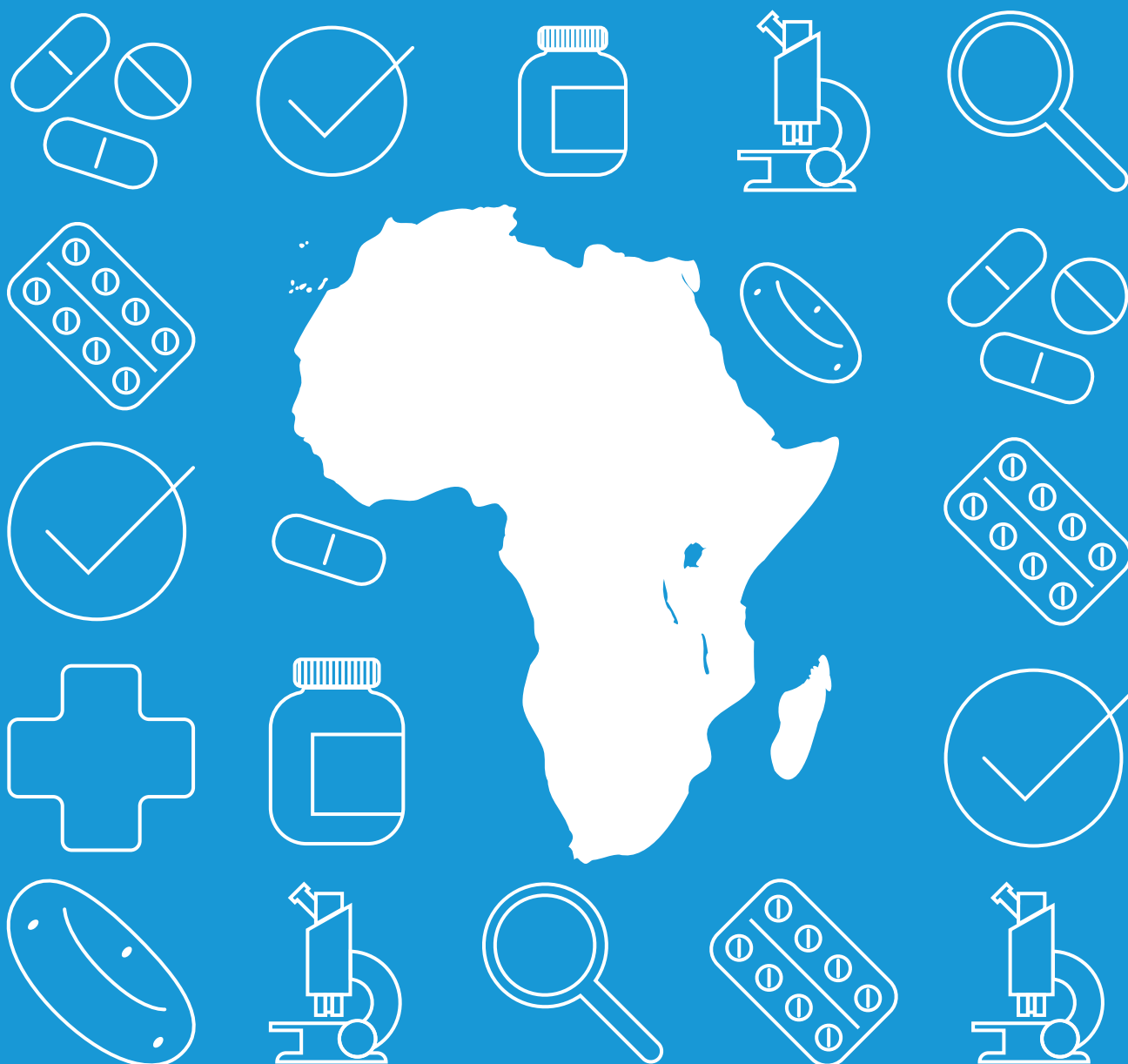


# Strategy to respond to antimalarial drug resistance in Africa





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# Foreword



**Dr Tedros Adhanom Ghebreyesus**  
Director-General  
World Health Organization

## Tackling antimalarial drug resistance in Africa

Artemisinin-based combination therapy (ACT) is the mainstay of malaria care in Africa, where the disease is by far the most prevalent. The treatment, introduced in the early 2000s, has played a major role in lowering the burden of malaria across Africa over the last two decades.

In recent years, however, WHO has been concerned by reports of emerging drug-resistant malaria in South-East Asia, and more recently, in Africa. Parasites in some areas have developed partial resistance to artemisinin – the core compound of ACTs – and there are worrying signs that they may also be resistant to other drugs that are commonly partnered with artemisinin. Vigorous measures are needed to protect their efficacy.

Our experience in South-East Asia shows that it is possible to prevent cases of malaria and save lives, even in the face of drug resistance. With strong leadership, sustained financing and community engagement, countries of the Greater Mekong have achieved a dramatic reduction in malaria incidence over the last 10 years. We're convinced that the same can be done in Africa, with the same level of commitment, energy and momentum.

The strategy in these pages contains recommendations for responding to drug resistance in the African region, building on our experience in South-East Asia, and on documents including the *Global technical strategy for malaria 2016–2030*, the *Strategy for malaria elimination in the Greater Mekong subregion 2015–2030*, and the *Global action plan on antimicrobial resistance* (2016).

A top priority is to address gaps in information and data, which blind us to the extent of resistance, and which areas and populations need the most attention. Improving data collection and dissemination systems will help countries track and respond to drug resistance more effectively. Stimulating research and innovation will also be critical to delay the spread of resistance to ACTs, and to develop viable alternative treatments.

Above all, strong health systems are the backbone of any successful response to malaria. Investments in primary health care can play a crucial role in addressing people's health needs close to where they live and work while, at the same time, reducing the cost of care and enhancing equity.

An estimated 200 million people in Africa will be newly infected with malaria this year alone. WHO stands ready to support affected countries and our partners as we work together to limit the spread of drug resistance, provide efficacious treatment for all in need, and work towards our dream of a malaria-free world.

A handwritten signature in black ink, appearing to read "Tedros Adhanom". The signature is fluid and cursive, with a prominent initial "T" and "A".



# Acknowledgements

The *Strategy to respond to antimalarial drug resistance in Africa* was developed by the World Health Organization (WHO) Global Malaria Programme in collaboration with the WHO Regional Office for Africa and WHO Regional Office for the Eastern Mediterranean.

The work was coordinated by the WHO Global Malaria Programme, with the direct support of Boston Consulting Group and funding from the Bill & Melinda Gates Foundation.

WHO would like to thank the leadership team, the members of the workstreams and the many individuals that through interviews supported the preparation of this Strategy; as well as the many individuals who participated in the open consultation, and the Malaria Policy Advisory Group (MPAG) for the review and the comments on the draft document (see **Annex 1**).

# Abbreviations and acronyms

ACT	artemisinin-based combination therapy
COVID-19	coronavirus disease
GDP	gross domestic product
GMS	Greater Mekong subregion
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GTS	Global technical strategy for malaria
HCW	health care worker
HRP	histidine-rich protein
MPAG	Malaria Policy Advisory Group
NMP	national malaria programme
PCR	polymerase chain reaction
<i>PfKelch13</i>	<i>Plasmodium falciparum Kelch13</i>
RSA	ring-stage survival assay
RDT	rapid diagnostic test
TACT	triple artemisinin-based combination therapy
TES	therapeutic efficacy study
WHO	World Health Organization

# Executive summary

The *Strategy to respond to antimalarial drug resistance in Africa* is a technical and advocacy document, grounded in the best available evidence to date and aimed at minimizing the threat and impact of antimalarial drug resistance of *Plasmodium falciparum* parasites in Africa. Its objectives are to: i) improve the detection of resistance to ensure a timely response; ii) delay the emergence of resistance to artemisinin and artemisinin-based combination therapy (ACT) partner drugs; and iii) limit the selection and spread of resistant parasites where resistance has been confirmed. Although the Strategy focuses on Africa, antimalarial drug resistance is a threat in all malaria-endemic countries. As such, the interventions highlighted in this document could be applied to other geographies, but they would have to be tailored to local specificities.

The Strategy builds on lessons learned from past global plans and complements existing strategies, including broader efforts to respond to antimicrobial resistance. Implementing the Strategy should not divert resources from other malaria goals. It further builds on priorities highlighted in the *Global technical strategy for malaria 2016–2030* (1).

## Context

Africa bears almost the entire burden of malaria, accounting for 96% of global malaria cases in 2020 and 98% of global malaria deaths; poor and vulnerable populations experience the highest burden. Children under 5 accounted for about 80% of all malaria deaths in the World Health Organization (WHO) African Region in 2020. Although there have been significant efforts to tackle malaria in Africa over the last 20 years, progress has stalled and the funding gap between calculated needs and funds available has widened in recent years (2). In addition, new threats in Africa, such as the emergence of artemisinin partial resistance, have made progress difficult.

To treat uncomplicated *P. falciparum* malaria cases, WHO recommends the use of ACTs. While WHO currently recommends six ACTs, the majority of patients in Africa are treated with either artemether-lumefantrine or artesunate-amodiaquine.

Artemisinin partial resistance can be defined as delayed parasite clearance after treatment with a drug containing an artemisinin derivative. Significant reduction of treatment efficacy has not been observed in association with delayed parasite clearance after treatment with a drug containing an artemisinin derivative. However, increases in the proportion of parasites carrying *P. falciparum Kelch13 (PfKelch13)* mutations indicate that parasites with this mutation have an advantage under current treatment strategies and transmission dynamics; this could be due to higher transmissibility or improved fitness.

In the absence of partner drug resistance, delayed clearance after treatment with an ACT does not necessarily lead to increased treatment failure rates. However, partner drug resistance has been seen to cause treatment failure. Artemisinin partial resistance puts partner drugs at greater risk because of the increased numbers of parasites exposed to the partner drug alone. Although not confirmed to date, there is also a concern over the potential loss of efficacy of artesunate monotherapy for severe malaria cases in the presence of artemisinin partial

resistance. Especially in populations with a high level of immunity, *PfKelch13* mutations can be detected earlier than delayed clearance. Therefore, an increased proportion of parasites with *PfKelch13* mutations can act as an early warning and warrant a response.

## The threat of antimalarial drug resistance in Africa

Recent studies have confirmed the emergence of artemisinin partial resistance in several areas of Africa, notably in Rwanda, Uganda and Eritrea. Although resistance to the ACT partner drugs currently in use has not been confirmed, there are some worrying signals. Data are lacking from several countries and areas, meaning that resistance may be present in other areas. There are contradictory findings on ACT efficacy that need to be further assessed, particularly for artemether-lumefantrine.

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

It should be emphasized that ACTs remain highly efficacious for the time being. However, full-blown ACT treatment failure would have tremendous consequences in Africa. Researchers at Imperial College London estimated that a scenario with widespread artemisinin partial resistance and high partner drug resistance could result in ~16 million additional malaria cases and ~360 000 hospitalized severe cases (3). Assuming that a portion of these additional cases would lead to additional deaths, this scenario could result in an excess 80 000 deaths per year. The yearly economic impact would be US\$ 1 billion across the continent in that same scenario.

