated with partial resistance to artemisinin.. Furthermore, a number of methods were used for genotyping to define treatment outcomes, resulting in some uncertainty about the relevance and comparability of some of the findings.

Continued emergence and spread of partial resistance to artemisinin in Africa is difficult to predict, and the timeline for development of novel antimalarials is uncertain. Evidence indicates that, to delay the development of resistance, MFT and combining

AL and ASAQ as triple therapy should be used. The greater efficacy of ASAQ over AL, in view of their counteracting resistance mechanisms, strengthens the case for adopting these strategies. Questions remain, however, about whether ASAQ will be acceptable to patients and about the higher cost of alternative ACTs such as DHA-PPQ and ASPY.

Comment

- The risk:benefit ratio of SPAQ for SMC and its potential impact on AQ resistance should be considered when using ASAQ in MFT.

2.3 Multiple first-line therapies: definition, objectives and components

Aim

To reduce the emergence and spread of antimalarial drug resistance.

Rationale

To expose a specific parasite population to several antimalarial molecules to prevent or delay the emergence or spread of drug-resistant parasites.

Definition

MFT consists of use of two or more effective ACTs for treatment, either simultaneously or in rotation (cycling), of uncomplicated malaria

Context

- MFT must be a deliberate, managed intervention at all levels of the health system, including the private sector.
- In MFT, all the antimalarial drugs used must be effective. Therefore, treatment policies must ensure that drug resistance does not undermine the clinical efficacy of any of the drugs in MFT.

Deployment strategies

Simultaneous deployment: mathematical modelling suggests the minimum consumption of each drug for effective delay of selection for resistance:

- > 35% if two drugs are used,
- > 25% if three drugs are used and
- > 15% if four drugs are used.

Rotation is more effective in deterring resistance as the duration between rotated therapies decreases:

- a 1-year rotation is as effective as simultaneous use, while
- 2 years appears to be the maximum duration at which there is a significant benefit.

Potential methods

MFT can be delivered in several ways, depending on the national context:

- simultaneously: segmented, randomized or stratified by:
  - population, such as by age;
  - level of the health system; or
  - geographical region (usually with rotations); or
- by rotation, by:
  - time, such as annually or bi-annually;
  - population, such as by age;
  - level of the health system; or
  - geographical region.

Key concepts

- All MFT strategies used in Africa require a relative decrease in use of AL.
- Mechanisms of resistance to AL and ASAQ counteract each other, and use of both may inhibit development of resistance to either drug.
- The efficacy of lumefantrine must be preserved, as it is used in both the triple ACT ALAQ and in ganaplacide-lumefantrine, which will probably be the next new antimalarial products to become available.
- The consequences and costs of no or delayed action are likely to be significant in areas in which there is resistance, and proactive measures should be taken to prevent increased numbers of malaria cases, treatment failures, hospital admissions and deaths.

3. Implementation of multiple first-line therapies

3.1 Experience from other WHO programmes

3.1.1 WHO AWaRe

The WHO EML has been revised regularly for nearly 50 years and now includes 502 medicines. Appropriate use and accessibility are emphasized. Since 2017, antibiotics on the WHO EML have been classified into three groups, Access, Watch and Reserve (AWaRe), to promote appropriate use and to manage resistance. In 2021, the WHO EML contained 39 antibiotics in these groups. The AWaRe classification is used to optimize use of narrow-spectrum antibiotics, standardize treatment guidelines and improve antibiotic stewardship.

The availability and affordability of essential medicines are not sufficient: they must also be used appropriately. The AWaRe system can be used to monitor and improve antibiotic use, with the aim of ensuring that at least 60% of antibiotics used are in the

Access group. MFT with these antibiotics can be managed efficiently and is generally well received by countries. MFT is also used for other medicines, such as anti-hypertensives, analgesics and contraceptives.

The 2023 WHO EML and its supporting documents are available online (Annex 1). They provide guidance for implementation of the AWaRe strategy, including structured prioritization to facilitate its adoption and proper use.

3.1.2 MFT approaches

Integration and planning of MFT require consideration of health-seeking behaviour, the capacity of health systems to make the transition (people, product, facility and geographical reach) and financing for the transition to ensure its affordability and integration into national reimbursement and procurement mechanisms.

MFT approaches are already established for antivirals for coronavirus disease 2019 (COVID-19), reproductive health products and first-line tuberculosis combination therapy. Adaptation of these models requires information on incidence rates, population data and clinical guidelines, which are used in deciding on whether deployment will depend on the geographical location, patient profiles or disease incidence rates. Subregional population data, contraindications and drug resistance must also be evaluated.

