Strategy to respond to antimalarial drug resistance in Africa

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### Abbreviations and acronyms

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<thead>
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<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
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<td>AL</td>
<td>Artemether-lumefantrine</td>
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<td>AMFm</td>
<td>Affordable Medicines Facility – malaria</td>
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<td>API</td>
<td>Active pharmaceutical ingredient</td>
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<td>ASAQ</td>
<td>Artesunate-amodiaquine</td>
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<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<td>DP</td>
<td>Dihydroartemisin-piperaquine</td>
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<td>GMS</td>
<td>Greater Mekong subregion</td>
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<tr>
<td>GFATM</td>
<td>The Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<td>GTS</td>
<td>Global Technical Strategy for malaria</td>
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<tr>
<td>HCW</td>
<td>Healthcare worker</td>
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<td>HRP</td>
<td>Histidine rich protein</td>
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<tr>
<td>IC</td>
<td>Inhibition concentration</td>
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<tr>
<td>IPTp</td>
<td>Intermittent preventive treatment of malaria in pregnancy</td>
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<td>IPTsc</td>
<td>Intermittent preventive treatment of malaria in school-aged children</td>
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<tr>
<td>IRS</td>
<td>Indoor residual spraying</td>
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<td>ITN</td>
<td>Insecticide treated nets</td>
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<td>MDA</td>
<td>Mass drug administration</td>
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<td>NMP</td>
<td>National malaria programme</td>
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<td>PCR</td>
<td>Polymerase chain reaction</td>
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<td>PDMC</td>
<td>Post-discharge malaria chemoprevention</td>
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<tr>
<td>PfKelch13</td>
<td><em>Plasmodium falciparum</em> Kelch 13</td>
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<td>pLDH</td>
<td><em>Plasmodium</em> lactate dehydrogenase</td>
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<td>PMC</td>
<td>Perennial malaria chemoprevention</td>
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<tr>
<td>QA/QC</td>
<td>quality assurance and quality control</td>
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<td>RSA</td>
<td>Ring stage assay</td>
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<tr>
<td>R&amp;D</td>
<td>Research &amp; development</td>
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<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
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<tr>
<td>SMC</td>
<td>Seasonal malaria chemoprevention</td>
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<tr>
<td>TES</td>
<td>Therapeutic efficacy study</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>TPP</td>
<td>Target product profile</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Executive summary

*This section will be written once the Strategy is finalized.*
Introduction

Purpose of the Strategy

The goal of the Strategy to respond to antimalarial drug resistance in Africa is to minimize the threat and impact of antimalarial drug resistance of Plasmodium falciparum in Africa.

The Strategy calls for three objectives that are instrumental to achieving the overarching goal:

- Improve the detection of resistance to ensure a timely response;
- Delay the emergence of resistance to artemisinin and ACT partner drugs;
- Limit the selection and the spread of resistant parasites where resistance has been confirmed.

Each strategic objective has been linked to the factors, relevant to the African context, that drive resistance. Addressing these drivers will have a direct impact on antimalarial drug resistance, as well as improve the overall quality of care.

Finally, the Strategy identifies practical interventions that should be implemented at global, regional, and country levels to address drivers of resistance.

Working definitions

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

Artemisinin partial resistance can be defined as delayed clearance of a parasite strain carrying a validated PfKelch13 mutation after treatment with a drug containing an artemisinin derivative. Delayed clearance alone does not lead to high ACT treatment failure rates. However, in combination with partner drug resistance, very high failure rates have been reported.

Detailed definitions of antimalarial drug resistance are provided in Annex I.

Structure of the Strategy

The Strategy to respond to antimalarial drug resistance in Africa is a technical and advocacy document. It provides guidance to different stakeholders at local, regional, and global levels. It consists of a core document, supplemented by six annexes with additional details.

The core document provides a comprehensive overview of the current situation of resistance in Africa, identifies key drivers of resistance and offers a detailed set of interventions to respond to the threat of resistance. Chapter 1 describes the context in which resistance is being considered. Chapter 2 analyses the current situation in Africa, listing the factors that call for immediate action. Chapter 3 looks at the elements that drive the emergence, selection, and subsequent spread of resistance. Chapter 4 lists recommended interventions to respond to resistance and provides guidance on how to conduct a baselining assessment at country level to select the most relevant interventions in each setting. Chapter 5 advocates for enabling mechanisms to be in place to facilitate the implementation of the interventions.
A total of six annexes provide additional technical content. Annex I includes a list of working definitions and technical background on resistance. Annex II guides countries in assessing their starting point in terms of resistance and of health system. Annex III details out the health and economic costs of inaction. Annex IV describes how interventions should be addressed at country, regional, and global levels. Annex V provides an overview of the existing evidence on the drivers of resistance in Africa. Annex VI describes the methodology and process that have led to the development of the Strategy.
1 Context

1.1 The malaria burden in Africa

Malaria is still a major public health problem worldwide. Nearly half of the world’s population is at risk of getting malaria, in 85 endemic countries. According to the 2021 World Health Organization (WHO) World malaria report, there were an estimated 241 million malaria cases and 627,000 deaths globally in 2020.

Africa bears almost the entire malaria burden – considering the WHO African region as well as the WHO Eastern Mediterranean countries on the African continent (Djibouti, Egypt, Libya, Morocco, Somalia, Sudan and Tunisia). In 2020, about 96% of malaria cases (232 million) were estimated to have happened in Africa. Five African countries with the highest estimated malaria burden accounted for more than half of the global malaria cases: Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%), Mozambique (4%) and Angola (3%). Africa also bears almost the entire burden of the global malaria deaths at 98% (612,000). *P. falciparum*, the deadliest malaria parasite, accounts for 99.7% of malaria cases in the WHO African Region.

Some population groups are more vulnerable as they have little or no immunity against the disease. These groups include children under five years old, pregnant women, people living with HIV/AIDS and populations with low immunity moving to areas with high transmission as travellers, migrant workers, and mobile populations. Children under five accounted for about 80% of all malaria deaths in the WHO African Region in 2020.

Over the last 20 years, significant efforts to tackle malaria have been made in Africa. Between 2000 and 2020, a 35% reduction in malaria incidence was achieved. Countries like Morocco and Algeria were certified malaria free in 2010 and 2019, respectively.

However, progress has stalled in recent years. Incidence increased in 2020, mainly because of disruptions to services during the COVID-19 pandemic. In addition, progress is made difficult due to new threats in Africa such as the emergence of artesiminin partial resistance, the spread of parasites with histidine-rich protein 2 and 3 gene (pfhrp2/3) deletions that goes undetected with the most widely used rapid diagnostic tests (RDTs), vector resistance to insecticides and reports in several countries of Anopheles stephensi, an urban malaria vector.

1.2 Artemisinin-based combination therapies at the heart of the response

An artemisinin-based combination therapy (ACT) consists of a combination of an artemisinin derivative and a partner drug. ACTs are recommended for the treatment of uncomplicated *P. falciparum* patients. The role of the artemisinin derivative is to reduce parasite biomass, while the role of the partner drug is to eliminate the remaining parasites. Even if used as a monotherapy, in the absence of resistance, a full dose of any partner drug used in the six WHO-recommended ACTs can clear parasitaemia and cure patients. Due to the very short half-life of the artemisinin derivative, the partner drug acts as a monotherapy, after the last dose of ACT has been administered. Consequently, ACTs differ from some other combination therapies and could be characterized as artemisinin-boosted antimalarials.
While WHO currently recommends six ACTs, the majority of patients is treated with either artemether-lumefantrine (AL) or artesunate-amodiaquine (ASAQ). AL is the most widely used treatment course, representing over 85% of ACTs procured by the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM), followed by ASAQ representing 10%3. Several factors explain this pre-eminence. AL was the first ACT to be developed. AL and ASAQ are the most affordable options, at $0.60 and $0.78 per adult course, respectively versus $2-3 for other ACTs4. AL is also the most accessible ACT; prequalified AL being produced by nine suppliers5 with significant production capacity.

2 The threat of antimalarial drug resistance in Africa

2.1 Artemisinin partial resistance in Africa

Significant reduction of treatment efficacy has not been observed in association with changes in *P. falciparum* sensitivity to artemisinin derivatives. So far, artemisinin partial resistance appears to only affect the *P. falciparum* ring stage, and to lead to delayed clearance of parasitaemia, which has been found to be associated with *PfKelch13* mutations. Consequently, after the three days of treatment a larger biomass remains, which must be eliminated by the partner medicine. In addition, a seven-day artesunate treatment showed over 90% efficacy even in areas of high prevalence of *Pfkelch13* mutations, suggesting that delayed clearance does not meet the standard definition of antimalarial drug resistance, and is therefore termed artemisinin partial resistance (see Annex I). There is no evidence that changes in sensitivity to artemisinin derivatives affect any asexual stage other than the ring stage and no evidence of artemisinin full resistance.

However, there are indications that *PfKelch13* mutations could facilitate the spread of artemisinin partial resistance. In the Greater Mekong, some strains carrying *PfKelch13* mutations have been shown to have an increased capability to generate gametocyte carriage, which could, if confirmed, significantly accelerate the spread of artemisinin partial resistance in Africa6.

Therapeutic efficacy studies (TES) remain the gold standard for determining antimalarial drug efficacy. In spite of their limitations, they provide decision-makers with an indication of efficacy for treating malaria in an at-risk group. To be comparable among countries and over time it is crucial to use standardized protocols. TES alone are not sufficient to confirm drug resistance. This must be confirmed through other means:

- **Molecular markers analyses (genotypic)** identify genetic changes in parasite genome that are associated with a change in parasite susceptibility or resistance to antimalarial drugs;
- **Ex vivo and in vitro assays (phenotypic)** test the sensitivity of fresh or culture-adapted parasites to antimalarial drugs by exposing them to different concentrations of a drug (typically for 48 or 72 hours) or to a pulse of a concentration of a drug (ring stage assay [RSA]) and observing the effect on parasite growth;
- **Measurements of drug levels in the blood** allow to monitor the concentration of drug that malaria parasites are exposed to and can help to distinguish whether a treatment failure is due to insufficient antimalarial drug exposure or resistance.

Evidence of the selection and spread of parasites with delayed clearance to artemisinin derivatives has been documented in several areas in Africa so far. Artemisinin partial resistance is confirmed in a site
when a quality-controlled study using an ACT or an artesunate monotherapy finds more than 5% of patients carrying PfKelch13 resistance-confirmed mutations and with delayed clearance as shown either by persistent parasitaemia detected by microscopy at 72 hours (± 2 hours, i.e., day 3) or a parasite clearance half-life greater than five hours. Currently, thirteen PfKelch13 mutations have been validated (i.e., significantly associated with delayed parasite clearance and reduced susceptibility using ring stage assay [RSA]) and ten are candidate markers (i.e., significantly associated with delayed parasite clearance or reduced susceptibility using RSA).

Areas with evidence of the selection and spread of parasites with delayed clearance to artemisinin derivatives:

- **Rwanda** – Two studies conducted by the national malaria programme between 2013 and 2015\(^8\) reported a clonal expansion of the PfKelch13 mutation R561H, and RSA confirmed that this mutation conferred reduced susceptibility to dihydroartemisinin. However, no evidence of delayed clearance or high treatment failure rates for AL or DP were reported. In a third study conducted in 2018\(^9\) with the support of US Centers for Disease Control and Prevention Atlanta, expansion of the PfKelch13 mutation R561H was confirmed, associated with delayed clearance but with continued efficacy of AL. Similarly, a fourth study reported a higher prevalence of the PfKelch13 mutation R561H (22%) also associated with delayed clearance and continued efficacy (> 94%)\(^10\).

- **Uganda** – Surveys in Uganda reported an elevated prevalence of the PfKelch13 mutations C469Y and A675V in multiple districts in northern Uganda\(^11\). More recently, isolates with C469Y and A675V mutations were associated with clinical delayed clearance in patients who were administered intravenous artesunate followed by an ACT. A675V and C469Y mutations were also associated with ex vivo and in vitro RSA reduced susceptibility.

- **Horn of Africa** – The R622I mutation has been reported in several countries in the Horn of Africa but evidence for any correlation with delayed parasite clearance has so far only been assessed in Eritrea in 2019. This mutation was shown to induce reduced susceptibility to artemisinin using RSA\(^2\).

Data are lacking from a number of countries and areas, meaning that artemisinin partial resistance may be present in other areas.

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\(^{2}\) Source: unpublished data from Eritrea NMP
2.2 Resistance to ACT partner drugs in Africa

There has been widespread resistance to antimalarials in the past in Africa. Indeed, the adoption and massive deployment of ACTs was driven by resistance to previously efficacious monotherapy treatments such as chloroquine, sulfadoxine-pyrimethamine and to a lesser extent amodiaquine.