## Drivers of resistance

Understanding the factors that play a role in driving the emergence and spread of resistance is critical to effectively respond to the threat of antimalarial drug resistance. A broad literature review and consultation process led to the identification of two categories of factors driving resistance: background drivers and treatment-related drivers. Background drivers include intrinsic factors linked to the parasite, host and drugs used, as well as environmental factors. Treatment-related drivers are those affecting how often, at what dose, and for how long a parasite population is exposed to a given drug.

This Strategy focuses primarily on identifying practical interventions to address treatment-related drivers of resistance, while calling for increased research on background drivers. The risk of the emergence and spread of resistance increases when a high number of parasites are exposed to drugs, when parasites are exposed to one drug only, when parasites are exposed to subtherapeutic drug levels, when parasites that are not fully sensitive are more likely to be transmitted, and when parasites are exposed to drugs to which they are not fully sensitive. Detailed treatment-related drivers of resistance are outlined in **Fig. 4** in **section 4.3** of the document.

## **Interventions to mitigate the risks and respond to the emergence and spread of antimalarial drug resistance in Africa**

The Strategy addresses the threat of antimalarial drug resistance in Africa through four pillars. Each pillar consists of a set of interventions (20 in total, see **Fig. 6** in **section 5.2** in the document) that can be implemented at the local, regional and global levels. While this Strategy gives a comprehensive overview of the gamut of interventions that can be implemented, implementing countries need to tailor the Strategy to their local context. An initial country assessment is needed to enable countries to focus on the factors that are most likely to drive the emergence and spread of resistance in their context, and to prioritize their efforts in responding to resistance.

### **Pillar I: Strengthen surveillance of antimalarial drug efficacy and resistance**

Our ability to respond appropriately and in a timely manner to the spread of artemisinin partial resistance and the potential emergence of resistance to partner medicines is hindered by the lack of up-to-date information. This information is gathered through efficacy studies, surveys and genotyping to evaluate the prevalence of molecular markers of drug resistance, and the use of 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 (or lack of standards) and protocols to ensure data of comparable quality, lack of planning to ensure that data are available from the areas where they are most needed, and sometimes years of delay between data collection and findings being shared with relevant stakeholders. This pillar calls for strengthened surveillance capacity, as well as increased technical and laboratory capacity to provide expanded coverage of the data on antimalarial drug efficacy and resistance in Africa. It builds upon the significant investments already made in regional networks and in-country collaborations.

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

Protecting the efficacy of existing ACTs is an immediate priority. The suboptimal use of existing diagnostics and therapeutics can increase 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 quality-assured drugs at country level, and the circulation of substandard or falsified drugs and non-recommended monotherapies can increase drug pressure unnecessarily. From a demand perspective, the lack of demand for alternative drugs to artemether-lumefantrine and artesunate-amodiaquine, as well as the inappropriate use of available antimalarial drugs and diagnostics due to provider or patient behaviour could 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, notably through better adherence to WHO recommendations and full use of the diversity of tools available in the set of antimalarial compounds. To ensure the availability, affordability and quality of these tools, the global malaria community should use its combined market-shaping power to achieve healthier malaria commodity markets, while being mindful of the need to promote innovation, in support of African-led efforts.

### **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, the focus should be on prioritizing optimal vector control and other preventive measures, such as chemoprevention and vaccines, in priority areas; restricting transmission from recrudescing cases; and limiting any advantage that higher gametocyte carriage could potentially confer to resistant parasites. Although the risk in different areas and groups should be assessed and is likely to differ by population, country and region, additional resources and efforts should be mobilized towards areas where resistance is confirmed, border areas where there is evidence of resistance in neighbouring areas, and towards areas with significant inflows of mobile and migrant populations from areas with known resistance. Underserved areas and hard-to-reach populations (e.g. displaced populations, migrant populations, forest goers) should not be omitted. Lastly, promoting collaboration across borders could ensure that resistance detected in one country is addressed through a regional response.

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

An effective response to the threat, limiting the potential impact of antimalarial drug 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 reached just over US\$ 619 million in 2020. Between 2021 and 2030, it is estimated that an average annual investment of US\$ 851 million in research and development is needed (2). This pillar calls for innovative approaches to better use current tools, for the development of new tools, and for increased modelling and research to characterize resistance, its impact, drivers and how corrective interventions might address those drivers. These interventions will rely on strong, endemic-country-led collaborations among African regional and global research communities and partners to conduct studies and implement pilots in order to test new approaches and improve the overall knowledge on malaria drug resistance.

**The time to act is now.** Antimalarial drug resistance poses a serious threat to achieving further gains in the fight against malaria in Africa. In light of recent evidence confirming the emergence of artemisinin partial resistance in Africa, the malaria community must act now and mount a swift and coordinated response to this major threat.

# 1. Introduction

## 1.1 Purpose of the Strategy

The *Strategy to respond to antimalarial drug resistance in Africa* is a technical and advocacy document, based on the best available evidence. It is an overarching strategy to provide guidance to key stakeholders in the malaria community.

The goal of the Strategy is to minimize the threat and impact of antimalarial drug resistance of *Plasmodium falciparum* in Africa. It should be noted that antimalarial drug resistance is a threat across all malaria-endemic countries, and that the interventions outlined in this document could be applied to other geographies, although they would have to be tailored to local specificities.

The Strategy has three objectives that are instrumental to achieving the goal:

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

To achieve these strategic objectives, factors driving the emergence and spread of resistance have been identified. Addressing these drivers will have a direct impact on antimalarial drug resistance and improve the overall quality of care.

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

## 1.2 Structure of the Strategy

The core document provides a comprehensive overview of the current situation of antimalarial drug resistance in Africa, identifies key drivers of resistance and offers a detailed set of interventions to respond to the threat of resistance. **Chapter 2** describes the context in which resistance is being considered. **Chapter 3** analyses the current situation in Africa and calls stakeholders to action. **Chapter 4** looks at the elements that drive the emergence, selection and subsequent spread of antimalarial drug resistance. **Chapter 5** lists recommended interventions to respond to resistance and provides guidance on how to conduct a baseline assessment at country level to select the most relevant interventions for each setting. **Chapter 6** advocates for enabling mechanisms to be in place to facilitate the implementation of the interventions by key stakeholders.

Six annexes provide technical content. **Annex 1** describes the methodology and process involved in the development of the Strategy. **Annex 2** includes a list of working definitions and technical background on resistance. **Annex 3** estimates the health and economic cost of inaction. **Annex 4** provides a granular view of the treatment-related drivers of resistance. **Annex 5** guides countries in assessing their starting point in terms of resistance and their health system's maturity. **Annex 6** describes how interventions should be addressed by each category of key stakeholders.

## 2. Context

### 2.1 The malaria burden in Africa

Malaria is still a major health problem worldwide. Nearly half of the world's population is at risk of being infected with malaria, in 85 endemic countries. According to the World Health Organization (WHO) *World malaria report 2021*, there were an estimated 241 million malaria cases and an estimated 627 000 deaths globally in 2020 (2). In addition, there is a vast number of asymptomatic malaria cases; these cases contribute greatly to the continuing transmission of malaria parasites and can have a negative health impact on those infected (4).

Africa<sup>1</sup> bears almost the entire burden of malaria. In 2020, 96% of global malaria cases (232 million) were estimated to have occurred in Africa. Five African countries with the highest estimated malaria burden accounted for more than half of the malaria cases globally: Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%), Mozambique (4%) and Angola (3%). Africa also bears almost the entire burden of estimated global malaria deaths – at 98% (612 000) in 2020. *P. falciparum*, the deadliest malaria parasite, accounted for 99.7% of malaria cases in the WHO African Region in 2020 (2).

In Africa, the poorest and most marginalized populations are at greatest risk of being infected by *P. falciparum*. Once infected, some population groups are more vulnerable to severe disease and death, as they have relatively little immunity against the disease. These groups include children under 5 years of age, pregnant women, people living with HIV/AIDS and populations with low immunity moving to areas with high transmission, such as travellers, migrant workers and mobile populations. Children under 5 accounted for about 80% of all deaths in the WHO African Region in 2020 (2,5).

Over the last 20 years, there have been significant efforts to tackle malaria in Africa. Between 2000 and 2020, a 35% reduction in malaria incidence was achieved (2). Morocco and Algeria were certified as malaria-free in 2010 and 2019, respectively.

However, progress has stalled and the funding gap has widened in recent years (2). Even before the emergence of the coronavirus disease (COVID-19) pandemic, global gains against malaria had levelled off, and the world was not on track to reach the 2020 milestones of the *Global technical strategy for malaria 2016–2030* (GTS) (1). During the COVID-19 pandemic, the situation worsened as many countries experienced disruptions to malaria prevention, diagnosis and treatment. Mainly because of these disruptions to services, the incidence of malaria increased in 2020. In addition, progress has been made difficult by new threats in Africa, such as the emergence of artemisinin partial resistance; spread of parasites that go undetected by the most widely used rapid diagnostic tests (RDTs) due to *P. falciparum* histidine-rich protein 2 and 3 (*Pfhrp2/3*) gene deletions; vector resistance to insecticides; and reports from an increasing number of African countries of invasion by *Anopheles stephensi*, an urban malaria vector originally confined to Asia. Despite these threats, the funding gap between the amount invested and the resources needed has widened dramatically in recent years, increasing from US\$ 2.3 billion in 2018 to US\$ 2.6 billion in 2019 and US\$ 3.5 billion in 2020 (2). The emergence and spread of antimalarial drug resistance will most likely further increase the need for funding, as it may force countries to switch to newer and more expensive products (6).

<sup>1</sup> 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).