Effective planning of the transition requires revision of the national EML and treatment guidelines, securing budgets, developing an allocation strategy and forecasting procurement and training, including plans for phasing medicines in and out. The logistics of stock delivery and phasing in and out must also be considered. Monitoring and evaluation must be initiated as early as possible, and flexibility must be ensured to adjust allocation strategies according to forecasts and to adjust procurement to avoid stockouts and oversupply. The process can take a minimum of 18 months.

Comments

- Personnel along the supply chain and health-care providers must be trained to ensure close alignment.
- Policies and practice should be aligned with the national EML, which may require both removal and addition of drugs.

3.2 Guidance for the effective implementation of multiple first-line therapies

Resistance to antimalarial drugs threatens the progress made against malaria in Africa. The emergence of partial resistance to artemisinin and ACT treatment failures in some areas are of concern. The WHO *Strategy to respond to antimalarial drug resistance in Africa (1)* stresses that new tools and innovative approaches should be used, including new ways of using currently available treatments.

Most countries are highly dependent on AL and therefore exert considerable drug pressure on and are vulnerable to any decrease in its therapeutic efficacy. Doing nothing is not an option. There must be a comprehensive response, and funding of MFT pilot studies and implementation in Africa by partner organizations is critical.

MFT consists not only of use of several ACTs but requires that those drugs be used optimally. MFT can improve the management of cases of uncomplicated malaria and efficient prescribing of antimalarial drugs. Local solutions should be developed to address contextual challenges to effective implementation, such as:

- private versus public sector dynamics;
- availability and affordability of drugs;
- preferences of health-care providers and patients;
- transmission dynamics, geography and seasonality;
- human displacement, cross-border movement and migration;
- health-care system structure and capacity;
- procurement system structure and capacity; and
- funding structures.

3.2.1 Country deployment

National policy and guidelines alignment: The national EML, treatment guidelines, NMCP policy and regulatory approval should be aligned. The time between policy changes and implementation, including procurement and training, should be minimized.

MFT strategy: The MFT strategy will depend on the country's context and the feasibility of approaches. Mathematical modelling could be used to evaluate the potential impact of different options. The strategy must ensure the effectiveness, accessibility, affordability and acceptability of antimalarial therapy. Additionally, it should:

- include specification of a different ACT for rescue therapy (second-line) for treatment failures;
- conform to patient preferences for access, convenience, price and adverse drug reactions;
- address preferences for inappropriate drugs (e.g. injectable artesunate for uncomplicated malaria); and
- be adjusted for SMC deployment to reduce the overall drug pressure of AQ, noting WHO's recommendation to avoid using ASAQ for treatment where SMC is conducted with SPAQ, for safety reasons .

Pilot studies and implementation plans: The aim of pilot studies to test MFT strategies in selected regions before broader implementation is to collect evidence for nationwide scaling up, provide a basis for implementation and for use in applications for further funding.

Cost and funding: Financial constraints and sustainable funding are recurring concerns, and strategies should be developed to reduce costs and secure resources for MFT. The entire cost of implementation, including capacity-building and training, should be estimated. It may be difficult to forecast demand; mathematical modelling can be used if sufficient data are available.

Procurement: Assurance is required that manufacturers can supply the required volumes of several ACTs, which are preferably WHO pre-qualified. Potential national or regional manufacture and approval should be explored. The quality of antimalarial drugs must be monitored to ensure their effectiveness, particularly for key products, if the volumes are known. ACTs must be affordable for both programmes and patients. Fortunately, funding partners are supportive of MFT and diversification of ACT use.

Capacity-building: Planning and pilot-testing can indicate areas in which the capacity of the health system requires strengthening for MFT implementation. Particular attention should be given to improving malaria case management, including in the private and informal sectors, by training health-care staff and ensuring effective supply systems and logistics.

Training: Health-care workers will require specific training, with appropriate materials. Training should encourage adherence to guidelines, reporting, monitoring and supervision. Training should be conducted throughout the supply chain to ensure alignment with the new guidelines and the expectations of health-care workers. The aim should be to strengthen malaria case management and particularly accurate diagnosis before treatment with effective antimalarial drugs.

Supply chain and logistics: Effective supply chain management is essential. Coordination of drug rotation and stock management are particular logistical challenges. Supply chain management could be digitized.

Social and behaviour change: Engagement of the community, including social and civil society and the peripheral health system, is necessary to prepare for introduction of new antimalarial treatments.

Efficacy and resistance: MFT requires that all the ACTs used are highly effective. TES and molecular marker surveillance should include all the drugs used in a country, and TES data should be stratified by genotype. Enhanced surveillance of molecular markers of drug resistance may be necessary.

Monitoring and evaluation: A robust monitoring and evaluation framework is essential to ensure that MFT results in a positive change with no unintended negative consequences. This may require extension and/or strengthening of existing systems for reporting and supervision of malaria case management. The aim is to ensure that objectives are met in terms of the quality of malaria case management and diversification of ACT prescribing, and to respond to changes in demand and supply.