Delayed clearance after a treatment with an ACT does not significantly lead to treatment failure in the absence of partner drug resistance. However, partner drug resistance can cause treatment failure. Published and unpublished data compiled in the WHO database allow for a deep analysis of the efficacy of the main ACTs. The conclusions of the analysis of more than 400 studies conducted between 2009 and 2019 are described in the following paragraphs:

- **Artesunate-amodiaquine:** Treatment failure rates greater than 10% after treatment with ASAQ have only been identified in two studies conducted in Liberia in 2017-2018. Additional studies have been initiated to gather further data.

- **Artemether-lumefantrine:** Treatment failure rates greater than 10% after treatment with AL were reported in several countries in Africa between 2009 and 2019. Recently, high treatment failures rates were reported in Burkina Faso, the Democratic Republic of the Congo, Uganda and Angola. Deviations from the WHO standard protocol mean that these results should be treated with caution. Analysis with a Bayesian algorithm is not recommended by WHO for reporting treatment outcome and can in high transmission settings yield higher treatment failure rates than by using the 2008 WHO standard methodology for Polymerase chain reaction (PCR) correction (updated in 2021). High failure rates were simultaneously reported for AL and dihydroartemisinin-piperaquine (DP) in Burkina Faso, in two sites in the Democratic Republic of the Congo and in two sites in Uganda. Concerns were raised about the quality of microscopy in Burkina Faso. Lumefantrine and piperaquine cross resistance is biologically improbable. If there is a signal for treatment failure for more than one drug with no biological explanation of the associated results, there should be close examination for the potential methodological confounding or failures.

- **Dihydroartemisinin-piperaquine:** Except for the studies in Burkina Faso, the Democratic Republic of the Congo and Uganda where treatment failures with DP were systematically associated with treatment failures with AL, high treatment failure rates after treatment with DP have not been reported in any other African countries.
• **Other ACT partner drugs:** Very few treatment failures have been reported after artesunate-pyronaridine or artesunate-mefloquine treatment in Africa.

There are contradictory findings that need to be further assessed for treatment failures associated with lumefantrine, the most commonly used partner drug

- TES have highlighted signals of high treatment failure rates, but sometimes studies deviated from WHO protocols.
- Many confounders of AL treatment failure are possible during a TES: poor drug absorption, non-adherence as the second daily dose is often unsupervised, and the short half-life of lumefantrine leads to higher reinfection rates, with some reinfections potentially misclassified as recrudescence during the monitoring period.
- Reports of AL treatment failures have been seen in travellers returning from Africa to the UK, Sweden and Portugal. However, information on lumefantrine blood levels was often unavailable and anecdotal failures in non-immune individuals do not prove the existence of drug resistance. In addition, AL treatment failures in travellers were successfully cured with a second treatment of AL in Turkey and Sri Lanka after treatment failure with a prior full treatment of AL.
- A few reports have shown increases in *in vitro* IC50s (i.e., mean drug concentration that inhibits 50% of the parasite’s growth) for lumefantrine, but trends are difficult to analyse, in part due to solubility limitations of the drug, and to no *in vitro* lumefantrine resistance threshold having been defined.
- High treatment failure rates for AL have not been reported in Lao PDR and Myanmar, where AL is the first-line therapy, despite high prevalence of artemisinin partial resistance.

2.3 The need for an African-wide strategy

*Given the heavy reliance on ACTs in Africa, the threat of artemisinin partial resistance and partner drug resistance must be addressed urgently.* All the more so since artemisinin partial resistance is putting additional pressure on partner drugs. The apparent rapid spread of some mutations means that vigorous measures must be taken before ACTs start failing in Africa.

*There is an urgent need to preserve the therapeutic lifespan of current ACTs, given the current drug pipeline outlook.* It is unlikely that drugs with a different mechanism of action will become available any time soon with the most promising non-artemisinin combination, ganaplace-lumefantrine, in patient exploratory phase (Phase 2b). Although such a formulation would address a situation of artemisinin partial and full resistance, its reliance on lumefantrine would pose a risk should resistance to that partner drug be confirmed, and millions of dollars of investments would be at stake.

*ACT treatment failure due to resistance could result in an increased number of cases, leading to additional severe cases and ultimately excess deaths.* Across Africa, preliminary estimates show that widespread artemisinin partial resistance (scenario in which there is artemisinin partial resistance for 50% of cases) and partner drug resistance (scenario in which 25% of ACTs are failing) could result in an additional 78 million cases over a 5-year period, a 7% increase in cases compared to a scenario with no resistance. Such a scenario could result in an estimated US$5.9 billion additional costs over a 5-year period across...
Africa, including direct health costs (e.g., additional diagnostic tests and treatments, additional costs for inpatient care due to excess severe malaria cases, costs of introduction of new first-line treatment) and productivity losses (absenteeism at the workplace due to disease burden or the need to care for a sick child). These are conservative estimates, since they do not account for costs such as the years of productive life lost due to premature deaths, the impact on economic growth, the long-term effects on children linked to education disruptions. It is likely that most vulnerable groups, such as women, children, poor, mobile, and rural populations would be disproportionately affected, further widening the inequality gap.

The **Strategy to respond to antimalarial drug resistance in Africa** builds on lessons learnt from past global plans and complements existing strategies. These include the Global plan for artemisinin resistance containment, as well as the Strategy for malaria elimination in the Greater Mekong subregion (2015-2030), that highlight the need for adequate surveillance, a strong regional collaboration, an involvement of a large panel of stakeholders including communities and sustained financing. The Strategy also takes part in a broader effort to respond to antimicrobial resistance. Strategic objectives outlined by the Global action plan on antimicrobial resistance were leveraged in the development of the Strategy, for instance the need to improve awareness and understanding of antimicrobial resistance through effective communication, education, and training. In line with this approach, effectively responding to resistance should include targeting the community level, raising awareness, and improving overall knowledge around malaria care, the risk of treatment failure and resistance. Finally, the Strategy uses key elements of the High Burden to High Impact approach, a country-led response, catalysed by WHO and the Roll Back Malaria Partnership, in which eleven African countries actively participate, in addition to India.

**Figure 2 – High-level learnings from the response to resistance in the Greater Mekong subregion (GMS)**

- **Adequate surveillance**: Surveillance has been a top priority, from increasing surveillance on resistance (e.g., TES) to strengthening overall malaria surveillance on drug quality, number of cases and deaths. Various tools have been leveraged from enabling collection of real time data (PSI GEMS) to implementation of a regional Malaria Elimination Database.

- **Regional collaboration**: A coordinated response towards the fight against malaria have been encouraged between countries through for example regional grant and sharing best practices and strategies.

- **Large stakeholders panel involvement**: Coordination between a large panel of stakeholders have been promoted: funders, multilateral agencies, technical partners, academicians and researchers, private sector, governments, communities (e.g., through advocacy meeting - RAI regional Steering Committee) have been enrolled in the strategy.

- **Community involvement**: Building community malaria networks, by leveraging village and mobile malaria workers (i.e., VMW, MMW) has been crucial in implementing the strategy and reaching populations at risk of resistance.

- **Financing**: Well-funded approach is key to finance broad and innovative interventions such as intensive training and procurement of commodities, to foster coordination between countries, to fund operational research, etc.

**This strategy should not divert resources from other malaria goals.** There shouldn’t be a trade-off between addressing antimalarial drug resistance and the need to ensure access to malaria prevention, diagnosis, and treatment as part of universal health coverage; the acceleration effort towards elimination and attainment of malaria-free status; and the transformation of overall malaria surveillance into a key intervention, as laid out in the strategic framework of the Global technical strategy for malaria (2016-)

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b Burkina Faso, Cameroon, Democratic Republic of the Congo, Ghana, Mali, Mozambique, Niger, Nigeria, Uganda, United Republic of Tanzania and Sudan since April 2022.
This strategy further builds on priorities highlighted in the GTS such as the need to protect the efficacy of ACTs and developing new non-artemisinin-based combinations.

3 Drivers of resistance

3.2 Overview of drivers of resistance

Effectively responding to the threat of resistance requires understanding the factors that can play a role in driving the emergence and spread of resistance. The emergence of drug-resistant parasites happens in two stages: first, the initial random genetic event that makes a parasite less sensitive to a drug, and second, the survival, selection, and subsequent spread of the parasites carrying the mutation providing some degree of protection from the effect of a drug. A range of factors ranging from patterns of drug use to transmission levels affects the likelihood that a mutation spreads.

What role the different factors will have in driving the emergence, selection, and spread of resistance will vary by drug and context. There is a good understanding of what factors may drive emergence and spread of resistance, but knowledge of their relative importance is limited by lack of available data and evidence.

Despite these caveats, a broad literature review and consultation process led to the identification of two categories of factors driving resistance: background drivers and treatment-related drivers. The background drivers include the environmental factors as well as intrinsic factors linked to the parasite, the host, and the drugs used. The treatment-related drivers are those affecting how often, at what doses and length of time a parasite population is exposed to a given drug.

This strategy focuses on identifying practical interventions to address the treatment-related drivers of resistance. A country assessment is needed to enable each country to focus on the factors that are most likely to drive the emergence and spread of resistance in their context; this initial assessment should enable countries to prioritize their efforts in responding to resistance (Annex II).

3.3 Background and intrinsic drivers of resistance

Parasite genetic background can influence the degree to which drug sensitivity is affected by a mutation as well as the likelihood that this mutation spread. Certain genetic background or additional mutations can improve resistant parasites’ ability to compete with other parasites even in the absence of drug pressure. Consequently, the effect and potential for spread of a mutation can differ in a specific African parasite strain from what has been observed in the Greater Mekong subregion.

The level of transmission impacts the risk of spread; high levels of resistance have first been observed in lower transmission areas. Higher transmission increases the risk that any beneficial background mutation is lost and increases the competition with other parasites strains. Additionally, a larger proportion of populations living permanently in higher transmission areas has some level of acquired immunity. Higher level of acquired immunity means that the host is better able to eliminate the parasite regardless of drug resistance.
A range of additional factors specific to a setting affects the emergence and spread of resistance. These factors include migration from areas with resistance as well as the ability of local mosquitoes to spread the resistance strain.

3.4 Treatment-related drivers of resistance

Drug pressure drives the selection and spread of resistant parasites. Malaria parasites are exposed to different antimalarials intended to save patients by eliminating the parasites and preventing their spread. However, continuous exposure to a drug, defined as drug pressure, can select parasites with reduced susceptibility to the drug in subsequent administrations. Drug pressure depends on the proportion of overall malaria infections that are treated, and the rate at which people use antimalarials.

Pressure on a parasite population from one drug only, increases the risk of selection and spread of parasites resistant to this drug. Where a parasite population is mainly exposed to one drug, the competitive advantage of having resistance to this drug and the risk of selection increases. In the past, the recommended treatment for uncomplicated *P. falciparum* was monotherapies such as chloroquine and sulfadoxine-pyrimethamine. Resistance to these drugs spread globally, reaching very high levels. The current recommended treatment is an ACT combining an artemisinin component and a partner drug. However, this recommendation is sometimes not followed, meaning that some patients are still treated with monotherapies. Furthermore, while the ACT is a combination of two drugs, the partner drug is alone in the blood for an extended period of time.

Exposing parasites to a sub-therapeutic drug level is thought to be an important selective force in the spread of resistance. A sub-therapeutic drug concentration in the blood prevents new drug-sensitive infections but allows resistant infections to be maintained and transmitted. Parasites’ exposure to sub-therapeutic drug concentration can be caused by a variety of factors including substandard or falsified drugs (SF), the use of non-pharmaceutical forms of *Artemisia* such as *Artemisia* tea, incomplete treatment, or suboptimal dosing of antimalarial drug.

Resistance can spread when parasites with reduced drug sensitivity are significantly more likely to be transmitted. This can happen when parasites with reduced drug sensitivity cause recrudescence and are transmitted, or when parasites with reduced drug sensitivity have increased gametocyte carriage.