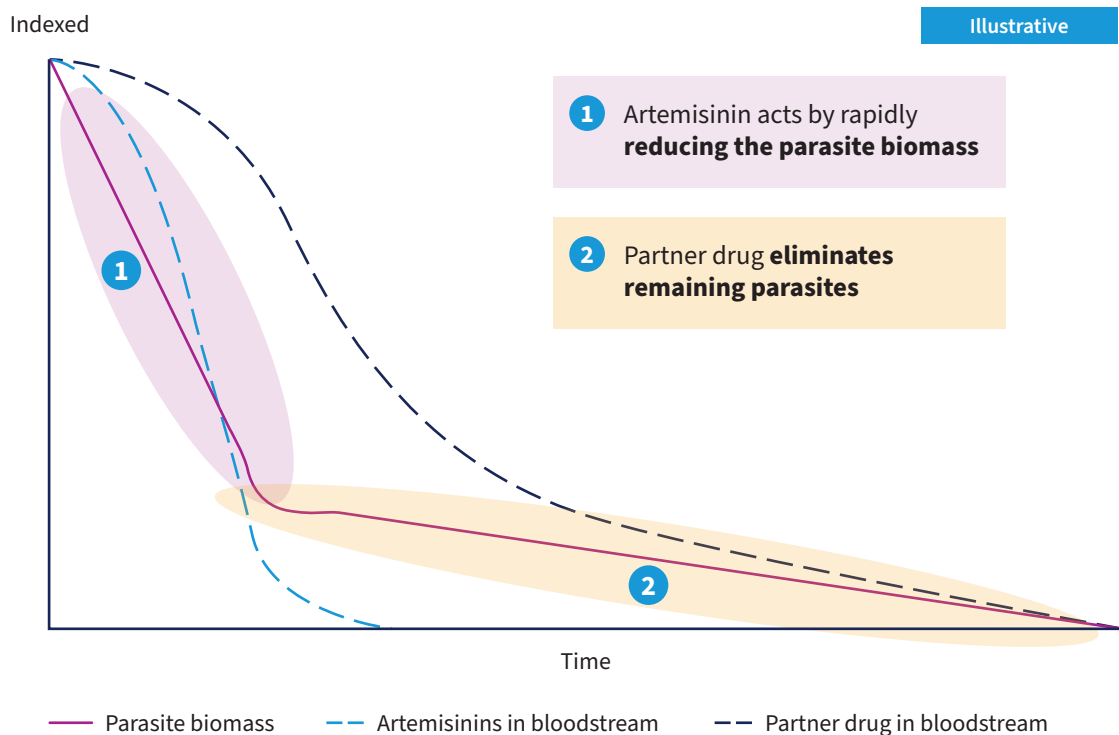


## 2.2 ACTs at the heart of the response

There has been widespread antimalarial drug resistance in Africa in the past. In 2001, WHO recommended the use of ACTs in countries where *P. falciparum* malaria was resistant to previously efficacious treatments, such as chloroquine, sulfadoxine-pyrimethamine and, to a lesser extent, amodiaquine (7, 8).

An ACT consists of a combination of an artemisinin derivative and a partner drug. ACTs are recommended for the treatment of uncomplicated *P. falciparum* malaria. The role of the artemisinin derivative is to rapidly reduce the parasite biomass, while the role of the partner drug is to eliminate the remaining parasites after artemisinin has been cleared from the blood (see Fig. 1). Even if used as a monotherapy, in the absence of resistance, a full dose of any partner drug included in the six WHO-recommended ACTs – artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperazine, artesunate-mefloquine, artesunate+sulfadoxine-pyrimethamine and artesunate-pyronaridine – can clear parasitaemia and cure patients. Due to the very short half-life of the artemisinin derivative, the partner drug acts as a monotherapy starting shortly after the administration of the last dose of ACT. Consequently, ACTs differ from most other combination therapies, in that they include drugs with very different pharmacokinetics; accordingly, they could be characterized as artemisinin-boosted antimalarials.

**Figure 1. Evolution of parasite biomass in the body following ACT administration**



While WHO currently recommends six ACTs, the majority of patients are treated with either artemether–lumefantrine or artesunate–amodiaquine. Artemether–lumefantrine 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 artesunate–amodiaquine representing 10% (9). Several factors explain this pre-eminence. Artemether–lumefantrine was the first ACT to be developed, and it is the first-line therapy in most African countries. Artemether–lumefantrine and artesunate–amodiaquine are the most affordable options, at US\$ 0.60 and US\$ 0.78 per adult treatment course, respectively, versus US\$ 2–3 for other ACTs (10). Artemether–lumefantrine is also the most accessible ACT, with prequalified artemether–lumefantrine being produced by nine suppliers with significant production capacity (11).

## 2.3 Defining and monitoring resistance

There are two main working definitions of resistance:

- **Antimalarial drug 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 after treatment with a drug containing an artemisinin derivative of a parasite strain carrying a particular mutation or set of mutations that are validated as associated with this delayed clearance, 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.

Detailed definitions of antimalarial drug resistance are provided in **Annex 2**.

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, leading to delayed clearance of parasitaemia. Consequently, after three days of treatment, a larger biomass remains, which must be eliminated by the partner drug. This delayed clearance has been found to be associated with *P. falciparum* *Kelch13* (*PfKelch13*) mutations. However, even in areas of high prevalence of *PfKelch13* mutations, a seven-day artesunate treatment has shown over 90% efficacy, suggesting that delayed clearance does not meet the standard definition of antimalarial drug resistance (12). The observed delayed clearance is, therefore, termed artemisinin partial resistance (see **Annex 2**). 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, i.e. leading to treatment failure following a full dose of artesunate.

There are indications that *PfKelch13* mutations could facilitate the spread of artemisinin partial resistance. In the Greater Mekong subregion (GMS), some strains carrying *PfKelch13* mutations associated with partial resistance appear to have an increased capability to generate gametocyte carriage (13). This has not been confirmed in Africa; however, the increases in the proportion of parasites carrying *PfKelch13* mutations now observed in some countries in Africa indicate that parasites with this mutation have an advantage under current treatment strategies and transmission dynamics; this could be due to higher transmissibility or improved fitness.

In areas with artemisinin partial resistance, delayed clearance after treatment with an ACT does not necessarily lead to an increase in treatment failure rates in the absence of partner drug resistance. However, partner drug resistance can cause treatment failure. In the GMS, ACTs have remained efficacious despite the presence of artemisinin partial resistance, provided that there is no resistance to partner drugs. Artemisinin partial resistance puts partner drugs at greater risk by exposing an increased number of parasites to the partner drug alone. As such artemisinin partial resistance likely played a role in the rapid spread of resistance to the ACT partner drug piperazine across countries in the GMS. Although not confirmed to date, there is also a concern over the potential loss of efficacy of artesunate monotherapy for severe malaria cases in the presence of artemisinin partial resistance.

Continuous monitoring is crucial. Therapeutic efficacy studies (TESs) remain the gold standard for determining antimalarial drug efficacy. These studies are prospective evaluations of patients' clinical and parasitological responses to treatment for uncomplicated malaria. TESs are conducted with a diagnosis validated by microscopy, using a quality-assured treatment and supervised drug administration. Despite their limitations, these studies provide decision-makers with an indication of the efficacy of drugs for treating malaria. To be comparable across countries and over time, it is crucial to use standardized protocols. TESs alone are not sufficient to confirm drug resistance; this must be confirmed through other means (14):

- **Molecular marker analyses (genotypes)** identify genetic changes in the parasite genome that are associated with a change in parasite susceptibility to antimalarial drugs.
- **Ex vivo and in vitro assays (phenotypes)** test the sensitivity of fresh or culture-adapted parasites to antimalarial drugs by exposing them to different concentrations of a drug (typically for 42 hours) or to a pulse of a high concentration of a drug (in ring-stage survival assay [RSA]) and observing the effect on parasite survival.
- **Measurements of drug levels in the blood** allow monitoring of 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 due to resistance.

# 3. The threat of antimalarial drug resistance in Africa

## 3.1 Antimalarial drug resistance in Africa

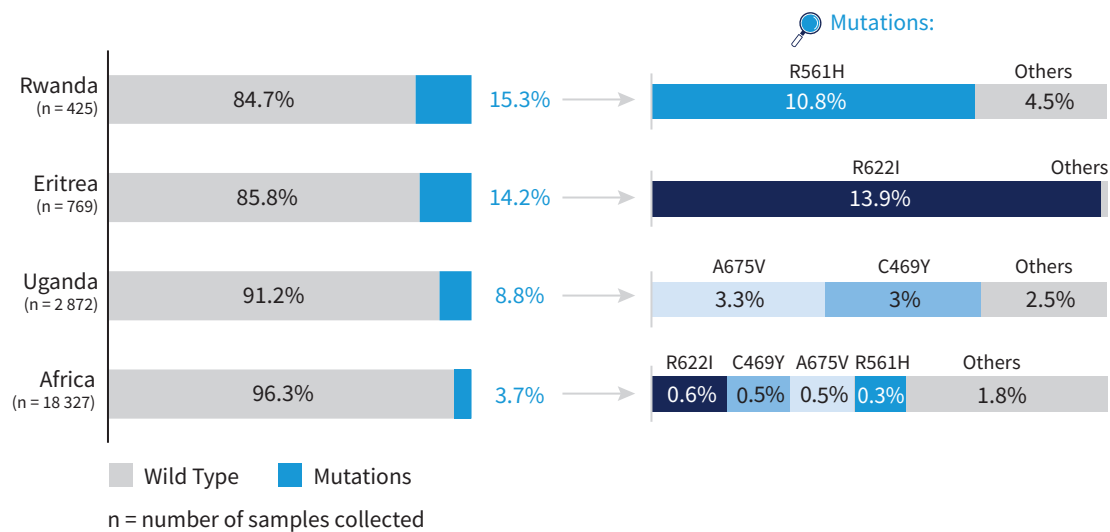
### 3.1.1 Artemisinin partial resistance in Africa

Evidence of the selection and spread of parasites with partial resistance to artemisinin derivatives has been documented in the following areas of Africa (see **Fig. 2**):

- **Rwanda:** Two studies conducted by the national malaria programme (NMP) between 2013 and 2015 reported a clonal expansion of the *PfKelch13* R561H mutation, and RSA confirmed that this mutation conferred reduced susceptibility to dihydroartemisinin (15). However, no evidence of treatment failure rates above 10% for artemether-lumefantrine or dihydroartemisinin-piperaquine was reported. In a third study conducted in 2018 with the support of the United States Centers for Disease Control and Prevention, expansion of the *PfKelch13* R561H mutation was confirmed (16). This mutation was associated with delayed clearance; nonetheless, artemether-lumefantrine displayed continued excellent efficacy. Similarly, a fourth study reported a higher prevalence of the *PfKelch13* R561H mutation (22%) that was also associated with delayed clearance, but with conserved artemether-lumefantrine efficacy (> 94%) (17). This suggests that the partner drugs and ACT regimens were still effective in Rwanda at the time of the evaluations.
- **Uganda:** Surveys reported an elevated prevalence of the *PfKelch13* C469Y and A675V mutations in multiple districts in northern Uganda (18). More recently, isolates with C469Y and A675V mutations were associated with clinical delayed clearance in patients who were administered intravenous artesunate followed by artemether-lumefantrine. The A675V mutation was also associated with in vitro RSA reduced susceptibility (19). Unpublished evidence also shows in vitro reduced susceptibility for C469Y (20). However, ACTs remained effective in Uganda at the time of the surveys.
- **Horn of Africa:** The R622I mutation has been reported in several countries in the Horn of Africa, but correlation with delayed parasite clearance has so far only been assessed in Eritrea, where this mutation was shown to induce reduced susceptibility to artemisinin using RSA in 2019 (Eritrea NMP, unpublished data).

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

**Figure 2. Countries with more than 5% of parasites with *PfKelch13* mutations and main mutations identified (2015–2020) (21)**



- Figure 2 describes the prevalence of mutations detected in *PfKelch13* genotypes as a percentage of the total samples genotyped in the country during the 2015–2020 period.
- The prevalence of mutations varies among countries but also locally within a given country.
- The prevalence of mutations reported at country level is impacted by the location and number of studies conducted. Typically, more studies are done in areas where high prevalence has previously been detected.