Private sector involvement: The system through which ACTs are delivered influences their use and differs considerably, from highly centralized, regulated systems, such as in Rwanda, to a free market, such as in Nigeria. The contribution of the private sector to malaria case management and the extent to which it can be influenced by the NMCP varies by country. Where the private sector is substantial, it should be considered part of the plan for MFT. The private sector can be influenced by manipulating the price of drugs, such as through subsidies and co-payments, as well as through regulation. In some areas, however, the private sector, particularly informal providers, is a key source of access to ACTs, and regulation should not reduce access but should improve the quality of medicines, improve diagnostic testing rates and encourage adherence to guidelines.

4. Recommendations for future research

Mathematical modelling should be used to analyse data and to predict the outcomes of MFT interventions. More data are necessary to improve the models, particularly from the private sector.

- Investigate potential additive or synergistic effects of increasing diagnostic testing plus use of MFT and of use of a single low dose of primaquine plus use of MFT.
- Model the spatiality of malaria transmission.
- Quantify the cost of doing nothing with regards to the numbers of deaths and cases and the financial implications and cost-effectiveness of MFT.
- Evaluate the impact of SMC on the development of AQ resistance in MFT.
- Model the effect of changes in prescription of antimalarials in the private sector.
- Estimate the impact of incentivization of the private sector.
- The perception that ASAQ is associated with unacceptable adverse drug reactions differs considerably by country. An analysis of the reasons for these differences might be useful for determining how the acceptability of ASAQ could be improved and how adverse drug reactions could be mitigated.
- How can the public and private sectors be aligned in their approaches to MFT? Can lessons be learnt from programmes for HIV or tuberculosis?
- The requirement of health systems for effective use of MFTs include:
  - logistics: managing drug stocks, coordinating drug rotation and
  - investment to ensure an acceptable quality of care.

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Annex 1. Resources

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Annex 2. Implications for national policy and implementation of multiple first-line

Nigeria

All the ACTs proposed for MFT are on the national EML and in national treatment guidelines, and the TES showed a high rate of efficacy. Extensive use of AL and minimal use of ASAQ is, however, a concern. A pilot project is planned in two areas of moderate-to-high transmission, one in the north where SMC is implemented and one in the south with no SMC, in both of which there is significant engagement of the private sector in malaria case management. The drugs used in the states in which SMC is implemented are 20% AL, 40% DHA-PPQ and 40% ASPY, and those used in the other states are 10% ASAQ, 20% AL, 35% DHA-PPQ and 35% ASPY.

The plans include training and activities to change social norms and behaviour to ensure adherence to the protocol. Health-care workers are being trained to improve malaria case management in preparation for the introduction of the new medicines. monitoring and evaluation framework has been established, and TES and surveillance of molecular markers is continuing for the four drugs used. Civil society and community engagement are planned, including private sector involvement. The size of the country and the higher prices of DHA-PPQ and ASPY are nevertheless challenges, and the role of the private sector should be addressed further.

Rwanda

Rwanda plans to introduce an MFT strategy in 2024–2025 in the public and private sectors. The strategy involves use of AL, DHA-PPQ and ASPY in rotation in six pilot districts, covering all provinces. Each drug will be used in two districts at a time, and one first-line ACT will be available at all levels of the health system. Rotation will be annual to improve coordination and stock management, with a central medical supply site and district branches. Monthly data monitoring and notification of stock-outs by community providers have been established.

The planned activities include revising the national treatment guidelines, finalizing a plan for integrated malaria surveillance and MFT implementation, reviewing procurement plans and implementing MFT over 3 years. AL will be maintained for 3 years in districts that are not receiving MFT, where DHA-PPQ and ASPY will be used as a back-up if AL fails.

Cascade training will be provided before each rotation, and integrated surveillance will be conducted at sentinel sites. Rwanda's logistics and supply infrastructure, including the Zipline drone delivery service for urgent supplies, will ensure rotation of drugs without waste. The aim of the pilot project is to collect evidence for extension nationwide and for use in funding applications.

Sudan

Registration of new medicines, updating of guidelines and a national EML are established; however, supply, logistics and poor adherence to guidelines are weak, as are reporting systems, which complicates quantification of demand. Funding is limited, and prioritization and reallocation of resources are required to introduce another ACT.

Uganda

A rotation approach is being considered, which will require planning, costing, procurement, training and guideline development. Partners will have to be consulted for support. Rotation is feasible for supply chain management, but the adherence of the private sector to guidelines is uncertain. Revised TES protocols will be necessary to monitor the efficacy of all the ACTs used in MFT.

United Republic of Tanzania

AL is available, ASAQ is shortlisted for the national EML, but ASPY is not yet registered. Funding and the scope of implementation, whether national or subnational, remain to be confirmed.

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