Exposing parasites to drugs to which they are not fully sensitive, allows the parasites to multiply and be transmitted. Delays in detecting resistance or changing treatment policy permits the resistant parasites to spread and reach high levels of prevalence.
Figure 3 – Driver tree of resistance

Background & intrinsic drivers

Parasite factors
- Intrinsic frequency with which the genetic changes occur and co-occur with other genetic changes (e.g., HRP2 S deletion)
- Degree of resistance conferred by the genetic change
- Fitness cost of the resistance mechanism
- Complexity of mutations (monogenic or complex genetic traits)
- Risk of losing supporting genetic background during crossover event
- Risk of resistant parasites being outcompeted depending on transmission intensity

Host and drug-related factors
- Level of immunity (e.g., low levels increasing the competitive advantage of resistant parasites)
- Patient genetic factors (e.g., poor metabolism)
- Drug properties (e.g., half-life, gametocidal component)

Environmental factors
- Importation risk due to migration patterns and mobility from neighboring areas of population carrying resistant parasites
- Degree to which local vectors can transmit resistant parasites
- Degree to which specific species (transmitting resistant parasites) are sensitive to the existing vector control

Transmission intensity

Treatment-related drivers

High number & proportion of parasites exposed to a drug
- Broad use of antimalarials for non-confirmed cases
- Failure to limit transmission with means other than antimalarial drugs
- Patterns of drug use / frequency of exposure
- Low level of immunity

Parasites exposed to one drug only
- Reliance on a few ACT treatments

Parasites exposed to subtherapeutic levels of a drug
- Substandard and falsified drug
- Broad use of non-pharmacological forms of Artemisinin
- Incomplete treatment (provider-related drivers)
- Inadequate treatment (provider-related drivers)
- Individuals with low drug blood levels infected with malaria
- Patient factors affecting blood levels (e.g., age, pregnancy, pharmacogenomics)

Parasites not fully sensitive more likely to be transmitted
- Recrudescence cases transmit malaria
- Increased gametocyte carriage of resistant infections

Parasites exposed to drug to which they are not fully sensitive
- Repeated treatment following treatment failure
- Lack of information on efficacy and resistance to inform treatment
- Impediments to implementing drug policy changes following treatment failures >20%
4 Interventions to mitigate the risks and respond to the emergence and spread of antimalarial drug resistance in Africa

This regional strategy addresses the threat of antimalarial drug resistance in Africa through four pillars:

I. Strengthen the surveillance of antimalarial drug efficacy and resistance.
II. Optimise and better regulate the use of diagnostics and therapeutics to limit drug pressure.
III. React to resistance by limiting the spread of antimalarial drug resistant parasites.
IV. Stimulate research and innovation to better leverage existing tools and to develop new ones against resistance.

Each pillar consists of a set of interventions that can be implemented at local, regional, and global levels. The relevance of each intervention to the drivers of resistance was assessed through a broad consultation process. Additionally, the interventions outlined in this strategy are informed by interventions already being deployed at global, regional, or local levels.

Although this strategy is applicable to the wider population of Africa, there is no one-size-fits-all recipe for success. While this document gives a comprehensive overview of the interventions that could be leveraged, the outcome of an intervention will vary depending on the implementation setting.

An initial country assessment is required to prioritize interventions and estimate the levels of resource mobilization and change required to implement this strategy for a given setting. For this strategy to be effectively implemented by each country and efficiently supported by regional and global stakeholders, the assessment should consist of:

(i) A country’s baseline with respect to the status and drivers of resistance
(ii) Available capabilities as well as the bottlenecks that have hindered the effective implementation and sustainability of interventions in the past.

Key enabling mechanisms will be needed at all levels to ensure feasible, impactful, and sustainable implementation of each activity. They are further detailed in Chapter 5.
4.1 Preliminary assessment to prioritize interventions

The assessment of the elements described below should be the first step of the implementation of the Strategy. Further details are provided in Annex II.

(i) Defining a country’s baseline with respect to the status of resistance and the underlying drivers of resistance

The relevance of each intervention will vary depending on the implementation setting. The initial assessment should identify areas and drivers of resistance that need to be addressed. The assessment is based on the following four building blocks:

- **Status of antimalarial drug efficacy and resistance and data availability**: A review of efficacy and resistance data in the target country as well as neighbouring countries is the starting point for this assessment. Identifying areas and populations with no recent data will inform the need for further studies.

- **Understanding of how diagnostics, drugs, and vector control interventions are being used**: The overuse and misuse of drugs can drive resistance. Analysing access, current behavioural drivers behind both patient and care provider choices, and patterns of drug and diagnostic use is required to design interventions to address these issues. The sub-optimal coverage and use of effective vector control interventions increases the reliance on pharmaceutical measures; identifying and addressing gaps in coverage can help reduce drug pressure.

- **Identification of areas and populations where the risk of resistance developing and spreading is high**: Additional resources and efforts should be mobilized towards underserved areas and hard-to-reach populations. In other parts of the world, resistance has been seen to first develop in areas with large populations using poor quality drugs without quality malaria diagnosis, and with no or
inadequate coverage of vector control interventions or other prevention measures. The risk linked to different areas and groups should be assessed and is likely to differ by population, country, and region.

(ii) Assessing capabilities and bottlenecks

The feasibility and impact of each intervention will depend on the capabilities and resources available in each country, such as the amount of funding and human resources available, and on the capacity of each country to identify potential roadblocks, leverage past success and existing opportunities and implement change.

The analysis of the strengths and bottlenecks should be based on past and ongoing experience in implementing malaria interventions. Elements that need careful assessment include, but are not limited to the following:

- **The maturity of the health and regulatory systems**: assess the health system structure and the institutional capacity to enforce national policies as it will play a key role in defining the feasibility and impact of each intervention.
- **The gap between the plans developed by the NMPs and their effective implementation**: identify the bottlenecks that have hindered past or ongoing implementation of interventions to fight malaria (e.g., obstacles to the withdrawal of monotherapies).
- **The synergies with other strategies and global plans**: identify interventions already being deployed within the framework of other strategies such as the Global action plan on antimicrobial resistance that could benefit and be further leveraged to respond to antimalarial drug resistance (e.g., raising awareness, training)

4.2 Actionable interventions to address key drivers of resistance

The following section provides more details on each pillar. Although most of the interventions could be deployed widely, in light of the threat of resistance, increased efforts should be focused in areas and for populations that are deemed at higher risk of developing resistance. Once specific groups have been identified, additional funding and resources should be dedicated to reaching them.
4.2.1 Pillar I: Strengthen the surveillance of antimalarial drug efficacy and resistance

Our ability to respond appropriately and timely to the spread of artemisinin partial resistance and the potential emergence of resistance to partner medicines is hindered by the lack of available information. Information is gathered through efficacy studies, genotyping to evaluate the prevalence of molecular markers of drug resistance, and additional tools such as in vitro testing and blood level measurement to confirm resistance. However, these efforts are limited by many factors: insufficient capacity, lack of funding, limited political commitment and will, non-compliance with standards and protocols to ensure comparable quality data, lack of planning to ensure that data is available from the areas where it is most needed, and sometimes years of delay between data collection and sharing back findings with relevant stakeholders.

This pillar calls for a strengthening of surveillance capacity of antimalarial drug efficacy and resistance in Africa, building upon the significant investments already made on regional and country networks, to detect unexpected adverse events and reduced efficacy and to inform national treatment guidelines. Four key interventions to address these challenges have been identified. They have country, regional, and global components and will need to be prioritized based on the assessment of current local drug efficacy and resistance situation, data, and resource availability.

**Underlying issue**

There is a lack of available, good quality data on antimalarial drug efficacy and resistance in Africa. The limited quality and standardization of collected data hinders the effectiveness of the surveillance and of the response towards resistance. For example, TES are sometimes not conducted according to WHO standard protocols\(^1,36\), which has resulted in the need to repeat studies in the past. In addition, there is an insufficient capacity to conduct genetic and pharmacokinetic studies (i.e., measuring the drug levels in the blood during TES). The establishment of a strong resistance surveillance network in Africa faces several challenges such as the need to build an efficient quality control system to attest the reliability of the studies, the lack of human resources, as well as bottlenecks in terms of procurement. To date, it is often more expensive and time-consuming to conduct the studies directly in the continent rather than abroad.

**Suggested intervention**

**Promote adherence to standard TES protocols** – Production of standardised, comparable quality data requires adherence to WHO standard TES protocols. To conduct quality TES, Ministries of Health and research institutes must be supported through continual training, including for microscopists. A supervision and quality control system around microscopy, data entry and classification should be established to ensure that WHO protocols are followed. The analysis of known molecular markers of antimalarial drug resistance should be systematically included in the TES protocols.

**Set up or reinforce surveillance laboratories networks for genomic and pharmacokinetic studies** – Current investments to build a strong genomic expertise in Africa through knowledge sharing and dedicated training programmes should be pursued, building on the initiatives funded by the Bill & Melinda Gates Foundation (BMGF) and others. Additional investments and increased capacity building are needed to conduct drug levels studies, especially for lumefantrine in Africa. These networks could be built at...
national or regional level. At regional level, the establishment and strengthening of regional reference centres, in line with the experience gained during the COVID-19 pandemic, should be considered. This would increase capacity, quality and timeliness of PCR correction and molecular markers surveillance, ex-vivo drug susceptibility testing and measurement of drug levels in blood. Such centres should have the laboratory and analytic capacity needed to conduct national scale analysis for countries lacking internal capacity. These regional centres of reference could also act as potential training centres for neighbouring countries.

Establish a quality control system among these laboratories networks – Genetic, phenotypic, and pharmacokinetic data need to be standardised and of high quality. Strong quality control systems among laboratories are needed to prevent problems observed in the past such as contaminated samples. The regional reference centres should be equipped to check the quality of analyses conducted elsewhere (i.e., samples collected in a laboratory could be assayed in another laboratory).

Address procurement challenges – An increased effort and additional financing is needed to address procurement challenges linked to the establishment of an efficient surveillance system. Global and regional stakeholders should investigate ways to reduce delays in supplying surveillance commodities such as primers or consumables, and to improve the affordability of African-sourced supplies.

Pillar I – Intervention 2 | Increase coverage of surveillance systems on efficacy and resistance

Underlying issue

Knowledge on delayed clearance of parasites following an ACT treatment and on ACT treatment failures is limited by the currently insufficient coverage of TES. According to the WHO Malaria Threat Map, 18 endemic African countries have not conducted or shared TES results since 2017\textsuperscript{37}. The number and coverage of sentinel sites is constrained by limited funding and political attention, and by the lack of studies in hard-to-reach communities and low transmission areas. In addition, information on molecular markers plays an important role in tracking resistance and should be leveraged to detect early warning signals. When high treatment failures are detected in a good quality study, additional studies are rapidly needed, including the collection of information on drug levels in the TES protocol on day 7\textsuperscript{38}. These pharmacokinetics studies should be done especially for lumefantrine due to the pharmacokinetic profile of the drug.

Suggested intervention

Increase the number of sites per country and the frequency of TES conducted – The current recommendation is to conduct TES at least every two years at each site for first- and second-line drugs. Although no definitive scientific advice can be given about the number of sites needed, experience suggests that four to eight sites per country will achieve a balance between representativeness and practicality. In defining the number of sites, programme managers should consider geographical size, population distribution and density, malaria epidemiology or ecology and other factors deemed important to the programme. It is critical to select a ‘manageable’ number of sites to ensure proper monitoring and supervision\textsuperscript{39}. Based on the number and location of existing sites, countries should look at intensifying surveillance activities in areas where data is lacking or where the risk of resistance is considered high, for instance areas with influx of migrants from areas with known resistance.

Collect information on molecular markers – Surveys of molecular markers should be increased as they can be conducted more easily and frequently than TES. Although there is a lack of confirmed molecular marker of resistance for the partner drugs used in Africa, available molecular markers should be leveraged as early warning signal tools to track the spread of resistance.
Pillar I – Intervention 3 | Increase detailed data collection on resistance from select sites

Underlying issue

The collection of standard TES data (i.e., the evidence of treatment failure) is not always sufficient to confirm resistance. Identifying molecular markers will require establishing a correlation between clinical, in vitro and genetic evidence. This calls for increased detailed TES data with supervised treatment in selected sites (in vivo, in vitro and pharmacokinetic studies) with good longitudinal data over time.

Suggested intervention

Collect additional data from select sites. Such an increase in the depth of resistance surveillance should be considered preferably in sites where an academic institution can support its development. These sites should be leveraged to collect consistent and more detailed data over time. At these sites, additional resources and capacity should be dedicated to performing a broad spectrum of tests, for instance TES, molecular markers, in-vitro resistance studies (i.e., phenotyping assays), drug levels in the blood, and monitor trends, for instance of drug efficacy or treatment failure rates.

Pillar I – Intervention 4 | Improve data dissemination systems to facilitate reactive and coordinated response to resistance data

Underlying issue

A reactive and coordinated response requires consistent and timely sharing of information within and among countries. However, data is not systematically made available to NMPs, and sometimes years of delay occur between data collection and results being published and made available to the NMPs. Different networks have been built to facilitate data sharing, but their sustainability needs to be ensured.

Suggested intervention

Re-establish or strengthen subregional networks of antimalarial resistance and efficacy surveillance to facilitate transparent communication of data on drug efficacy and resistance. Within these networks, the processes, roles and responsibilities should be clearly defined to establish an effective and systematic communication for alerts, such as suspicion of artemisinin partial resistance or partner drug resistance. To ensure coordination and sustainability, the networks could leverage WHO’s experience as secretariat for similar networks, such as the Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT)40 or the Greater Mekong subregion therapeutic efficacy studies network41.

Feed a worldwide data repository – Data on antimalarial drug efficacy and resistance should be collected in a single repository to enable visibility and accessibility to resistance trends worldwide. To that effect, country, regional and subregional networks should more systematically share data with WHO to feed the Malaria Threat Map. The database already consolidates data on parasite drug efficacy and resistance in addition to data on insecticide resistance in malaria vectors, parasite Pfhrp2/3 gene deletions, and invasive vector species. Currently, data are submitted by Member States, academia, research institutions and WHO partners or are extracted from scientific publications.