### 3.1.2 Resistance to ACT partner drugs in Africa

Resistance to currently used ACT partner drugs has not been confirmed despite some worrying signals. Significant levels of resistance to an ACT partner drug in the presence of artemisinin partial resistance would result in low efficacy of the ACT. Published and unpublished data compiled in the WHO database allow for a deep analysis of the efficacy of the main ACTs. Results from some studies should be interpreted with caution, as deviations from WHO standard protocols can lead to underestimation or sometimes overestimation of the efficacy of some ACTs. The conclusions of an analysis of more than 400 studies conducted between 2009 and 2019 are described in the following paragraphs (14):

- **Artemether-lumefantrine:** Treatment failure rates greater than 10% after treatment with artemether-lumefantrine were reported in several countries in Africa between 2009 and 2019. Recently, high (i.e. over 10%) treatment failure rates were reported at some sites in Angola (22), Burkina Faso (23), the Democratic Republic of the Congo (24) and Uganda (25). Concerns were raised about the quality of microscopy in Burkina Faso (26). Analysis using a Bayesian algorithm (as for the studies in Angola, the Democratic Republic of the Congo and Uganda) is not recommended by WHO for reporting treatment outcomes and can, in high transmission settings, yield higher treatment failure rates than the 2008 WHO standard polymerase chain reaction (PCR) genotyping methodology (updated in 2021 (27)) to distinguish between reinfection

and recrudescence after treatment. Moreover, the interpretation of the cause of failures is hampered by the lack of lumefantrine drug levels and the lack of predictive genotypes for lumefantrine resistance. High failure rates were simultaneously reported for artemether–lumefantrine and dihydroartemisinin–piperaquine in Burkina Faso, the Democratic Republic of the Congo and Uganda. Lumefantrine and piperaquine cross-resistance is biologically improbable, putting these results into question. If there is a signal of treatment failure for more than one ACT with no biological explanation of the associated results, there should be close examination to check whether methodological issues potentially confounded the results.

- **Artesunate–amodiaquine:** Treatment failure rates close to 10% after treatment with artesunate–amodiaquine have been identified in two studies conducted in Liberia in 2017–2018 (28). Additional studies have been initiated to gather further data. Overall, surveillance of artesunate–amodiaquine efficacy and amodiaquine resistance has been neglected since WHO first recommended ACTs in 2001 and artesunate–amodiaquine was introduced.
- **Dihydroartemisinin–piperaquine:** Except for the studies in Burkina Faso (23) and the Democratic Republic of the Congo (24), where treatment failures with dihydroartemisinin–piperaquine were systematically associated with treatment failures with artemether–lumefantrine (see above), high treatment failure rates after treatment with dihydroartemisinin–piperaquine have not been reported in any other African countries (noting that dihydroartemisinin–piperaquine is not widely used in Africa), and resistance to piperaquine has not been confirmed in Africa.
- **Other ACT partner drugs:** Very few treatment failures have been reported after treatment with artesunate–pyronaridine or artesunate–mefloquine in Africa, although there has been minimal drug pressure to date. Resistance to sulfadoxine–pyrimethamine is widespread in Africa. Therefore, the use of artesunate+sulfadoxine–pyrimethamine is not recommended for the treatment of uncomplicated malaria in Africa. Sulfadoxine–pyrimethamine, however, is used for chemoprevention, either alone or in combination with amodiaquine.

There are contradictory findings that require further assessment regarding treatment failures with artemether–lumefantrine, the most commonly used ACT in Africa:

- Some TESs have highlighted signals of high treatment failure rates, as mentioned above; however, sometimes studies deviated from WHO protocols.
- During a TES, many confounders may potentially obscure measures of artemether–lumefantrine treatment failure: poor drug absorption, non-adherence (as the second daily dose is often unsupervised), and the short half-life of lumefantrine leading to high reinfection rates, with some reinfections potentially misclassified as recrudescence during laboratory analysis.
- There have been reports of artemether–lumefantrine treatment failures in travellers returning from Africa to Portugal (29), Sweden (30) and the United Kingdom of Great Britain and Northern Ireland (31). 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, artemether–lumefantrine treatment failures in

travellers were successfully cured with a second treatment of artemether-lumefantrine in Sri Lanka (32) and Türkiye (33).

- A few reports have shown higher in vitro 50% inhibitory concentrations (i.e. mean drug concentration that inhibits 50% of the parasite growth) for lumefantrine; however, the in vitro lumefantrine resistance threshold has not been defined and trends are difficult to analyse, in part due to limitations in the standardization of the in vitro lumefantrine test.
- High treatment failure rates with artemether-lumefantrine have not been reported in Lao People's Democratic Republic or Myanmar, where artemether-lumefantrine is the first-line therapy, despite high prevalence of artemisinin partial resistance (34).

### 3.2 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 monitored and addressed urgently. The apparent rapid spread of some mutations associated with artemisinin partial resistance means that vigorous measures must be taken before ACTs start failing in Africa.

There is an urgent need to preserve the therapeutic lifespan of ACTs. Given the current drug pipeline outlook, it is unlikely that drugs with a different mechanism of action will become available soon, with the most promising non-artemisinin-based combination, ganaplacide-lumefantrine, in the patient exploratory phase (Phase IIb). Although such a formulation would address a situation of artemisinin partial or full resistance, its reliance on lumefantrine poses a risk should resistance to that partner drug be confirmed.

ACT treatment failure due to resistance is likely to result in an increased number of cases, leading to additional severe cases and ultimately excess deaths. A study by researchers at Imperial College London published in 2016 (3) provided preliminary estimates for Africa, showing that a scenario with widespread artemisinin partial resistance (54% of infected individuals experiencing delayed parasite clearance) and high partner drug resistance (45% of treated individuals recrudescing) could result in an additional ~16 million cases per year in Africa – a 7% increase in cases compared to a scenario with no resistance. Under the same scenario, the additional severe cases derived from the increased transmission were estimated at around 365 000 per year. Ultimately, assuming that a portion of these additional cases would lead to additional deaths, this scenario could result in an additional 80 000 deaths per year, assuming that around 20% of hospitalized severe cases lead to death (see **Annex 3**). Although such a scenario is hypothetical and there are many limitations to the model used, this could lead to an economic impact of US\$ 1–1.1 billion in additional costs per year across Africa. This figure includes the direct health costs that would be borne by individuals and health service providers (e.g. additional diagnostic tests and treatments, additional cost for inpatient care due to excess severe malaria cases, incremental cost of a new commodity following the introduction of a new first-line treatment) and lost productivity (e.g. absenteeism in the workplace due to disease burden or the need to care for a sick child, lost productivity due to premature death). At the same time, these are conservative estimates, since they do not account for the dramatic consequences that resistance would have in other areas, such as the impact on economic growth, the long-term effects on children linked to education disruptions

and the effect on the population's overall well-being. Finally, it is likely that population groups most at risk of malaria, such as poor, mobile and rural populations, and the most vulnerable women and children would be disproportionately affected, further widening the inequality gap.

The *Strategy to respond to antimalarial drug resistance in Africa* needs to build on lessons learned from past global plans and complement existing strategies. These include the *Global plan for artemisinin resistance containment (35)* and the *Strategy for malaria elimination in the Greater Mekong Subregion (2015–2030) (36)*, which highlight the need for adequate surveillance, strong regional collaboration, involvement of a large panel of stakeholders including NMPs and communities, and sustained financing (see **Fig. 3**). The Strategy also takes place within the context of a broader effort to respond to antimicrobial resistance. Strategic objectives outlined by the *Global action plan on antimicrobial resistance (37)* were leveraged in the development of the Strategy, including the need to tackle structural issues such as inequity, fractured health systems and entrenched poverty, and need to improve awareness and understanding of antimicrobial resistance through effective communication, education and training. Finally, the Strategy uses key elements of the “High burden to high impact” approach, a country-led response, catalysed by WHO and the RBM Partnership to End Malaria, in which 11 African countries<sup>1</sup> actively participate, in addition to India (38).

In the GMS, the initial response to resistance developed into escalated efforts to achieve malaria elimination, a goal likely to be reached within the next few years. The scale of the challenge and the multitude of different settings in Africa vastly exceed those of the GMS. In some countries, elimination may be a feasible short-term goal, either nationwide or at the subnational level. However, in many countries, the near-term goal needs to be the optimization and expansion of activities based on the interventions outlined in this Strategy.

This Strategy should not divert resources away from efforts on other malaria goals. This Strategy further builds on the priorities highlighted in the GTS: the need to protect the efficacy of ACTs and develop new non-artemisinin-based combinations (1). It will also contribute to broader malaria control objectives by ensuring access to malaria prevention, diagnosis and treatment as part of universal health coverage.

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<sup>1</sup> Burkina Faso, Cameroon, Democratic Republic of the Congo, Ghana, Mali, Mozambique, Niger, Nigeria, Uganda and the United Republic of Tanzania, with the addition of Sudan in April 2022.



Figure 3. High-level learnings from the response to resistance in the GMS



#### Adequate surveillance

- Surveillance has been a top priority, from **increasing surveillance of antimalarial drug efficacy and resistance** to **strengthening overall malaria surveillance** of drug quality, number of cases and deaths.
- Various tools have been leveraged, from **app enabling collection of real-time data** to the implementation of a **regional malaria elimination database**.



#### Regional collaboration

- A **coordinated response** towards the fight against malaria has been encouraged between countries, for instance through regional grants and sharing of best practice and strategies.
- **Cross-border interventions** have been fostered to target hard-to-reach populations and foci of resistance, such as mobile populations in forested and remote areas.



#### Involvement of a large panel of stakeholders

- **Coordination between a large panel of stakeholders** has been promoted: funders, multilateral agencies, technical partners, academia and researchers, private sector, governments and communities have been enrolled in the strategy, through region-wide initiatives and dedicated steering bodies (e.g. the Mekong Malaria Elimination programme).



#### Community involvement

- **Building community malaria networks**, by leveraging village and mobile malaria workers has been crucial in implementing the strategy and reaching populations at risk of resistance.



#### Financing

- A **well funded approach** is key to financing broad and innovative interventions, such as intensive training and procurement of commodities, in order to foster coordination between countries, fund operational research, and so on.

# 4. Drivers of resistance

## 4.1 Overview of drivers of resistance

Effectively responding to the threat of antimalarial drug resistance requires an understanding of the factors that 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 parasites carrying one or more mutations that provide some degree of protection from the effect of a drug.

The role the different factors play in driving the emergence, selection and spread of resistance will vary by drug and context. There is good consensus on the factors that may drive the emergence and spread of resistance, but knowledge of their relative importance is limited by the lack of available data and evidence.

A broad literature review and consultation process led to the identification of two categories of factors driving resistance: background drivers and treatment-related drivers (see **Fig. 4** and **Annex 4**). Background drivers include intrinsic factors linked to the parasite, host and drugs used, as well as environmental factors. Treatment-related drivers are those affecting how often, at what dose, and for how long a parasite population is exposed to a given drug.