Leverage in-country working groups – At country-level, NMPs should leverage existing working groups or build dedicated ones to disseminate data and ensure reactive measures are taken in response to resistance data. The working groups should include a diversified panel of stakeholders, such as researchers, academics, care providers and representatives of the Ministry of Health, with the breadth of their scope defined by each country.
Pillar II: Optimise and better regulate the use of diagnostics and therapeutics to limit drug pressure

Protecting the efficacy of existing ACTs is an immediate priority. The suboptimal use of existing diagnostics and therapeutics increases drug pressure on the parasite population. From a supply perspective, factors such as the inability to enforce stringent regulatory standards, the lack of availability of a diversified portfolio of drugs at country-level, the prevalence of substandard or falsified drugs and the circulation of non-recommended monotherapies all increase drug pressure unnecessarily. From a demand perspective, the inappropriate use of antimalarial drugs due to inadequate provider or patient behaviour can further contribute to the emergence and spread of antimalarial drug resistance.

This pillar calls for a more deliberate use of diagnostics and antimalarials to reduce drug pressure. Additionally, the global malaria community should use its combined market-shaping power to achieve healthier malaria commodity markets, while being mindful of trade-offs between key market dimensions such as availability, affordability, quality, and innovation. Seven interventions to address these challenges have been identified. The prioritization of these interventions should be based on each country’s baseline assessment in terms of treatment policy and enforcement capacity, access, availability and use of diagnostics and drugs, and of the current behavioural drivers behind care provider and patient choices.

Pillar II – Intervention 1 | Develop national treatment policies that promote deliberate use of existing treatments to prevent the emergence and the spread of resistance

**Underlying issue**

National treatment guidelines in Africa don’t systematically recommend an ACT for both first- and second-line treatment of uncomplicated *P. falciparum* cases. When countries do not include a different ACT as second-line treatment in their guidelines, patients with recrudescence will be treated with the same drug again. The continued use of failing ACTs can exert a strong selective pressure on malaria parasites increasing the risk of transmitting parasites that have reduced drug sensitivity.

Additionally, although the private sector is often the first place that many patients go to seek treatment for febrile illness, it is poorly regulated and unsupervised which leads to non-compliance with national policies and guidelines. There is often no clear guidance or policies to support collaboration between the public sector and private medicine retailers’ outlets (PMR)\(^42\).

**Suggested intervention**

All national treatment policies should include ACTs for both the first- and second-line treatment for uncomplicated *P. falciparum* cases. In a given country, there should be no use or limited use of drugs that are recommended as first- or second-line treatment for mass drug administration or chemoprevention. Additionally, regional patterns of resistance and drug use should be considered when developing a national treatment policy. Where possible (e.g., in presence of a well-structured private formal sector), national policies should be disseminated and promoted to non-public providers as well.

NMPs should develop and regularly update detailed national treatment guidelines that take into account the latest evidence on local antimalarial drug efficacy and resistance patterns and health system capacities, as recommended by the GTS. For new ACTs to be introduced into national policies, they should have over 95% efficacy demonstrated through therapeutic efficacy monitoring in local sites. For ACTs already recommended in the guidelines, a significantly declining trend in treatment efficacy over time, even if failure rates have not yet reached the 10% cut-off as per the WHO Guidelines for malaria\(^43\), should alert...
programmes to undertake more frequent monitoring and to prepare for a potential policy change. To that effect, and in line with the GTS recommendations, countries should plan for a rapid treatment policy change, to switch to another ACT. Once it has been confirmed that the failure rate is over 10% using the WHO protocol, the treatment policy change should be implemented to ensure patients receive an efficacious treatment and prevent further spread or increase of any resistance.

Country policies and regulations should be reviewed and revised to support and promote the implementation of appropriate case management in the private sector. For instance, there should be clarity and consistency of policies and regulations on where antimalarials can be accessed and who can prescribe and/or sell them, taking into account patient care-seeking practices. Policy makers and regulators should also be aligned on the technical specifications required for health products (diagnostics and medicines).

Pillar II – Intervention 2 | Promote the availability of a diversified drug portfolio in countries

Underlying issue

The diversity of antimalarial drugs available globally is not necessarily reflected in the drugs available within countries in Africa. The higher costs of ACTs other than AL and ASAQ and the logistics challenges of managing a second-line treatment result in a lack of demand for these alternative treatments. This lack of demand is illustrated by the limited number of suppliers for alternative prequalified ACTs to AL and ASAQ. To date, there is only one single supplier producing prequalified artesunate-pyronaridine, as well as one producing prequalified artesunate-mefloquine. Prequalified dihydroartemisinin-piperaquine is produced by only two manufacturers. This lack of manufacturers increases the high vulnerability of countries should resistance to other partner drugs such as lumefantrine or amodiaquine be confirmed. In addition to the limited production, bottlenecks along the supply chains lead to challenges such as stock outs, a major obstacle in the roll-out of quality treatments on the continent. Poor country preparedness to rapidly introduce new drugs can impede a prompt and efficient response towards ACTs’ loss of efficacy.

Suggested intervention

A diversified drug portfolio and production capacity are needed to limit the reliance on a few drugs and manufacturers, in order to ensure availability of second-line treatments for both specific few needs but also in case countries need to rapidly shift to another ACT.

Registration – Beyond continued research into new treatments, it is important to ensure that drugs currently available globally are also available in country when needed. An important step towards building a diversified portfolio in country is the promotion of ACT registration by national regulatory authorities. Countries should streamline their internal processes, for instance by creating expedited registration pathways for products that are already prequalified by WHO, to cut time to marketing authorization.

Production capacity – For the most used treatments, AL and ASAQ, production capacity is geographically consolidated far from where they are consumed, creating inefficiencies that can compromise the timely supply of the treatments. Countries should look at reducing their vulnerability towards global supply chain disruptions as emphasized by the significant disruptions observed during the Covid-19 pandemic. Therefore, diversifying production capacity is key to ensuring the availability of these treatments. Locally based manufacturing should also be considered to increase ownership and diversify supply chains as well as facilitate the roll out of drugs across Africa. Nonetheless, it would bring some challenges such as higher costs (e.g., lower volumes, tariffs on imported APIs, export taxes, limited...
infrastructure), or ensuring international quality standards are met. Such challenges should be investigated considering a country’s specific setting. For the ACTs with other partner drugs, the lack of demand results in a very limited number of manufacturers producing these alternative treatments. Countries with the support of global partners should work at ensuring there is sufficient demand for these treatments, starting by ensuring the availability of an ACT second-line treatment.

**Procurement** – Finally, a diversified product portfolio relies on an efficient procurement system. Regional pooled procurement initiatives could be explored to complement the global pooled procurement mechanisms such as the Pooled Procurement Mechanism operated by the Global Fund. Pooling demand could support the need for rapid procurement when changing policies (e.g., switching ACTs rapidly) but also respond to the need for small batches, for instance, if few second line treatments are needed. As initiatives to meet minimum order quantities have been done in few cases by the Global Fund and U.S. President’s Malaria Initiative, they could be further developed in the future. Similar initiatives were piloted during the Covid-19 pandemic in Africa, such as the Africa Medical Supplies Platform for diagnostics and therapeutics or the African Vaccine Acquisition Task Team for vaccine access under the African Union umbrella and funded through World Bank loans. Potential bottlenecks – such as inventory holding costs, risk of expiry, risk of deterioration, administratively burdensome processes, country specific requirements, such as packaging – should be evaluated and accounted for. At country-level, efficient and flexible national procurement plans should be designed so that drugs can be quickly available, and stockouts avoided. Capacity building to conduct local needs assessments and demand quantification should be undertaken. Incentivizing facilities to measure and communicate their needs regularly and accurately should also be considered to improve national forecasts.

Global partners should pursue their effort to ensure that such a diversified marketplace for antimalarials is viable, healthy, and sustainable for countries to implement the change. Working with countries, partners should identify opportunities to expand access to ACTs with different partner drugs, increasing demand for less used partner drugs, applying strategies to lower costs and de-risking for country programmes and for manufacturers. This should be done prior to complete partner drug failure to ensure a strong supply base to respond to future failures. The significant volumes procured should also be leveraged to shape the market (see box below), for example by directing volumes to local manufacturers and by ensuring that the market is not too fragmented so that price-breaking volumes can be achieved across multiple manufacturers. In addition to guaranteeing sustainable production of existing ACTs, this should also incentivise innovation to develop new medicines.

**Pillar II – Intervention 3** | Prevent exposure to subtherapeutic drug levels driven by substandard and falsified ACTs by promoting drug quality

**Underlying issue**

Many factors affect the quality and efficacy of antimalarial drugs. A subtherapeutic drug dosage could be due to improper manufacturing, for example in case of a lower active pharmaceutical ingredient concentration, to alteration, for instance due to poor storage and distribution conditions, in particular under tropical conditions, or to plain falsification. Exposing parasites to subtherapeutic drug levels increases the risk of selection and spread of resistant parasites. Substandard and falsified drugs are widely available in Africa, especially in the private sector.

**Suggested intervention**

To prevent the circulation of substandard and falsified drugs in Africa, three main steps should be undertaken: 1) establish stringent regulations, 2) monitor the quality of ACTs throughout the supply chain and 3) ensure enforcement of quality standards.
**Stringent regulation** – A stringent regulatory framework should be established on product quality standards for both imported and exported ACTs. Stringent regulation can be achieved by empowering regulatory authorities within each country and supporting quality assurance of generic ACTs according to WHO standards (e.g., prequalification). In addition, a regional harmonization process of regulatory systems should be strongly encouraged to ensure consistent quality standards in the region, for instance, by ratifying the Treaty for the Establishment of the African Medicines Agency\(^46\).

**Quality monitoring** – The quality of ACTs should be monitored and managed along the supply chain, through sampling and testing at targeted locations such as customs, storage locations, distribution network, points of sale in both public and private sector outlets. Sampling and testing activities should follow an approved protocol with well-defined objectives, and a dedicated budget\(^47\).

**Enforcement of quality standards** – Quality standards should be enforced to ensure concrete results. A clear list of sanctions for the manufacturing and wholesale purchase of SF drugs (e.g., fines, shop closing, withdrawal of import license) should be defined, and resources should be dedicated to this purpose. The circulation of substandard and falsified drugs should be closely monitored at borders and prevented through international and regional collaboration. National, regional and global regulatory authorities should jointly investigate the source of illegal substandard and falsified ACTs and take coordinated measures to stop their production and exportation (e.g., defining clear roles and responsibility at borders, strengthening data sharing processes between national authorities) to reduce the availability of substandard and falsified drugs on African markets.

Although harder to reach and to regulate, the private informal sector should be a priority setting for the above-mentioned efforts, and relevant stakeholders should be engaged and incentivised to support government initiatives.

**Pillar II – Intervention 4 | Remove non recommended monotherapies from both the public and private sectors and ensure that other monotherapies are used in accordance with national and WHO Guidelines for malaria**

**Underlying issue**

WHO recommends the use of ACTs to treat children and adults with uncomplicated *P. falciparum* malaria. Recommendations around the use of monotherapies should be strictly followed as these are an important threat to resistance management.

In 2007, WHO Member States called for the progressive removal of oral artemisinin-based monotherapies from markets, as these were identified as driving the emergence of resistance. By 2012, all countries in Africa banned the marketing of these monotherapies except for 3 countries. Similarly, the continued availability and use of partner medicines as monotherapies (e.g., amodiaquine, mefloquine) can compromise the value of ACTs by selecting for drug resistance. Despite significant progress\(^48\), weak capacity to enforce the bans and the continued production and distribution by pharmaceutical companies prevent the complete withdrawal of remaining non-recommended monotherapies from the markets. Additionally, non-pharmaceutical forms of *Artemisia* (e.g., *Artemisia* tea) should not be used for the prevention or treatment of malaria\(^44\). The varying artemisinin content of *Artemisia annua* or *A. afra* herbal remedies means that widespread use of these remedies could lead to many people having sub-therapeutic levels of artemisinin in their blood, increasing the risk for resistance to develop or to spread. Current knowledge concludes that any potential weak antimalarial activity of other compounds in *A. annua* or *A. afra* would not be sufficient to protect artemisinin from resistance.
Parenteral or rectal monotherapies are recommended for treating severe malaria and when oral treatments are not tolerated. An overuse of these treatments in the absence of a clinical rationale is reported in certain areas, which increases drug pressure by over exposing parasites to these drugs. Using monotherapies for patients with severe malaria without completing the full treatment (e.g., administering a parenteral or rectal antimalarial treatment without providing a subsequent full ACT treatment) represents a risk for resistance as it may favour *de novo* emergence and spread of resistant parasites. Anecdotal evidence suggests that non-recommended monotherapies could also be more widely available in the informal sector.