This Strategy focuses primarily on identifying practical interventions to address treatment-related drivers of resistance, while calling for increased research on background drivers. An initial country assessment is needed to enable countries to focus on the factors that are most likely to drive the emergence and spread of resistance in their context, and to prioritize their efforts in responding to resistance (see **Annex 5**).

## 4.2 Background drivers of resistance

Parasite genetic background can influence the degree to which a mutation affects drug sensitivity and the likelihood that the mutation will spread (39). Certain genetic backgrounds 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 between *P. falciparum* parasite strains from Africa and those from other malaria-endemic regions.

The level of transmission could impact the risk of spread (40). Higher malaria transmission results in many strains circulating in a population and a higher chance of mixing genetic material during a parasite's sexual reproduction. Therefore, higher malaria transmission increases the risk that some potential background resistance mutations will be lost and increases the competition with other parasite strains. Additionally, populations living in higher transmission areas have some level of acquired immunity, meaning that the host is better able to eliminate parasites regardless of the level of drug resistance (41).

A range of additional setting-specific factors affect the emergence and spread of resistance. These factors include human migration from areas with resistance, the ability of local

mosquitoes to spread the resistant strain (42), and climate change, which alters temperature, humidity and rainfall, potentially shifting the geography and seasonality of transmission (43).

### 4.3 Treatment-related drivers of resistance

Drug pressure drives the selection and spread of resistant parasites. Malaria parasites are exposed to different antimalarial drugs that are intended to cure patients by eliminating the parasites. However, continuous or repeated exposure to a drug 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 antimalarial drugs. The exposure of a parasite population to drugs depends on a range of issues, including access to quality diagnosis and treatment, and other use of antimalarial drugs such as for chemoprevention. Chemoprevention strategies can impact resistance and select parasites that are less sensitive to the drug used for chemoprevention. This impact will depend on the drugs used, the prevalence of resistance, the epidemiology and health system of the target area, the population covered, and the quality of the chemoprevention intervention. Chemoprevention with a drug not used for treatment could potentially decrease the risk of losing treatment drugs to resistance. However, the key challenge in the use of chemoprevention as part of a resistance strategy is the few drugs available.

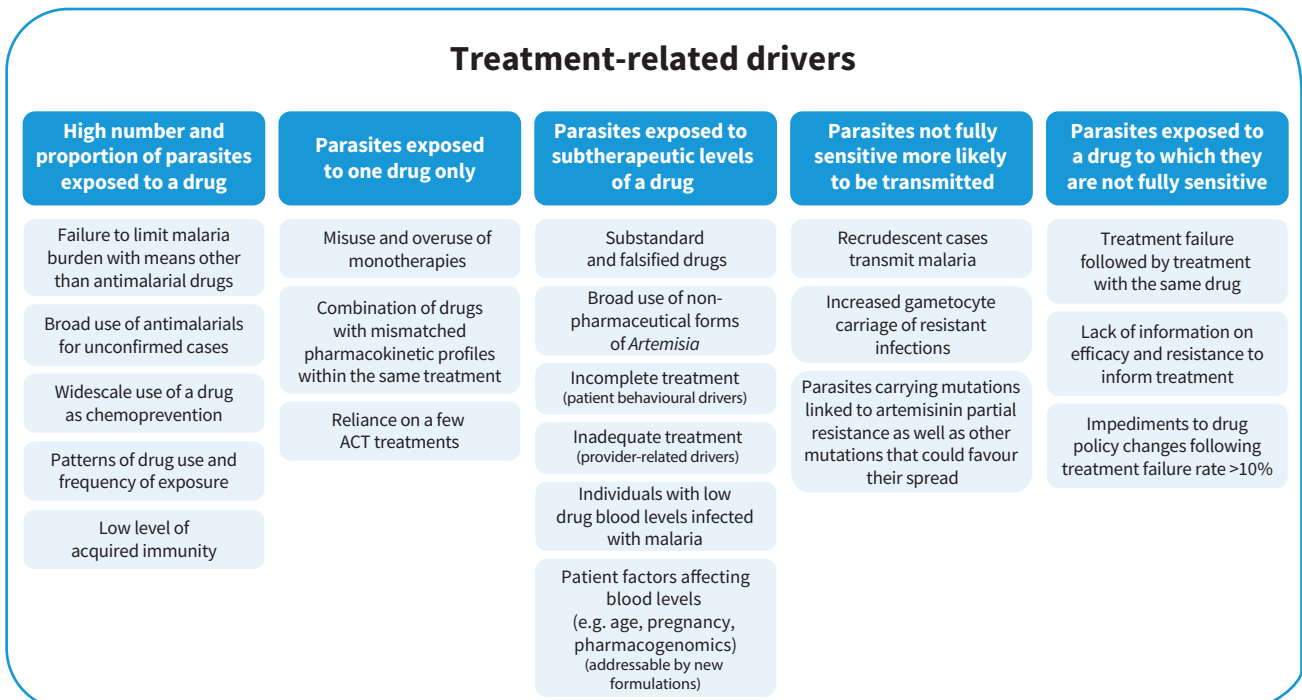
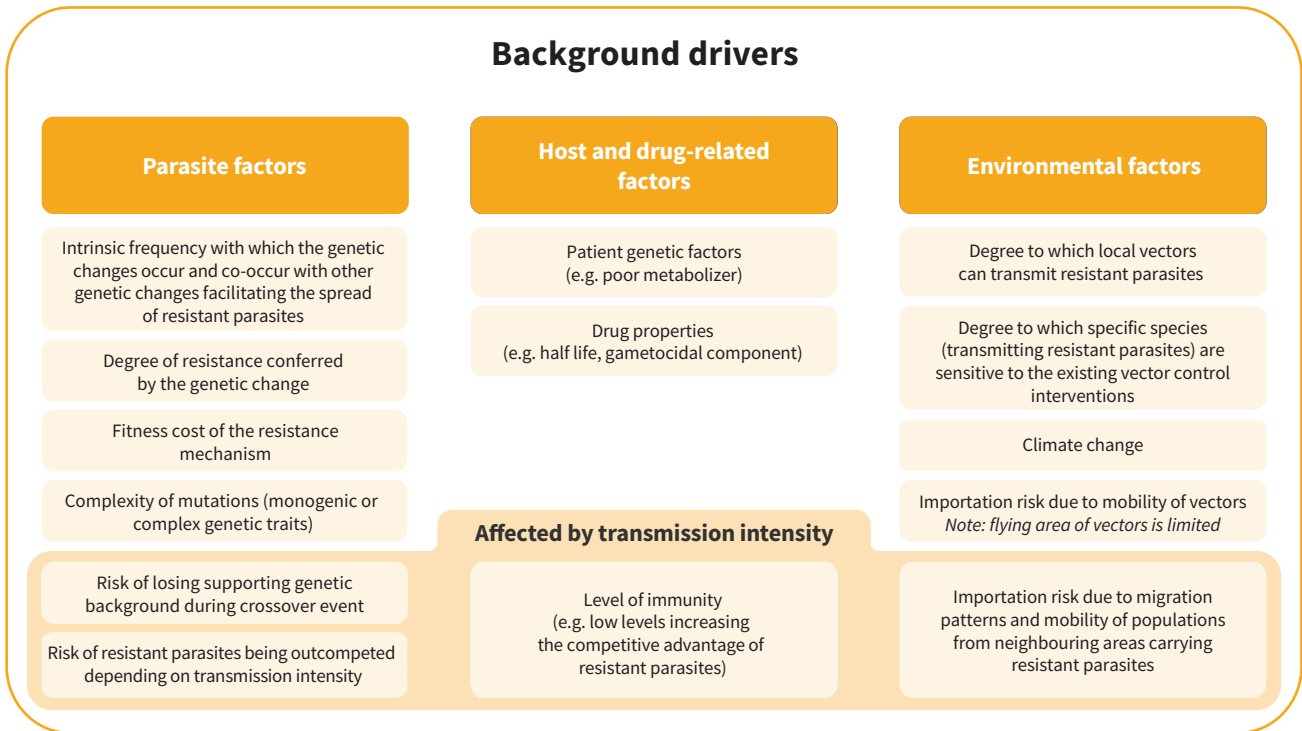
Pressure on a parasite population from a drug increases the risk of selection and spread of parasites resistant to that drug (42). When a parasite population is mainly exposed to one drug, the competitive advantage of having resistance to that drug and thus the risk of selection increases. In the past, uncomplicated *P. falciparum* was treated with chloroquine and sulfadoxine-pyrimethamine. Resistance to these drugs spread globally, reaching very high levels of prevalence. Although the current recommendation is treatment with an ACT combining an artemisinin component and a partner drug, 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 after the short-acting artemisinin component has been cleared.

Exposing parasites to subtherapeutic drug levels is thought to be an important selective force in the spread of resistance (42). Subtherapeutic drug concentrations in the blood allow resistant infections to be maintained and transmitted. The exposure of parasites to subtherapeutic drug concentrations can be caused by a variety of factors, including the use of substandard or falsified drugs, use of non-pharmaceutical forms of *Artemisia* such as *Artemisia* tea (44), poor compliance with treatment regimens or suboptimal dosing of an 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 (45) and are subsequently transmitted, or when parasites with reduced drug sensitivity have increased gametocyte carriage (13).

Exposing parasites to drugs to which they are not fully sensitive enables the parasites to multiply and be transmitted. Delays in detecting resistance and in responding to this problem by changing the treatment policy enable resistant parasites to spread and reach high levels of prevalence.

**Figure 4. Drivers of resistance**



# 5. 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 (see **Fig. 5**):

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

Each pillar consists of a set of interventions that can be implemented at the local, regional and global levels (see **Fig. 6**). The relevance of each intervention to address the drivers of resistance has been assessed through a broad consultation process.

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. It should also be noted that the interventions outlined in this document could be applied to other malaria-endemic regions.

Therefore, the immediate next step should be for each country to conduct an assessment of its current situation and, based on the results of the assessment, to use the Strategy to guide the development of recommendations tailored to the local context, with the support of global and regional stakeholders. An initial country assessment is required to prioritize the interventions, and estimate the resources and changes required to implement this Strategy in a given setting. Details of this assessment are included below in **section 5.1** and in **Annex 5**. The resulting recommendations may be included in broader national strategic plans for malaria and/or antimicrobial resistance action plans.