**Suggested intervention**

**Remove non recommended oral monotherapies** – Countries should intensify their ongoing effort to remove non-recommended monotherapies from the market to reach complete withdrawal, including in the informal sector. Withdrawal should be considered at exportation, importation, and distribution levels. National regulatory authorities should be empowered and strengthened to regulate and enforce the withdrawal of oral monotherapies from markets, including both artemisinin-based and partner drugs (e.g., amodiaquine, mefloquine). To that effect, additional resources should be dedicated to targeted areas where the circulation of oral monotherapies is reported. Moreover, national authorities should work with the main importing stakeholders such as foreign governments, distributors, and local manufacturers to define a joint strategy to withdraw monotherapies from the market.

At continental level, regional organizations could work with exporting stakeholders (e.g., governments, manufacturers). Strong collaboration among neighbouring countries can ensure an efficient surveillance of drug flows at borders. In areas where frequent use of oral monotherapies is reported or suspected, stakeholder engagement and communication campaigns should be developed to raise awareness among private providers (e.g., pharmacies, general retailers, clinics) on the risks associated with these monotherapies. The Population Services International Myanmar experience could be taken as an example of how to remove artemisinin monotherapy: negotiations with the largest importer and distributor of artesunate in Myanmar led to the replacement of oral artemisinin-based monotherapies by a quality assured ACT.

Similarly, the use of *Artemisia* herbal remedies should be avoided. Care providers and patients should be sensitized to the risks incurred by patients and the threat to resistance management.

**Prevent the misuse of recommended artemisinin-based monotherapies** – The use of injectable artesunate and artemether or of rectal artesunate in non-recommended ways, such as for uncomplicated cases, should be avoided to reduce unnecessary drug pressure from these life-saving treatments. Depending on the underlying reasons, be it insufficient training and lack of supervision, insufficient health system financing encouraging the prescription of treatments that can be charged in full to the patient, wide availability and accessibility of the treatments or perception of efficacy, a different set of activities should be implemented. Health care workers should be trained to ensure broad knowledge of guidelines on the treatment of uncomplicated malaria. A communication plan could be developed to address communities’ beliefs and personal preferences. Procurement and supply chains could be strengthened to ensure the availability of alternative treatments and prevent stockouts of ACTs. Additional existing barriers, financial, social, gender-related, geographical among others, should be addressed to enable access to the correct treatment (ACTs) for patients with uncomplicated malaria - see intervention 2.5.

**Ensure complete treatment of severe malaria cases** – Patients with severe malaria not receiving the recommended ACT following the initial monotherapy could contribute to the *de novo* emergence and spread of resistance. To address this risk, health care workers must be trained to follow the recommended
treatment of severe malaria: a patient treated with injectable artesunate/artemether should subsequently receive a full ACT course, a patient treated with rectal artesunate needs to be referred to a health facility to receive, as needed, an injectable treatment followed by a full ACT course. Other financial, social, gender and geographical barriers should be addressed as well to ensure access to the correct treatment (ACTs) - see intervention 2.5.

**Pillar II – Intervention 5 | Promote equitable access to quality drugs**

**Underlying issue**

The lack of access to quality treatment increases the risk of resistance, as it favours the circulation of SF drugs used, thus increasing the number of parasites exposed to subtherapeutic drug levels. Additionally, the availability of drugs at point of sale can sometimes guide patients and care providers in terms of treatment selection. Resistance has historically been observed to emerge first in areas and populations with poor access to quality malaria services. In these areas, a large proportion of patients seek treatment through private health care providers, especially pharmacies, authorized and informal drug shops, and other medicine sellers. The quality of case management in these facilities varies widely and is often poor, especially in terms of access to quality ACTs and malaria diagnostic testing prior to treatment.

**Suggested intervention**

A diversified portfolio of quality medicines at country level is not sufficient to ensure equitable access in all areas and populations. Further efforts should be made to reach the populations that are currently underserved as well as improving quality of care in the private sector, where insufficient quality standards are frequently reported.

**Increase access to quality health services for underserved communities and populations** – In other parts of the world, resistance has been seen to first develop in areas with underserved and hard-to-reach populations. Accessibility of care can be affected by many factors including geographical, financial, social and gender barriers. Barriers and the risk of resistance developing in different areas and communities should be assessed country by country. Once specific groups have been identified (see Annex II) efforts should be intensified to reach them. There are different ways of achieving this; one way is leveraging community workers to provide quality diagnostics (cf. intervention 2.6) and treatments to these specific groups. A potential way to minimize the financial barrier is to develop policies that can drive down the cost of treatments for individual patients (e.g., private sector co-pay mechanisms and cost-recovery systems).

**Improve access to quality of care in the private sector** – The private sector plays a prominent role in some parts of Africa but often operates without efficient government oversight. The lack of alignment with national treatment guidelines can result in the distribution of lower quality or inadequate products.

Countries should ensure that only quality antimalarial medicines and diagnostic testing are available from private providers. This is achieved through adequate regulation and its enforcement by the national and state regulatory authorities. However, as is well established, many countries have insufficient resources to achieve this objective, even if the regulations themselves are adequate. Similar mechanisms such as the Affordable Medicines Facility – malaria (AMFm) programme, hosted by the GFATM, should be explored. The AMFm subsidized ACTs in the private sector and led to tangible results in improving access to quality-assured ACTs in the private sector (ACT availability increased by at least 20 percentage points in
six of the eight pilot countries) and making ACTs more affordable (ACT full treatment course prices in the private sector dropped by $1.28-$4.82 in six of the eight pilots). Countries should promote adherence to national treatment guidelines with private providers. To deliver quality case management in private medicine retailers, providers must be supported by training, supervision and protocols that are tailored to the characteristics of the delivery channel and providers. Engagement with community-based organizations and non-governmental organizations (NGOs) can be effective in bridging the gap between public and private sectors.

Pillar II – Intervention 6 | Promote equitable distribution of and access to high quality diagnostics to reduce drug pressure

**Underlying issue**

With malaria symptoms being non-specific, clinical diagnosis accuracy tends to be poor, which can lead to over-diagnosis of malaria, which in turn unnecessarily increases drug pressure and the risk of resistance. Malaria diagnoses should be made with either quality-assured malaria microscopy or WHO-prequalified rapid diagnostic tests (RDTs). Microscopy must be performed by adequately trained health care workers, with well-maintained equipment. RDT performance relies not only on the manufacturing quality but also on compliance with transport and storage requirements, training and supervision of operators and knowledge of local epidemiology in terms of the major and minor vector species.

**Suggested intervention**

Promote the use of quality RDTs – WHO recommends all suspected cases of malaria have parasitological confirmation of infection prior to treatment. The *Universal Access to Malaria Diagnostic Testing* document provides technical and operational guidance to countries to strengthen or set up routine malaria diagnostic services. Countries should promote and assess adherence to this guidance. Based on a routine surveillance needs assessment, an adequate number of tests should be made available to the population, including in the private sector. Both quality and access should be monitored and enforced (cf. intervention 2.5).

Improve quality of microscopy – In 2016, WHO published the second version of the *Malaria Microscopy Quality Assurance Manual*, detailing the key requirements of a malaria microscopy quality assurance programme and in parallel published a complete series of standard operating procedures (SOPs) for malaria microscopy. NMPs should ensure a central coordination and advocacy effort, defining a reference (core) group of microscopists with demonstrable expertise in overseeing programme training and validation standards. Before taking service, and on a regular basis after first being trained, microscopists should receive quality training with competency standards that must be met before they work in a clinical setting leveraging the WHO AFRO External Competency Assessment for Malaria Microscopists (ECAMM). The quality of processes and equipment should follow clear SOPs, including supplies of consumables and maintenance of microscopes and other equipment. Finally, donors and partners should support NMPs and allocate adequate budgets to improve the quality of microscopy.
**Market shaping implications**

Equitable access to quality and affordable therapeutics and diagnostics is a key requirement to ensure good malaria care but also to prevent the emergence and spread of resistance. While WHO Malaria Guidelines currently recommend six different ACTs, AL and ASAQ represent the bulk of ACTs procured through pooled procurement channels (85% and 15% of Global Fund Pooled Procurement Mechanism orders, respectively). There is a global need for widely available and affordable alternative treatments to AL and ASAQ, as a preventive measure to diminish drug pressure, but also as a reactive measure for countries to be able to rapidly switch first- or second-line treatments in the event of suspected or confirmed partner drug resistance. The uptake of alternative treatments such as dihydroartemisinin-piperaquine or artesunate-pyronaridine is hampered by several market challenges, such as high prices and limited production capacity, resulting in a vicious circle of limited supply and demand. For instance, to-date there is only one supplier producing prequalified artesunate-pyronaridine and it is four times more expensive than the equivalent AL course. On the diagnostic front, since parasites with dual Pfhrp2 and Pfhrp3 gene deletions have been reported to also carry PfKelch13 mutations, a molecular marker of artemisinin partial resistance, there is a need for non-HRP2 only RDTs, for instance RDTs targeting the Plasmodium lactate dehydrogenase (pLDH) protein, in addition to the HRP2 protein. HRP2 RDTs still represent the vast majority of the malaria RDT market, with limited options for combo pLDH+HRP2 RDTs. Additionally, the malaria RDT market faces multiple challenges as it is extremely concentrated and heavily commoditized, with limited space for innovation. Focusing on these two product categories, there is a unique opportunity to identify and implement appropriate market interventions, that could help shape these markets into healthier markets, with the objective of reaching price-breaking volumes while not disincentivizing investments in innovation. Lessons learnt from more successful product introductions, such as that of dual active ingredient insecticide treated nets should be analysed and leveraged: the new nets initiative combined a volume guarantee underwritten by BMGF and a co-pay mechanism funded by a Global Fund strategic initiative and Unitaid funding and resulted in a rapid increase in the availability of dual insecticide nets and a sharp decline in prices, while at the same time generating critical data to support a WHO recommendation. It is now critical for global partners to join forces and address these market failures. Country-level activities such as updating national guidelines and registering these products will also be critical to make this a reality.

**Pillar II – Intervention 7 | Empower patients, health care workers and other stakeholders to make informed decisions and provide appropriate treatment**

**Underlying issue**

Antimalarial drug resistance can result from a misalignment between treatment recommendations and practice. The misuse or overuse of antimalarial treatments, due to poor patient adherence, incorrect prescription or treatment of unconfirmed cases by care providers all contribute to drug resistance. In addition, safeguarding against antimalarial drug resistance should not be done at the expense of other life-saving treatments. Special attention must be paid to ensure that the rationalization of usage of antimalarial treatments won’t result in excessive use of other antimicrobial treatments (i.e., antibiotics).

**Suggested intervention**

Raise awareness of populations and key stakeholders – Raising awareness can be done through the development and financing of a communication plan on the importance of quality diagnosis,
adherence to treatment, policy, good practices, to name a few. The messaging needs to emphasize the importance of testing prior to administering antimalarial treatment, adherence to the full treatment course, need for correct and quality treatment, for instance by warning against the risk of using non-pharmaceutical forms of Artemisia, and the need for referral to the nearest health facility. Specific stakeholders could also be targeted: dedicated communication materials about regulatory policies can be developed for and distributed to private sector outlets. In case of failing ACTs and a switch to a new treatment, public information and education will be needed to ensure understanding and compliance with the new guidelines.

Provide training to health care workers (HCWs) – Training should be provided to HCWs to ensure full understanding and operational solutions to follow national treatment guidelines, such as when to use second-line treatment, and to ensure patients complete the full treatment, for example by ensuring synchronous intake of food to increase treatment tolerability and thus adherence. A treatment policy change, following for instance the failure of the existing first-line ACT will require dedicated training. Continuous training should also be provided to HCWs on the use and interpretation of RDT and microscopy results, tailoring training to the specific instructions of the brands used in the country. While limiting the use of antimalarial treatments to confirmed cases, public authorities should ensure that appropriate alternative treatments are being administered. Training should be considered from a holistic perspective through improved integrated community case management and integrated management of childhood illness to prevent the excessive use of other life-saving treatments, and especially antibiotics.

4.2.3 Pillar III: React to resistance by limiting the spread of antimalarial drug resistant parasites

Efforts to limit the transmission of malaria will affect both resistant and sensitive parasites. However, to limit the risk of resistant parasites being selected and spreading, focus should be placed on prioritizing optimal vector control as well as other preventive measures such as chemoprevention and vaccines in priority areas, containing transmission from recrudescent cases and limiting the advantage that higher gametocyte carriage could provide to resistant parasites. Lastly, promoting collaboration across borders could ensure that resistance detected in one country is addressed through a regional response.

This pillar calls for a dedicated effort to limit the selection and transmission of resistant parasites. Four interventions to address these challenges have been identified. They rely on strong collaboration among countries and should be based on countries’ prior assessment of their treatment guidelines regarding preventive measures and on the availability and use of vector control interventions.