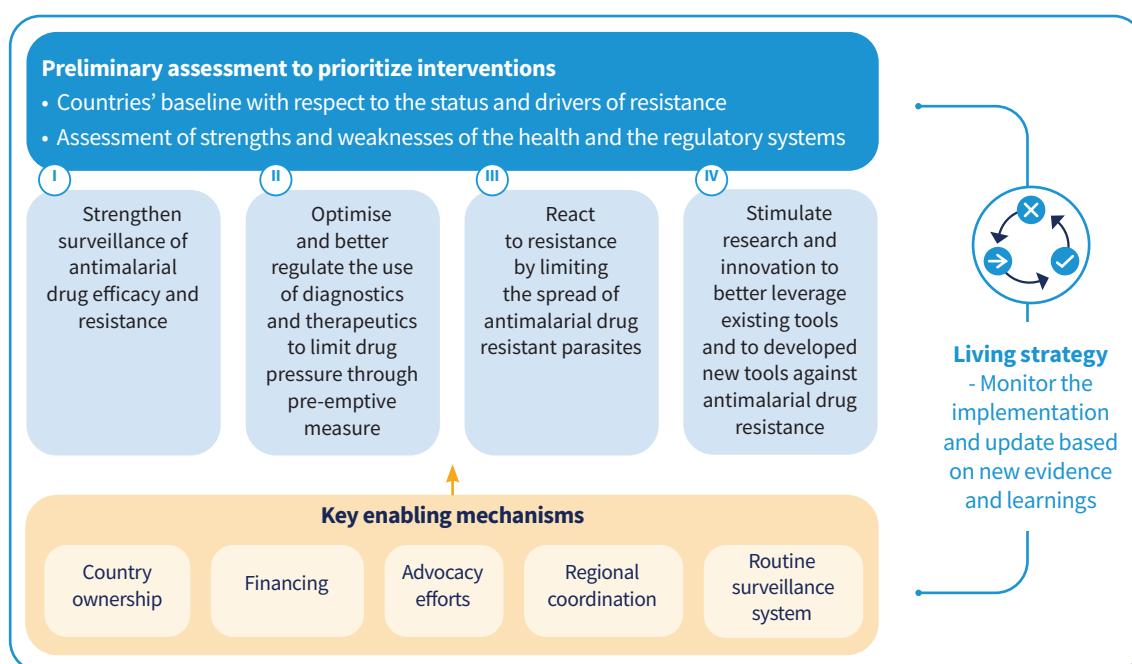
Key enabling mechanisms will be needed at all levels to ensure the feasible, impactful and sustainable implementation of each intervention. These mechanisms are further detailed in Chapter 6.

Countries should monitor and evaluate their implementation of the Strategy. Countries will need to define indicators and targets as part of the development of recommendations in order to monitor the implementation of the Strategy. Responding to antimalarial drug resistance should be a continuous process that will require adjustments based on lessons learned and

the latest evidence collected. A robust surveillance system, including surveillance of both antimalarial drug efficacy and resistance, and routine surveillance (see **Chapter 6**), will inform the need and the extent of implementation.

Although each country will have to perform a detailed analysis of its own starting point, some high-level guidance can be provided based on whether artemisinin partial resistance and/or partner drug resistance is confirmed or suspected. In the event of confirmed resistance, immediate efforts should be focused on i) assessing the extent of the problem by strengthening and expanding drug efficacy surveillance coverage for both artemisinin and partner drugs; ii) if partner drug resistance has been confirmed, ensuring continued efficacy of malaria treatment by rapidly switching to a second-line ACT if treatment failures are above a 10% threshold and by ensuring that health care workers (HCWs) are properly trained to use the new drug; and iii) limiting the onward transmission of drug-resistant parasites using both pharmacological and non-pharmacological tools. These reactive measures should be considered priorities that can then be complemented by additional, more advanced interventions based on resource availability. Countries with no confirmed resistance should strengthen drug efficacy and resistance monitoring and implement pre-emptive measures that will limit unnecessary drug pressure and thus delay the emergence of resistance.

**Figure 5. High-level framework of the Strategy: preliminary assessment, strategic pillars and enablers**



## 5.1 Preliminary assessment to prioritize interventions

To translate the Strategy into recommendations tailored to the local context, countries should undertake an initial assessment of the elements described below. The assessment can be based on information from routine surveillance, surveys and interviews with key stakeholders, but also on the use of in-country consultants or standardized data collected. Where no information is available, data collection can be incorporated into the proposed activities prioritized as part of a country's national action plan to progressively better target interventions.

The assessment should focus on three main areas: status of resistance and epidemiology, drivers of resistance, and overall health and regulatory systems. **Annex 5** details two levels of the assessment: a first level with only critical data to be collected, and a second level with a more comprehensive set of elements to be included, if there are sufficient resources.

### 1. Status of resistance and epidemiology

The assessment should include the following priority elements:

- **Determine the status of antimalarial drug efficacy and resistance, and data availability:** a review of efficacy and resistance surveillance data in the target country, as well as in neighbouring countries, is the starting point for this assessment. Identifying high-priority areas with no recent data will inform the need for further studies.
- **Identify the main characteristics of in-country malaria epidemiology:** factors such as the patterns of malaria transmission, parasite species, vector species and characteristics of the human population (e.g. levels of immunity) should be assessed.
- **Analyse the mobility of the human population:** understand human population movements and migration patterns.

### 2. Drivers of resistance

The assessment should include the following priority elements:

- **Understand the in-country availability and use of drugs:** analysis of access, current behavioural drivers of both patient and care provider choices, and patterns of drug and diagnostic use is required to design interventions to address these issues.
- **Assess adherence to treatment guidelines:** care providers' access to key resources for malaria case management (e.g. national treatment guidelines) and their knowledge and understanding of the treatment guidelines should be assessed.

### 3. Strengths and weaknesses of the health and regulatory systems

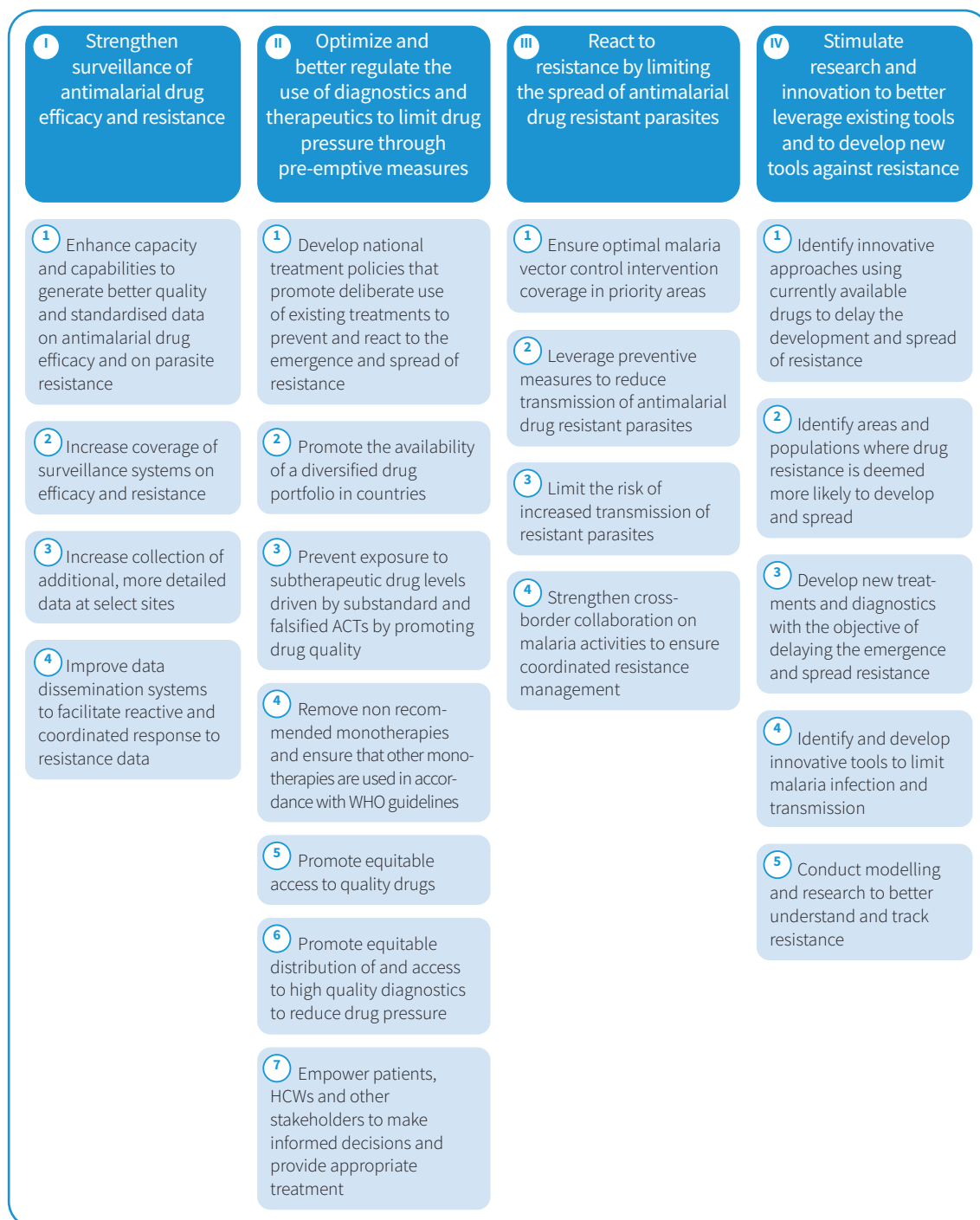
The feasibility and impact of each intervention will depend on the capabilities and resources available in each country, such as the amount of funding and human resources available, and on the capacity of each country to identify potential roadblocks, leverage past successes and existing opportunities, and implement change. Analysis of the strengths and bottlenecks should be based on past and ongoing experiences in implementing malaria interventions. Elements that need careful assessment include the following:

- **Strengths of the health and regulatory systems:** assess the health system structure and the institutional capacity to enforce national policies and regulations, as these will play a key role in defining the feasibility and impact of each intervention.
- **Gaps between the plans developed by the NMP 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).
- **Synergies with other strategies and global plans:** identify interventions that are already being deployed within the framework of other strategies, such as the *Global action plan on antimicrobial resistance (37)*, which could be beneficial and further leveraged to respond to antimalarial drug resistance (e.g. raising awareness, training).

## 5.2 Interventions to address key drivers of antimalarial drug 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 on areas and populations that are deemed at higher risk of developing resistance. Once specific groups and areas have been identified, additional funding and resources should be dedicated to reaching them.

**Figure 6. Twenty interventions clustered into the Strategy's four pillars to address resistance**





### 5.2.1. Pillar I: Strengthen surveillance of antimalarial drug efficacy and resistance

Our ability to respond appropriately and in a timely manner 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, surveys and genotyping to evaluate the prevalence of molecular markers of drug resistance, and the use of 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 (or lack of standards) and protocols to ensure data of comparable quality, lack of planning to ensure that data are available from the areas where they are most needed, and sometimes years of delay between data collection and findings being shared with relevant stakeholders.

This pillar calls for strengthened surveillance capacity, as well as increased technical and laboratory capacity to provide expanded coverage of the data on antimalarial drug efficacy and resistance in Africa. It builds upon the significant investments already made in regional networks and in-country collaborations. Four key interventions to address the challenges have been identified. They have country, regional and global components and will need to be prioritized based on the assessment of the current local drug efficacy and resistance situation, data and resource availability.