Pillar III – Intervention 1 | Ensure optimal malaria vector control interventions coverage in priority areas

**Underlying issue**

Limiting the onward transmission of resistant parasites requires an efficient malaria vector control strategy. Vector control interventions are often logistically challenging. Their efficacy can be considerably hindered by delayed deployment, limited coverage, or inaccurate targeting.

**Suggested intervention**

**Targeted deployment** – Intensified efforts to prioritise and optimise vector control interventions should be considered to limit the transmission of resistant parasites while preserving the efficacy of available drugs. Such efforts should be both preventive, targeting areas and populations where resistance is deemed more likely to develop or spread, and reactive in areas where resistance has been confirmed, be it artemisinin partial resistance or, if evidence becomes apparent, areas with partner drug resistance. The
feasibility and effectiveness of such efforts will depend on the ability to identify priority interventions, the capacity to tailor the interventions based on local epidemiological and entomological data and on market preparedness.

**Timely deployment** — Once priority areas have been identified, recommended vector control interventions such as the distribution of insecticide treated nets (ITNs) and indoor residual spraying (IRS) operations should be made as efficient as possible to reduce onward transmission of resistant parasites, once resistance has been detected. Initiatives developed by global partners, such as the New Nets Project by the Global Fund and Unitaid, to address the barriers preventing rapid scale-up of vector control interventions should be further encouraged and leveraged.

**Innovative deployment** — Leveraging new digital tools should be considered to further improve the efficacy of vector control interventions. For instance, geospatial technology should be leveraged for planning, implementing, and targeting future IRS campaigns. Geospatial generated maps would complement the existing manual, on foot process of collecting data on infrastructure and population, facilitating the identification and sizing of structures to be sprayed.

**Pillar III – Intervention 2| Leverage preventive measures to reduce transmission of antimalarial drug resistant parasites**

**Underlying issue**

As stated in the GTS, preventive treatment strategies are highly cost-effective elements of the multipronged strategy to reduce disease burden and transmission. Faltering progress in malaria control since 2015 has drawn attention to the need to substantially expand the use of chemoprevention in countries seeking to reduce their malaria burden. While chemoprevention interventions can be challenging in terms of planning and delivery, for example through the need to use different drugs for chemoprevention and first-line treatment, they can limit the risk of emergence and further spread of resistant parasites, when conducted in targeted areas. Evidence shows that both asymptomatic infections and school-aged children are important contributors to the malaria infectious reservoir and could be targeted by malaria control interventions.

While being detailed under this section, both chemoprevention and vaccine could contribute to decreasing the number of cases, thus decreasing the overall drug pressure, relating to the objective of Pillar II.

**Suggested intervention**

**Chemoprevention interventions** cure existing infections and prevent new infections. In terms of drug resistance management, chemoprevention can have the added benefit of diversifying the drug pressure on the parasite population. WHO-recommended preventive treatment strategies against malaria presently include intermittent preventive treatment of malaria in pregnancy (IPTp), perennial malaria chemoprevention (PMC), seasonal malaria chemoprevention (SMC) for children belonging to age groups at high risk of severe malaria, intermittent preventive treatment of malaria in school-aged children (IPTsc), post-discharge malaria chemoprevention (PDMC) and mass drug administration (MDA). These interventions are recommended in areas of moderate to high malaria transmission, except for MDA that is recommended in areas with very low to low levels of *P. falciparum* transmission and SMC recommended only during peak malaria transmission seasons. Chemoprevention strategies should be tailored to the local context; for example, the number of rounds of SMC should be sufficient to cover the transmission season.

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\(^c\) Formerly intermittent preventive treatment of infants (IPTi)
and alternative delivery strategies for IPTp, and potentially IPTsc, should be considered to maximize coverage. Chemoprevention interventions should be adequately conducted: the deployment of the intervention should be targeted, closely monitored, and use drugs that are not used as first-line treatment.

**Vaccination campaigns** could significantly increase the immunity of a given population and decrease the risk of resistance. In October 2021, WHO recommended the expanded use of RTS,S among children living in settings with moderate to high malaria transmission. The malaria vaccine pilots have shown that it substantially reduces deadly severe malaria and health facility visits for malaria by 55% during the first year after vaccination and 40% over 4 years. The impact of the vaccine on antimicrobial (both antimalarial and antibiotic) resistance could be substantial and intensified investments should be made to enable the scale up of this first-generation vaccine.

**Pillar III – Intervention 3 | Limit the risk of increased transmission of resistant parasites**

**Underlying issue**

Delaying diagnosis and care seeking increases the likelihood of transmitting parasites. Additionally, after the return of symptoms in a recrudescent case, parasites are more likely to have reduced drug sensitivity with an increased gametocyte carriage. Finally, some resistant parasites may have higher gametocyte carriage. Looking at lowering this gametocyte carriage and onwards transmission of these gametocytes could help prevent the further spread of resistance.

**Suggested intervention**

**Limit the risk of transmission from recrudescent cases** – To limit the risk of transmission from recrudescent cases, patients and caregivers must be informed about the need to take the full treatment and to seek immediate care if symptoms return. In addition, patients should be encouraged to use insecticide-treated nets where available. National guidelines should be in place, clearly stating the need to move to second-line treatment after recurrence of malaria within a set time period (28 or 42 days). Providers should routinely ask questions on patients’ previous treatment history to facilitate the switch to a second-line treatment when needed.

**Limit gametocyte carriage for artemisinin partially resistant cases** – To reduce transmission, WHO Guidelines for malaria currently recommends the use of a single dose of 0.25 mg/kg bw primaquine with an ACT in low-transmission areas to patients with *P. falciparum* malaria, except pregnant women, infants aged under 6 months and women breastfeeding infants aged under 6 months. Depending on the national treatment guidelines, this could also be considered in areas of confirmed or suspected artemisinin partial resistance and in case of suspected recrudescence.

**Good case management, including early diagnosis and treatment will reduce the risk of transmission.** Although not specific to resistance, interventions aimed at improving the overall management of malaria cases can have a positive impact on limiting the transmission of resistant parasites.

**Pillar III – Intervention 4 | Strengthen cross-border collaboration on malaria activities to ensure coordinated action**

**Underlying issue**

The lack of coordination among neighbouring countries in the deployment of malaria control interventions significantly hinders the effectiveness of their strategies in limiting the spread of resistant parasites. For instance, inflows of mobile and migrant populations from areas where resistance has emerged, need to inform activities in countries where these populations move to.
Suggested intervention

Building upon the GMS experience, collaboration among countries is needed to ensure the timely and effective deployment of interventions in key priority areas. Following communication of an early warning of artemisinin partial resistance or partner drug resistance, countries should ensure coordinated and timely deployment of prevention, diagnosis, and treatment in the identified at-risk areas. Existing regional economic communities and their health initiatives should be leveraged, and resistance management actions should be further included in their mandate. Multinational organizations such as WHO and donors can play an important role in supporting this cross-country coordination. The coordinating role of supranational agencies becomes even more fundamental in areas where political tensions, cross-border conflicts, competing priorities, lack of resources or infrastructure undermine malaria control activities.

4.2.4 Pillar IV: Stimulate research and innovation to better leverage existing tools and to develop new ones against resistance

The response to the threat and potential impact of antimalarial resistance relies on a robust and sustainable pipeline of both therapeutic and non-therapeutic tools. According to WHO’s latest World Malaria Report, funding for malaria-related research and development (R&D) reached just over US $619 million in 2020. Between 2021-2030, it is estimated that an average annual investment of US$ 851 million in R&D is needed.

This pillar calls for innovative approaches to better use the current tools, the development of new tools and increased research and modelling into characterizing resistance, its impact, drivers and how corrective interventions might address these drivers. Five interventions to address these challenges have been identified. These interventions will rely on strong collaboration among global partners, the research community and malaria endemic countries to conduct studies and implement pilots to test new approaches and improve the overall knowledge on malaria resistance.

Pillar IV – Intervention 1 | Identify innovative approaches of using currently available drugs to delay the development and the spread of resistance

Underlying issue

Preserving the therapeutic lifespan of current ACTs is fundamental until alternative viable solutions become available. Yet the lack of knowledge and evidence on the impact on resistance of an intervention or a combination of interventions limits the number of options to respond to resistance. This strategy calls for increased efforts to identify ways of using currently available drugs while delaying the development and the spread of resistance through a wide variety of research topics, for instance operational or socio-economic.

Suggested intervention

Continued efforts to develop innovative approaches using currently available drugs to reduce drug pressure and delay the emergence of resistance should be undertaken.

New schemes in the use of treatments at national level – Currently, a treatment is recommended until failure rates reach 10%. Deploying the currently available treatments differently, for instance by rotating drugs before high failure rates are detected or using multiple first-line treatments, could possibly prolong the lifespan of existing ACTs. Research should be expanded to better understand the complexity and relative impact of implementing different schemes of ACTs (e.g., differentiate ACTs for different age
groups or geographies, rotate ACTs). The operational feasibility of such approaches should be further studied to understand the logistical challenges, costs, and acceptability by countries. Modelling efforts should also be pursued to assess the impact of multiple first-line therapies on drug resistance.

**Extended treatment regimens** – Extending the duration of treatment beyond the current 3 days may also be relevant and should be further investigated to build the evidence needed before considering making new global policy around the use of these treatments. Such research should include an assessment of the potential risks, including safety, and solutions, especially regarding the adherence of patients to the extended regimen.

**Pilots to build a healthy marketplace** – Market-related interventions such as diversifying the portfolio of currently available drugs or enabling a timely deployment of alternative treatments or vector control interventions, require proactive and deliberate market-shaping. The merits of various market interventions such as volume guarantees, co-pay mechanisms, buys-down and others should be assessed for individual products, with an overall objective of increasing their availability and affordability. To do so, pilots combining both economic research and procurement operations could be conducted to test new approaches.

**Transmission-blocking interventions** – The lack of understanding on PfKelch13 mutants’ gametocyte carriage and transmissibility in Africa is an important knowledge gap. The deployment of transmission-blocking interventions in areas where resistant parasites are prevalent, such as the deployment of low-dose primaquine, should rely on evidence that such parasites have a transmission advantage. Hence, there is a need for further research and modelling to evaluate the impact of implementing single dose primaquine to reduce transmission in areas with confirmed artemisinin partial resistance, in areas with high risk of resistance emergence (e.g., lower transmission areas) and in areas with high transmission.

**Pillar IV – Intervention 2** | Identify areas and populations where drug resistance is deemed more likely to develop and spread

**Underlying issue**

To help inform the design of interventions and where to deploy them, better information is needed on the biological, environmental, economic, and social factors driving resistance (e.g., importation risk, vector composition). Better understanding these factors will facilitate the identification of areas and populations where resistance is more likely to develop or spread in Africa. Historically, the areas where resistance first emerged have been low endemicity areas with an influx of populations with limited immunity, lacking access to quality diagnosis and treatment and with high, unregulated usage of antimalarials. However, current knowledge specific to the African setting is limited and such assumptions require further research.

**Suggested intervention**

**Conduct setting-specific modelling and research** - Collect information to identify the areas and populations where resistance is more likely to develop and spread and tailor the implementation of the interventions accordingly. The dataset collected could include results of efficacy studies, treatment rates, patterns of drugs used (symptomatic vs. asymptomatic, private vs. public sector), proportion of patients adhering to treatment guidelines, delay between symptoms and treatment, population movements and migration patterns, age-related data, and other socio-demographic data. Setting-specific models should then be leveraged to estimate the risk of artemisinin partial resistance and partner drug resistance emergence, spread, and extent (e.g., assessing the role of immunity).
In-depth monitoring and research around local transmission dynamics, including insecticide resistance and vector genomics is needed. For instance, research could be conducted to understand the degree to which local vectors can transmit parasites with resistance mutations. Additionally, research to assess the effectiveness of specific vector control interventions in controlling key vectors in a given area will help to tackle existing intervention gaps, most importantly that of outdoor biting prevention.

**Pillar IV – Intervention 3 | Develop new treatments with the objective of delaying the emergence and the spread of resistance**

**Underlying issue**
As clearly stated in the GTS, the long-term usefulness of any medicine or combination is threatened by resistance. Additionally, formulation and dosage for certain population groups for some available treatments are sub-optimal and may need to be revised.

**Suggested intervention**
R&D should be focused on improving current ACTs and on developing treatments using different compounds. For ACTs, the focus should be on improving formulations for specific population groups (e.g., children, pregnant women). The development of a paediatric formulation for 8-aminoquinolines should be accelerated.

Global stakeholders should increase efforts and coordination to establish Target Product Profiles (TPPs) that list minimum requirements that new medicines have to meet across different dimensions. Such TPPs should focus on novel compounds for treatment and prevention, beyond ACTs. For alternative treatments, focus should be placed on non-artemisinin-based combinations such as ganaplace-lumefantrine and innovative multiple combinations, such as medicines with better matching pharmacokinetic profiles and different modes of action, with existing or novel agents.

**Pillar IV – Intervention 4 | Identify and develop innovative tools to limit malaria infection and transmission**

**Underlying issue**
R&D should focus on finding new ways of controlling malaria infection and transmission. The aim is to limit transmission by means other than the use of antimalarials and thereby decrease drug pressure, and the likelihood that drug resistance develops and spreads.

**Suggested intervention**
Investments should be pursued in the R&D of pharmaceuticals and vaccines\(^69\). Additionally, second-generation vaccines and monoclonal antibodies (mAbs)\(^70\) could represent promising tools to limit malaria infection and transmission.

*Innovation in the area of vector control and vector surveillance should be encouraged*\(^71\).*

The improvement of existing vector control interventions – ITNs and IRS – and rigorous evaluation of these improvements is a priority area that requires further attention, as stated in the GTS. Regarding nets, the priority should be to make them more effective and to ensure their quality. More effective nets should be developed and deployed, in particular in areas with pyrethroid resistance. Effective nets could include nets treated with two different insecticides (dual insecticide nets) but also nets with an added synergist such as piperonyl butoxide or growth regulator such as pyriproxyfen. Ensuring the quality of nets should be of prime focus, the search for lower prices should not be at the detriment of quality. Higher quality nets should ensure both physical quality and residual activity of insecticides on the nets. New types of IRS and/or formulations that would be longer lasting than current IRS would also be helpful. Innovative
methods of delivering IRS in areas where housing is becoming increasingly modernized should also be considered.

Numerous other interventions are in development such as spatial repellent, endectocides (e.g., ivermectin), manipulation of vectors with gene drive, attractive toxic sugar baits to prevent outdoor biting. Moreover, innovative larval source management strategies should be rigorously evaluated to assess their potential contribution towards malaria control. New candidate larvicides should be evaluated in different eco-epidemiological setting for larval control. Drone technology to identify breeding sites could be leveraged for optimal deployment of larval intervention.

NMPs should collect and analyse comparative data on the effectiveness of existing tools and new tools (e.g., impact, sustainability, acceptability) to improve the decision-making process amidst the variety of interventions available.

Pillar IV – Intervention 5 | Conduct research and modelling to better understand and track resistance

Underlying issue

Many unknowns remain both on resistance mechanisms and the health impact of resistance and how interventions can address drivers of resistance. Advanced research on intrinsic and background drivers such as parasite genetics, the role of different vector species, the impact of transmission intensity, and importation risks will help tailor interventions to specific settings, including local specificities of hosts, vectors, and parasites. Moreover, intensifying research efforts on antimalarial resistance detection (e.g., molecular markers) will strengthen surveillance and allow for timely response to threats.

Suggested intervention

Advanced research on resistance should be fostered at international, regional, and national levels. Priority research topics (this list is not exhaustive and additional topics should be identified for further research) could include the followings:

- Gametocyte carriage and transmissibility in Africa among parasites with mutations associated with artemisinin partial resistance.
- Identification of new molecular markers for artemisinin partial resistance and partner drug resistance to monitor the emergence and the spread of resistance to each component compound individually.
- Assessment of the degree of resistance conferred by genetic changes in different parasite backgrounds.
- Assessment of the fitness cost of genetic changes mediating resistance in different parasite backgrounds.
- Assessment of the outcomes in patients with severe malaria infected by parasites carrying Pfkelch13 mutations compared to outcomes in severe malaria patients infected by parasites carrying Pfkelch13 wild type.
5 Role of stakeholders and enabling mechanisms

5.1 Role of key stakeholders

Addressing resistance throughout the African continent requires a coordinated effort from many stakeholders. From ensuring a continued support to stakeholders implementing activities in the field to encouraging continued involvement of others, a coordinated approach will ensure an efficient implementation of interventions and sustainable response to resistance.

The section below provides an overview of eight categories of stakeholders that should be involved to ensure this strategy is successfully implemented. Roles and responsibilities of each stakeholder are detailed in Annex IV.

**Ministries of Health of malaria endemic countries** are the cornerstone of this response. Strong institutional capacity is required to enable efficient and sustainable implementation of this strategy. NMPs should be the leveraged by countries to define a national strategy suitable to their specific situation and malaria programme managers should be empowered to implement this strategy efficiently. NMPs should assess the country’s priorities based on its starting point in light of the drivers of resistance and allocate resources accordingly, with support from regional and global stakeholders. NMPs should act as a connector, involving other government agencies along with the key stakeholders presented below. NMPs are in charge of consolidating data retrieved from the field, disseminating data through regional networks and ensuring strong collaboration with global stakeholders.

**National regulatory agencies** should further harmonize and strengthen quality assurance and quality control (QA/QC) requirements and processes. They should adopt clear standard operating procedures and dedicate additional efforts and resources to the enforcement of policies and guidelines.

**Regional organizations** should promote and enhance collaboration between countries. This strategy calls for strong coordination between all African countries in the response to antimalarial drug resistance. Regional organizations should use their supranational influence to ensure coordinated implementation of consistent strategies throughout the continent.

**Multilateral organizations** should actively advocate for the identified interventions and share knowledge and best practices with regional and countries authorities. Multilateral organizations should further support the development of regional networks, acting as third parties to ensure alignment to WHO standards and protocols. These organizations should support countries in implementing their national strategies through their regional offices.

**Funding agencies and donors** should call for action and seek to ensure adequate levels of financing and technical support for regional and local implementation of the interventions. Beyond supporting countries in the operational implementation of the Strategy, they should play a prominent role in building an overall viable and sustainable implementation framework for the response to antimalarial drug resistance in Africa. They should contribute to the establishment of a healthy marketplace with innovative strategies for procuring and distributing diagnostics and antimalarials but also support the implementation of strong surveillance capacities in Africa.
Academia and research organizations (e.g., universities, research centres, R&D units of pharmaceutical companies and other research-based organizations) should work to advance research on resistance and on innovative products and strategies. Research and modelling are key to continue to improve the response to resistance and a robust pipeline of antimalarials is needed to build a future line of defence against malaria.

Civil Society Organizations (CSOs) should mobilise resources, support advocacy efforts and foster community engagement around the Strategy. CSOs should liaise with different stakeholders, for instance with the public and private sectors, and support the adoption of national strategies by care providers and patients.

Care providers (public and private) play an important role in promoting adherence to guidelines, sensitizing on antimalarial drug resistance and delivering quality care. Care providers should be involved in working groups established by the NMPs to give visibility on the demand-side of malaria care, highlighting roadblocks at facility-level such as stock outs or lack of visibility on and understanding of guidelines. They should collaborate with programme managers to ensure adequate implementation of the guidelines.

Figure 6: Roles of each stakeholder
5.2 Ensuring that key enabling mechanisms are in place

Transversal conditions – “enablers” – are needed in all settings and at all levels to ensure feasible, impactful, and sustainable implementation of each activity. Promoting strong regional collaboration, ensuring sufficient financing and a sustained advocacy effort, building strong country ownership, and collecting quality data to guide implementation through routine surveillance will be key to turning this regional effort into a success.

5.2.1 Five transversal enablers to build a successful strategy

To build a successful strategy, five transversal enablers are needed at all levels:

- **Country ownership**: political commitment at local and regional levels should first focus on building strong governance to lead this effort. The issue of antimalarial drug resistance needs to be elevated to ministerial level to ensure interventions are implemented efficiently. A periodical assessment should be put in place to ensure accountability of all stakeholders, measurement of progress, and areas for improvement.
- **Financing**: implementing these activities will require a significant financial effort. Ministries of Health will have to mobilize domestic budgets. Donors, private sector and other stakeholders will need to invest and collectively unlock funding for capacity strengthening to diagnose, treat and monitor, foster local capacity, and ensure that research is conducted.
- **Advocacy effort**: responding to antimalarial drug resistance should become a priority. Global advocacy should focus on increasing awareness to ensure buy-in from global partners to grassroots stakeholders, and ensure efforts and resources are targeting priority areas.
- **Strong regional coordination**: this strategy provides a regional approach to responding to resistance. Despite the diversity of settings, cross-country coordination is required to ensure the reach and effectiveness of interventions. Adopting a coordinated approach through the mutualization of efforts, knowledge and resources will maximize its impact.
- **Strong routine surveillance system**: optimizing the response to resistance will require an overall routine surveillance system to monitor local specificities of each setting and further develop locally driven research.

In the Greater Mekong Subregion, the initial response to resistance developed into escalated efforts to reach malaria elimination, a goal likely to be reached within the next few years. The scale of the challenge and multitude of different settings in Africa vastly exceed that of the Greater Mekong Subregion. In some countries, elimination may be a feasible short-term goal, either nation-wide or at sub-national level. However, in many countries, the near-term goal needs to focus on optimizing and expanding activities based on the interventions outlined in this strategy.

A key learning from the response to antimalarial drug resistance in the Greater Mekong Subregion is the importance of surveillance systems. Surveillance has been a top priority, from increasing surveillance on resistance (e.g., TES) to strengthening overall malaria surveillance of cases, deaths and malaria control interventions and strategies. Various tools were leveraged, from apps enabling collection of real-time data to implementation of a regional Malaria Elimination Database. While TES (addressed in the previous section) are valuable tools to monitor drug resistance at patient-level, good quality, well-structured and geographically widespread routine malaria surveillance is fundamental to ensure that prioritized
interventions are adequate, feasible and impactful. The following sections present a list of areas where good quality data is required to adequately direct the interventions outlined in this strategy.

5.2.2 Core principles for the design and establishment of a robust routine malaria surveillance system

Decisions about programme policies, strategies, approaches, structures, and priorities must be based on the best available data to ensure that interventions are as impactful as possible, given constrained resources. A robust routine surveillance system consists of the following:

- Accurate parasitological diagnosis of malaria cases and deaths. Diagnoses should be made with either quality-assured malaria microscopy or WHO-recommended RDTs.
- All health sectors (public, formal and informal private, and community) reporting malaria data to a national surveillance system, in a concerted effort to include cases detected in any sector.
- A malaria surveillance system integrated into broader health management information systems (HMIS).
- Front-line staff involved in the detection, recording and reporting of cases as well as being the first users of data. Thus, staff at all levels should be trained in examining and evaluating data from surveillance of both disease and operations to monitor programme progress, allocate resources effectively, target interventions, and detect problems that require action. The system itself should allow users to visualize core data quality and epidemiological indicators in near real-time.
- Stable financial investments in surveillance and health system integration and strengthening, including in human resources.
- Surveillance systems assessed routinely to ensure their coverage, completeness, timeliness, accuracy, reliability and integrity.

5.2.3 Strong routine surveillance as a key enabler to optimize the impact of interventions addressing resistance

Building on the recommendations laid out in the GTS (Global Technical Strategy for Malaria 2016-2030\textsuperscript{(9)}) and in the Malaria Surveillance, Monitoring & Evaluation: A Reference Manual\textsuperscript{(2)} (2018), the paragraphs below highlight the areas where good quality data is needed to adequately direct the interventions detailed in section 9.1.

1. **Information on malaria burden** – Understanding the burden of malaria is the first step to plan, implement, monitor, and evaluate malaria programmes, and implement interventions targeted at addressing gaps that increase the risk of resistance. Good quality data on the burden of malaria provides the basis for directing resources to those in need. The data should be disaggregated by gender and age-groups and be analysed at the lowest administrative level possible. Required information on malaria burden includes:

   - Reporting completeness of data on malaria burden by geography and identification of information gaps
   - Number of cases and incidence by geographical region down to the lowest administrative level available
   - Standardized and continual collection of data on:
     - Suspected cases
     - Cases tested with microscopy or RDT
     - Confirmed cases through adequate diagnostic tests (quality-assured malaria microscopy or WHO-recommended RDTs)
2. **Information on quality of care** – Data on prescription and consumption needs to be interpreted based on an understanding of factors such as the availability of commodities, seasonal trends, and patient preference and non-compliance. Conducting routine surveillance of treatment through national surveillance or surveys, detailed records and other activities such as sample analysis at point of care will help to select which interventions to deploy.

The data should be disaggregated by gender, age-groups and provider (e.g., public, private) and be analysed at the lowest administrative level possible. Required information on the quality of care includes:

- **Compliance with national guidelines for case management:**
  - Proportion of suspected cases tested
  - Proportion of cases confirmed
  - Proportion of cases treated (with any first line, with ACTs)

- **Monitoring indicators over time and by geography related to access to care and hospitalisation that inform care seeking patterns:**
  - All cause outpatients (care seeking in general population for all diseases)
  - All cause inpatients (hospitalisations for any cause which may indicate delays in care seeking or poor quality of care)
  - All cause deaths (indication of delays or poor access to care or poor quality care)
  - Malaria proportion of all out-patients
  - Malaria proportion of all in-patients
  - Malaria proportion of all in-patient deaths
  - Malaria case fatality rate

3. **Supply chain management and post-marketing surveillance** – Routine monitoring of drug quality through outlet surveys and other post-marketing surveillance activities will help quantify the issue of substandard drugs, falsified drugs, degraded stocks, non-recommended monotherapies, stock-outs, etc.