#### **Pillar I – Intervention 1 | Enhance capacity and capabilities to generate better quality and standardized data on antimalarial drug efficacy and parasite resistance**

##### ***Underlying issue***

There is a lack of available, good-quality data on antimalarial drug efficacy and resistance in many areas of Africa. The low quality and limited standardization of collected data hinder the effectiveness of the surveillance and response to resistance. For example, TESs are sometimes not conducted according to WHO standard protocols, which has resulted in the need to repeat some studies in the past (46). In addition, there is insufficient capacity to conduct genetic and pharmacokinetic studies. The establishment of a strong resistance surveillance in Africa, including adequate protocols, external quality assessment systems, laboratory capacity and data analytics, faces several challenges.

##### ***Suggested interventions***

**Promote adherence to standard TES protocols:** producing standardized data of comparable quality requires adherence to WHO standard TES protocols, available on the WHO Global Malaria Programme website (47). To conduct quality TESs, ministries of health and research institutes must be supported through continuing training, including for microscopists. Supervision and quality control around microscopy, data entry and classification should be strengthened to ensure that WHO protocols are followed. All TESs must be done with preferably prequalified drugs or quality-controlled. In addition, the analysis of known molecular markers of antimalarial drug resistance (see list provided in the WHO *Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010–2019)* (14)) should be systematically included in TES protocols. When frequent treatment failures are detected in a good-quality study, additional TES studies are rapidly needed, including the

collection of information on drug levels in the blood on day seven, especially for lumefantrine (see **section 3.1**) as set out in the TES protocol (48). A major challenge in high transmission settings is to correctly distinguish recrudescence from new infection. A possible strategy in sites located in high transmission settings where high failure rates have been reported is to provide insecticide-treated nets and topical repellents for patients enrolled in TESs to limit the risk of reinfection. Nevertheless, reinfections can provide valuable information on the prophylactic effect of an antimalarial drug, which starts to decline when susceptibility to the drug is decreasing. Reinfections could be considered early signals of emerging resistance, with the limitation that these signals should be interpreted based on the drug's half-life (49).

**Set up or reinforce laboratories for genomic and pharmacokinetic studies:** current investments to build strong genomic expertise in Africa through knowledge sharing and dedicated training programmes should be pursued, building on currently funded initiatives. Similarly, additional investments are also needed for increasing laboratory capacity for accurate measurement of antimalarial drug concentrations. Regional reference centres should be considered, using the experience gained during the COVID-19 pandemic. These regional reference centres would increase the capacity, quality and timeliness of PCR correction and surveillance of molecular markers, as well as measurements of drug levels in blood. They could conduct analyses for countries lacking internal capacity and act as training centres for neighbouring countries. Finally, strong quality control systems among laboratories are needed. Field specimens, control strains, and a mixture of both could be cross-analysed by the reference laboratories.

Although in vitro/ex vivo studies can be useful tools in the absence of confirmed molecular markers, setting up dedicated laboratories at the national level, conducting external quality control and sharing blood samples will raise specific issues.

**Address procurement challenges:** increased effort and additional financing are needed to address the 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 (e.g. through faster customs clearance, customs tax exemptions) and to improve the affordability of African-sourced supplies.

## **Pillar I – Intervention 2 | Increase coverage of surveillance systems for efficacy and resistance**

### ***Underlying issue***

The currently insufficient coverage of TESs limits the knowledge available on delayed clearance of parasites following ACT treatment and on ACT treatment failures. According to the WHO Malaria Threats Map, 18 endemic African countries have not conducted or shared TES results since 2017 (21). 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 lower transmission areas. Information on molecular markers plays an important role in tracking resistance and should be leveraged to detect early warning signals.

### ***Suggested interventions***

**Review and potentially reconsider the number of sites per country to conduct TESs:** the current recommendation is to conduct TESs 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 per country, experience suggests that ideally four to eight sites, depending on the country's size, will strike a balance between representativeness and practicality. In defining the number of sites, programme managers should consider the country's geographical size, population distribution and density, malaria epidemiology or ecology, and other factors deemed important by the programme. It is critical to select a "manageable" number of sites to ensure proper monitoring and supervision (50). Based on the number and location of existing sites, countries should look at intensifying surveillance activities in areas where data are lacking or where the risk of resistance is considered high, for instance areas with an influx of migrants from areas with known resistance. Studies done in populations with partial immunity can result in higher efficacy estimates and lower delayed clearance. TESs should, therefore, aim to enrol populations with no or limited immunity, such as children under 5 years of age.

**Collect information on molecular markers:** in addition to systematically including molecular markers in TESs, further surveys of molecular markers should be done independently, as such surveys can be conducted more easily and frequently than TESs. Although there is a lack of confirmed molecular markers of resistance for most partner drugs used in Africa, available molecular markers should be used as early warning signals and as tools for tracking the spread of resistance once it has emerged. Surveys should also be leveraged to collect information on additional markers, such as *Pfhrp2/3* deletions.

### **Pillar I – Intervention 3 | Increase collection of additional, more detailed data at select sites**

#### ***Underlying issue***

The collection of standard TES data (i.e. evidence of treatment failure or delayed clearance) is not always sufficient to confirm resistance. For instance, identifying new molecular markers will require a correlation between clinical, in vitro and genetic evidence. This calls for increased data collection during TESs in select sites, combining 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. At these sites, additional resources and capacity should be dedicated to performing, consistently and over space and time, a broad spectrum of tests in addition to TESs: molecular markers, in vitro resistance studies (i.e. phenotyping assays), drug levels in the blood, and monitoring trends.

## Pillar I – Intervention 4 | Improve data dissemination systems to facilitate a 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 are not systematically made available to NMPs; sometimes years of delay occur between data collection and results being published and made available to NMPs. Different networks have been built to facilitate data sharing, but their sustainability needs to be ensured.

### *Suggested interventions*

**Re-establish or strengthen subregional networks of antimalarial drug resistance and efficacy surveillance:** these networks should facilitate transparent communication of data on drug efficacy and resistance, and, to ensure coordination and sustainability, they should leverage WHO's experience as Secretariat for similar networks, such as the Horn of Africa Network for Monitoring Antimalarial Treatment (51) or the Greater Mekong subregion Therapeutic Efficacy Study Network (52).

**Collate data into a worldwide data repository:** data on antimalarial drug efficacy and resistance should be collated into a single repository to enable visibility on and access to resistance trends worldwide. WHO should be leading and coordinating this effort. To this end, country, regional and subregional networks should more systematically share data with WHO to inform the Malaria Threats Map (21). This Strategy calls for strengthening the existing system, as 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 anopheline vectors. 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 collect, analyse and discuss data, and to ensure that reactive measures are taken in response to high treatment failures reported in TESs. The working groups should include a diverse panel of stakeholders, such as researchers, academics, care providers, representatives of the ministry of health, and civil society, with the breadth of scope defined by each country.

### 5.2.2. Pillar II: Optimize and better regulate the use of diagnostics and therapeutics to limit drug pressure through pre-emptive measures

Protecting the efficacy of existing ACTs is an immediate priority. The suboptimal use of existing diagnostics and therapeutics can increase 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 quality-assured drugs at country level, and the circulation of substandard or falsified drugs and non-recommended monotherapies can increase drug pressure unnecessarily. From a demand perspective, the lack of demand for alternative drugs to artemether-lumefantrine and artesunate-amodiaquine, as well as the inappropriate use of available antimalarial drugs and diagnostics due to provider or patient behaviour could 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, notably through better adherence to WHO recommendations and full use of the diversity of tools available in the set of antimalarial compounds. To ensure the availability, affordability and quality of these tools, the global malaria community should use its combined market-shaping power to achieve healthier malaria commodity markets, while being mindful of the need to promote innovation, in support of African-led efforts. 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 current behavioural drivers of care provider and patient choices.

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

### ***Underlying issue***

Not all national treatment guidelines in Africa systematically recommend different ACTs for first- and second-line treatment of uncomplicated *P. falciparum* cases. For first-line treatment, there is an over-reliance on a limited number of ACTs in Africa, increasing the risk of the emergence and spread of partner drug resistance. For second-line treatment, when countries do not include a different ACT in their guidelines, patients with recurrent infections (potentially recrudescence infections) are likely to be treated with the same drug again. The continued use of failing ACTs can exert additional selective pressure on malaria parasites, increasing the risk of transmitting parasites with 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 often poorly regulated and unsupervised. This leads to non-compliance with national policies and guidelines. There is often no clear guidance or policies to support collaboration between the public and private sectors (53).

### ***Suggested interventions***

**Include different ACTs for first- and second-line treatment** of uncomplicated *P. falciparum* cases in all national treatment policies.

**Develop and regularly update detailed national treatment guidelines:** the guidelines should take into account the latest evidence on local antimalarial drug efficacy and resistance patterns and health system capacities, as recommended by the GTS (1). Additionally, regional patterns of resistance and drug use should be considered when developing a national treatment policy. As a pre-emptive measure to delay the emergence and spread of partner drug resistance, countries could consider adding alternative ACTs recommended by WHO to their national treatment guidelines. For new ACTs to be introduced into national policies, they should have over 95% efficacy, as demonstrated through therapeutic efficacy monitoring. 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* (54), should alert programmes to undertake more frequent monitoring and to prepare for a potential policy change. To this effect, and in line with the

GTS recommendations (1), countries should pre-plan for a rapid treatment policy change, with the support of global partners including funding agencies and donors, to avoid delays when switching to another ACT. Once it has been confirmed that the failure rate is over 10% in quality-controlled studies using the WHO protocols, the treatment policy change should be implemented to ensure that patients receive efficacious treatment and to prevent the further spread or increase of any resistance.

**Review and revise country policies and regulations to support and promote the implementation of appropriate case management across health sectors, with an intensified effort towards the private sector (52):** there should be clarity and consistency of policies and regulations regarding where antimalarials can be accessed and who can prescribe and/or sell them, as well as where and by whom RDTs can be performed, taking into account patient care-seeking practices. Where possible (e.g. in the presence of a well structured private sector), national policies should be disseminated and promoted to non-public providers. Policy-makers and regulators should also be aligned on the technical specifications required for health products (diagnostics and medicines) (53). There should be robust supervision and enforcement of existing and new regulations, supported by training and follow-up programmes.

**When conducting mass drug administration and chemoprevention strategies this should be done with drugs that differ from those used for treatment:** in a given country, there should be no or limited use of the drugs or long-acting components of existing first- or second-line treatment in the regimens used for mass drug administration or chemoprevention strategies.