- Structured and comprehensive post-marketing surveillance including all steps of the drug value chain (e.g., production, distribution, storage, etc.)
- Treatment volumes by health facility and forecast of stock availability
- Stock-out reporting
- Continuous monitoring of availability and use of monotherapies across the country to identify outliers (e.g., through procurement data)

4. **Biological threats surveillance**

*Surveillance of antimalarial drug efficacy and resistance*: the emergence of multidrug resistance is a public health concern that threatens the sustainability of global efforts to eliminate and reduce the burden of malaria. Regular monitoring of drug efficacy is needed to inform treatment policies in malaria-endemic countries, and to ensure early detection of, and response to, drug resistance.
WHO calls on countries and global malaria partners to monitor the efficacy of antimalarial medicines so that the most appropriate treatments can be selected for national policies.

**Surveillance of pfhrp2/3 deletion:** diagnosis accuracy is under serious threat as a result of the emergence of parasites not expressing the HRP2 protein due to genetic mutations. Consequently, HRP2-based RDTs are unable to detect infections with such parasites. This can have a significant impact on public health, putting patients at risk of misdiagnosis, significant increasing morbidity and potentially death, and may additionally represent a threat to drug resistance management as parasites with dual *pfhrp2* and *pfhrp3* deletions have been reported to also carry *PfKelch13* mutations. This combined ‘diagnostic and drug’ resistant parasites, already expressing increased gametocyte carriage, will be more likely to spread undetected. Surveillance for *pfhrp2/3* deletions and their impact on RDT results is essential to inform RDT procurement and avert missed or delayed diagnosis. In addition, should the local prevalence of *pfhrp2/3* deletions causing false-negative *pfhrp2/3* RDTs be over 5%, a different testing strategy should be immediately put in place, as called for by the Malaria Policy Advisory Group in 2021, to avoid missing cases that could further transmit infection by resistant parasites.

Understanding other mutations these parasites carry may provide clues to their expansion beyond selection pressure from *pfhrp2/3* RDT. Therefore, surveillance for *pfhrp2/3* deletions should be integrated into other molecular surveillance efforts wherever possible, such as for markers of drug resistance. A TES offers such an opportunity, but it is not a replacement for representative surveys for *pfhrp2/3* deletions which need to span all transmission zones.

5. **Entomological surveillance** – Adequate entomological surveillance would enable the selection of the most efficient vector control interventions to limit the spread of drug resistance in areas with high-risk of emergence, and the transmission of resistant parasites where resistance has emerged.
   - Identification of malaria vector species
   - Measurement of species-specific vector densities and ascertainment of vector composition
   - Determination of vector blood-feeding habits (e.g., human biting rate, host preference, biting time and location, resting location) and assessment of other vector behaviours
   - Measurement of the rates of infection of the vector with the malaria parasite (sporozoite rate, oocyst rate)

Routine surveillance is critical but can be challenging, especially in terms of logistics. For it to be effective, in the short term, stakeholders should share data transparently and timely (e.g., volumes of treatments) and communicate effectively (e.g., periodical meetings among the NMP, manufacturers, researchers, etc). In the longer term, data infrastructure at national (and potentially regional) level should be put in place to enable consolidation of multi-source information; additionally, forecast capabilities should be added on top of data analysis efforts to inform policy and interventions.
Annex I – Definition of resistance

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

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

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

Artemisinin partial resistance can be defined as delayed clearance of a parasite strain carrying a validated *PfKelch13* mutation after treatment with a drug containing an artemisinin derivative, despite the administration and absorption of the drug given in doses equal to or higher than those usually recommended but within tolerance of the subject. Delayed clearance can be shown either by persistent parasitaemia by microscopy at 72 hours (± 2 hours, i.e., day 3) or by a parasite clearance slope half-life ≥ 5 hours.

Though sensitivity to artemisinin could decrease further, it should be emphasized that no observations have been made so far of a change from delayed clearance towards “artemisinin full resistance”. It is difficult to create “artemisinin full resistance” in vitro and the biological chances to see its emergence are small. Therefore, using ‘artemisinin resistance’ is not currently accurate based on available data. Using the terminology ‘partial resistance’ or ‘tolerance’ would allow to change the message should the situation worsen. The term “artemisinin tolerance” was used in WHO’s first document on this topic in 200874. The word “tolerance” was used to describe antibacterial delayed clearance75, which from a biological perspective is in line with current *PfKelch13* observations in the GMS and Africa.

However, even though scientifically speaking tolerance is more accurate to describe the phenomenon, the wording should focus on delivering the right message and the sense of urgency to the audience of this strategy. The targeted audience, not exclusively composed of scientific experts, might not embrace the nuance of tolerance being more scientifically accurate. As a result, “partial resistance” should be used, putting the right stress on the “partial”.

The major threat correlated to artemisinin partial resistance is the increased risk of de novo emergence of resistance (correlated to biomass) or of spread of pre-existing resistance to partner drugs, leading to an eventual ACT treatment failure. Concerns over delayed clearance do not change the need to expand access to ACTs. *Pfkelch13* mutations do not necessarily predict treatment failure for ACTs.

The term “ACT resistance” was not endorsed by the Technical Expert Group on Drug Resistance in 2015 and was replaced with “ACT treatment failure”, which refers to a treatment failure caused by partner drug
treatment failure (or resistance if confirmed by in vitro tests, pharmacokinetic data and/or molecular markers), regardless of its association with delayed parasite clearance. It is essential to use appropriate wording: artemisinin partial resistance and ACT treatment failure rather than artemisinin resistance or ACT resistance.
Annex II – Preliminary country’s assessment to prioritize interventions

To implement the Strategy, each country should start by assessing their baseline with respect to the status and drivers of resistance as well as the available capabilities and the bottlenecks that have hindered the effective implementation and sustainability of interventions in the past. This assessment will aim at prioritizing the different interventions suggested in this strategy.

The assessment can be based on information from routine surveillance, surveys, and interviews with key stakeholders. Where no information is available, collection of the information can be incorporated into proposed activities in the strategy to progressively better target interventions.

(i) Defining a country’s baseline with respect to the status of resistance and the underlying drivers of resistance

1. Assessing the current status of antimalarial drug efficacy and resistance and data availability
   • **Review of efficacy data in the country and region**: An overview of efficacy data for first- and second-line treatment as well as evidence for other ACTs. Data should be examined periodically and overtime to also look for changing patterns/emergence of resistance.
   • **Review of data on known molecular markers in the country and region**: An overview of data on molecular markers for artemisinin partial resistance (PfKelch13 mutations) and, where relevant, markers of ACT partner drug resistance.
   • **Map of the coverage of data**: Efficacy studies are resource consuming, and a limited number of studies can be conducted each year. However, where data is only available from a few geographical provinces or transmission setting, these gaps need to be recognised and addressed.
   • **Capacity and quality**: Highlight issues and challenges of capacity to perform TES, surveys, and laboratory analysis.
   • **Processes of data sharing in-country and with neighbouring countries**: Review current process and challenges with data access and sharing.

2. Identifying potential drivers of drug resistance in the country
   2.1. **Understanding the access to, availability and use of diagnostics, drugs, and vector control interventions**
       • **Treatment seeking patterns**: Review available information on where patients can seek and receive treatment for malaria
       • **Drug availability in country**: Provide overview of:
         - Antimalaria drug(s) recommended in national malaria treatment policy
         - Antimalaria drug(s) registered by type
         - Antimalaria drug(s) produced and main procurement mechanism of drugs into the country
         - Antimalaria drug(s) available to patients by sector
- Availability of non-recommended monotherapies such as oral artemisinin treatment
- Availability of non-pharmaceutical forms of Artemisia (e.g., Artemisia tea)

**Drug use:** Review available information on what treatments are used by patients including use of non-pharmaceutical forms of Artemisia.

**Regulation of private sector:** Review existing regulation in place for the private sector.

**Supply chain management:** Describe the supply chain management including main distribution channels and storage, as well as frequency and reasons of stockouts.

**Quality of drug throughout supply chain:** Review available data on quality of drugs throughout the supply chain, key potential reasons of drug degeneration (e.g., heat in facilities), as well as the systems in place to monitor this.

**Diagnosis availability, use and quality:**
- Data on the availability and use of diagnosis by sector, including what proportion of patients treated with antimalarials receive a parasitological diagnosis
- Quality of diagnosis including list of key challenges with the quality of the diagnosis, and availability of information on presence and prevalence of HRP2/3 deletions

**Vector control availability and use:**
- Availability of entomological data (on species, biting patterns and insecticide resistance) to ensure good targeting of vector control tools
- Availability and coverage of vector control tools by type
- Use of vector control and main challenges encountered in increasing usage

**2.2. Understanding of the current behavioural drivers behind care providers and patient choices**

**Care providers:** Review information on the knowledge, attitude, and practices of care providers (by provider type as available):
- **Knowledge and understanding:** Should include knowledge of symptoms, prevention, the need for parasitological diagnosis, and the correct treatment.
- **Practices:** Should include patterns of diagnosis, prescription, and communication to patients, including the role of traditional healers
- **Communication:** Main sources of information on malaria prevention and treatment, including traditional and social media
- **Felt needs and preferences:** This should include the preference for prescribing certain type and dosage of treatment, perceived benefits of parasitological diagnosis and malaria treatments, perceived value in spending time to ensure that patient understand importance of taking full treatment.
- **Barriers and incentives that could affect effectiveness of interventions:** Barriers against treating patients as per the national treatment guidelines (e.g., availability of drugs) as well as incentives for providing non-recommended treatment (e.g., financial)

**Patients:** Review information on the knowledge, attitude, and practices of patients:
- **Knowledge and understanding:** Should include knowledge of symptoms, prevention, the need for parasitological diagnosis, and the correct treatment.
- **Practices:** Should include when and where treatment is sought, compliance to prescribed treatment and use of vector control.
- **Communication**: Main sources of information on malaria prevention and treatment, key challenges in communication (e.g., language)
- **Felt needs and preference**: This should include the preference for certain source, type and dosage of treatment, perceived benefits of parasitological diagnosis and malaria treatments, perceived value in taking the full treatment, perceived key challenges in accessing quality treatment and vector control.
- **Barriers and incentives that could affect effectiveness of interventions**: Barriers against, for instance seeking treatment, as well as incentives, for instance for taking full treatment.

### 3. Identifying the areas and populations where the risk of resistance developing and spreading is high.

The drivers identified will differ across areas and populations. Analysis of this will include:

- **Burden and transmission**: Geographical, demographic, and social distribution of malaria burden.
- **Data gaps**: Areas and population from where no information is available, for instance areas and populations not covered by surveillance systems.
- **Demographic and social patterns of access to services and vector control**: This will include geography, gender, age, and ethnicity.
- **Demographic and social patterns of over- and misuse of treatment**: This will include geography, gender, age, and ethnicity.
- **Population groups with limited or no access to regular health services and groups with increased risk of malaria**: These can include migrants and mobile populations (internal or international), refugees or populations in conflict zones.

#### (ii) Assessing capabilities and bottlenecks

Elements that need careful assessment include, but are not limited to the following:

1. **Assessing the maturity of the health and regulatory systems**:
   
   **Health system**
   
   - **Healthcare funding mix**: e.g., mix between the donor-provided funds, the domestic public funding, private health insurance and out-of-pocket payments.
   - **Structure of care provision**: e.g., assessment of the role and importance of the different sectors of care (e.g., public, private formal and informal sector).
   - **Integrated delivery of care**: e.g., level of maturity and integration of care delivered throughout the patient journey (e.g., referral to inpatient care) and across the different diseases (e.g., integrated community case management).
   - **Quality of care**: e.g., indexes measuring the coverage (e.g., the universal health coverage index), the infrastructure (e.g., number of operating rooms) and the health outcomes (e.g., neonatal mortality).
   - **Human resources**: e.g., the availability of resources (e.g., number of nurses per 1000 people), the deployment of HCWs across the country and their level of training.
   - **Health information system and monitoring**: e.g., assessment of the systems and processes in place to monitor, analyse and evaluate ongoing programmes
Regulatory system

- **National guidelines evaluation**: e.g., inclusion of an ACT second-line treatment
- **Enforcement capacity**: e.g., capacity to assess, and proactively monitor the quality of drugs

2. **Understanding the gap between the plans developed by the NMPs and their effective implementation**

- Countries should rely on existing monitoring & evaluation frameworks, on interviews of local, regional, and global stakeholders to identify the bottlenecks that have hindered past or ongoing implementation of interventions to fight malaria (e.g., obstacles to the withdrawal of monotherapies).

3. **The synergies with other strategies and global plans**:

- Identify interventions already being deployed within the framework of other strategies that could benefit and be further leveraged to respond to antimalarial drug resistance: e.g., training and awareness campaigns suggested in the Global action plan on antimicrobial resistance.
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