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

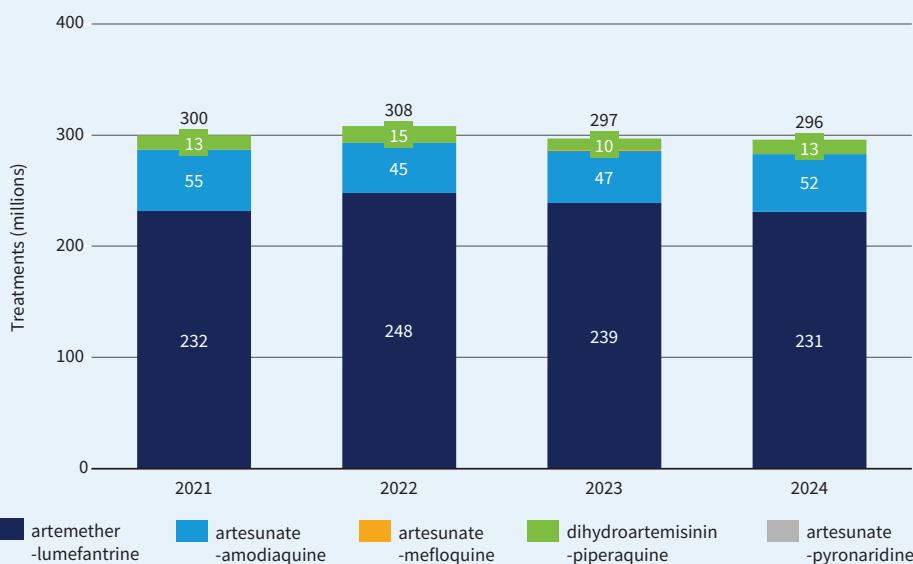
### ***Underlying issue***

A diversified drug portfolio and production capacity, especially in endemic countries, is needed to limit the reliance on a few drugs and manufacturers. This will ensure that alternative ACTs are available and countries are able to use all ACTs recommended in their national treatment guidelines. However, the diversity of antimalarial drugs available globally is not necessarily reflected in the drugs available in countries in Africa. The higher cost of ACTs other than artemether-lumefantrine and artesunate-amodiaquine and the logistical challenges of managing a second-line treatment have resulted in a lack of demand for alternative treatments (see **Box 1**). Lack of demand can hinder supply and generate a vicious cycle that leads to a limited number of suppliers for alternative WHO-prequalified ACTs, such as artesunate-pyronaridine and dihydroartemisinin-piperaquine. To date, there is only one supplier producing prequalified artesunate-pyronaridine, one producing prequalified artesunate-mefloquine and two producing prequalified dihydroartemisinin-piperaquine (11). This limited number of manufacturers increases the vulnerability of countries should resistance to partner drugs such as lumefantrine or amodiaquine be confirmed in Africa. In addition to limited production, problems along the supply chain, such as stockouts, limit access to quality treatment (55). Poor country preparedness to rapidly introduce new drugs can impede a prompt and efficient response to the loss of an ACT's efficacy.

**Box 1. Forecasted donor-funded ACT procurement by drug (2021–2024), Clinton Health Access Initiative (56)**

Figure 7 shows that artemether–lumefantrine is expected to maintain 77–88% of the market share. Artesunate–amodiaquine volumes are expected to remain the second highest for ACTs. Dihydroartemisinin–piperaquine and, to a greater extent, artesunate–mefloquine and artesunate–pyronaridine volumes are projected to stay marginal in the short term.

**Figure 7. Donor-funded ACT procurement from 2021 to 2024**



**Suggested interventions**

**Streamline local registration of ACTs:** beyond continued research into new treatments, it is important to ensure that the 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 reduce time to marketing authorization (57). Globally, a concerted effort should be aimed at reducing the overall timelines for the introduction of new products – from inclusion in WHO guidelines to in-country roll-out.

**Address production capacity issues:** as for the most used treatments, artemether–lumefantrine and artesunate–amodiaquine, production capacity is geographically consolidated far from where the drugs are consumed, creating inefficiencies that can compromise the timely supply of treatments. Countries should seek to reduce their vulnerability to global supply chain disruptions – as highlighted by the significant disruptions experienced during the COVID-19 pandemic. Therefore, diversifying production capacity, for instance by increasing production capacity in Africa, should be considered to ensure the availability of these treatments. The significant volumes procured should also be leveraged to further shape markets (see **Box 2**), for example by directing volumes to local manufacturers and 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 incentivize

innovation to develop new medicines. However, this diversification might bring some challenges, such as higher costs (e.g. lower volumes, tariffs on imported active pharmaceutical ingredients, export taxes, limited infrastructure) and the need to ensure that international quality standards are met. Therefore, such efforts should be further analysed and discussed among relevant stakeholders. The lack of demand for other ACTs has resulted in a very limited number of manufacturers producing these alternative treatments. To encourage an increase in production capacity, the global malaria community should work to ensure sufficient demand for treatment alternatives to artemether-lumefantrine and artesunate-amodiaquine, starting by ensuring that ACTs are recommended and procured as second-line treatments.

## Box 2. Market-shaping implications

Equitable access to quality and affordable therapeutics and diagnostics is a key requirement not only to ensure good malaria care, but also to prevent the emergence and spread of resistance. While the WHO Guidelines for malaria (54) currently recommend six different ACTs, artemether-lumefantrine and artesunate-amodiaquine represent the bulk of ACTs procured through pooled procurement channels (85% and 15% of GFATM Pooled Procurement Mechanism orders, respectively). There is a global need for widely available and affordable alternative treatments to artemether-lumefantrine and artesunate-amodiaquine, not only as a preventive measure to diminish drug pressure, but also as a reactive measure to enable countries 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, limited demand and few suppliers, resulting in a vicious circle of limited supply and demand.

On the diagnostic front, since parasites with dual *Pfhrp2* and *Pfhrp3* gene deletions have been reported, there is a need for non-HRP2-only RDTs, for instance RDTs targeting the *Plasmodium* lactate dehydrogenase protein, alone or in combination with the HRP2 protein. HRP2 RDTs still represent the vast majority of the malaria RDT market, with limited options for combination *Plasmodium* lactate dehydrogenase + 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, with the objective of reaching price-breaking volumes while not disincentivizing investment in innovation.

Lessons learned from more successful product introductions, such as that of dual active ingredient insecticide-treated nets, should be analysed and leveraged. The New Nets Project combines a volume guarantee underwritten by the Bill & Melinda Gates Foundation and MedAccess with a co-pay mechanism funded by a GFATM strategic initiative and Unitaid funding. This project has resulted in a rapid increase in the availability of dual active ingredient nets and a sharp decline in prices, while generating critical data to inform a WHO recommendation. Such initiatives will also be critical to prepare for the introduction of the next-generation therapeutics currently under development. A concerted effort will be required to commercialize the new molecules in a timely manner, widely and at an affordable price. Country-level activities, such as updating national guidelines, registering these products and designing procurement plans, will also be crucial to make this a reality. It is now critical for global partners to join forces and address market failures. The two examples described above regarding ACT diversity and RDT alternatives should be investigated as part of a broader market-shaping strategy. Such a strategy should aim at addressing both demand- and supply-side barriers.



**Further explore procurement opportunities:** finally, a diversified product portfolio relies on an efficient procurement system. Regional pooled procurement initiatives could be explored to complement global mechanisms such as the Pooled Procurement Mechanism operated by GFATM. Pooling demand could support the need for rapid procurement when changing policies (e.g. switching ACTs rapidly) and respond to the need for small batches, for instance, if only a few second-line treatments are needed. In a few instances, GFATM and the United States President’s Malaria Initiative have implemented initiatives to meet minimum order quantities, and these could be further developed in the future. Similar initiatives were piloted in Africa during the COVID-19 pandemic, such as the Africa Medical Supplies Platform for diagnostics and therapeutics and 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 cost, risk of expiry, risk of deterioration, administratively burdensome processes, and country-specific requirements – should be evaluated and accounted for. At country level, efficient and flexible national procurement plans should be designed so that drugs can quickly be made 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.

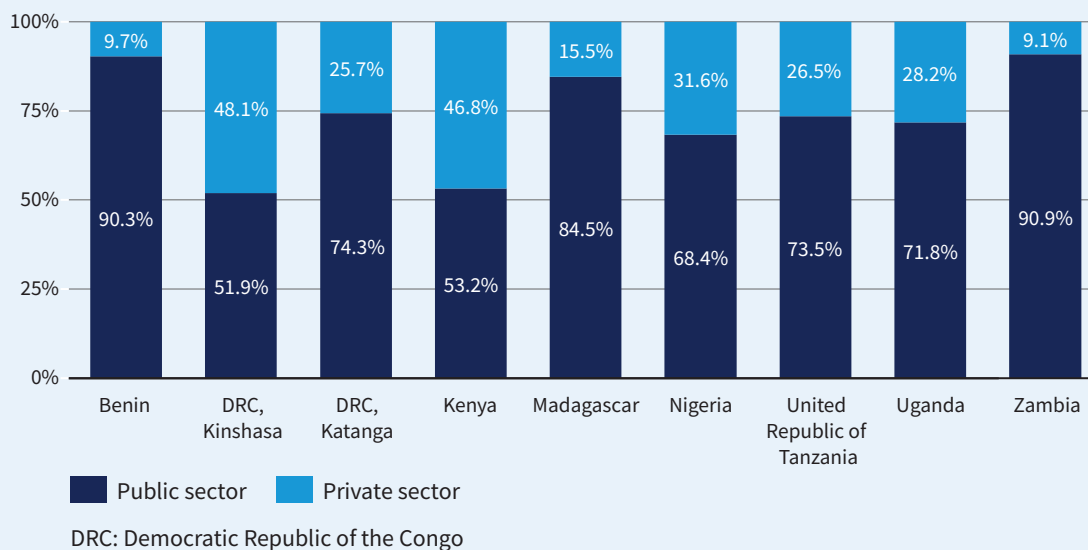
Activities suggested under this intervention should be part of a holistic approach, requiring further consideration. This document should be a call to action for global and regional partners to build a consolidated market-shaping strategy that will help foster the appropriate market dynamics to address the threat of antimalarial drug resistance and improve overall malaria care management. Such a strategy requires a dedicated effort from all relevant stakeholders, as well as dedicated funding. Initiatives such as the upcoming GFATM catalytic investments (2023–2025) could be leveraged, as GFATM is planning to dedicate funds to address biological threats in malaria case management (up to US\$ 20 million) and for NextGen Market Shaping (up to US\$ 140 million) (58).

**Ensure a diversified, healthy and sustainable marketplace for antimalarials and diagnostics** (see **Box 3**): while such a strategy is likely to be developed at a global level, regional stakeholders will play a key role in advocating for, harmonizing and coordinating continent-wide initiatives. This should be done before widespread partner drug failure is reported in order to ensure the availability of alternative treatments.

**Box 3. Case study: ACT watch project to investigate the availability of malaria diagnostics in sub-Saharan countries from 2009 to 2015 (59)**

**Findings of the study:** most of the malaria testing was performed in the public sector (see Fig. 8). In the private sector, the availability of diagnostic tests was higher in private for-profit facilities than in antimalarial stocking pharmacies and drugstores – which are the most common suppliers of antimalarial drugs. Where tests are available, price may act as a barrier to uptake, particularly for young children, as paediatric ACT courses can cost less than testing.

**Figure 8. Malaria testing market share across sectors – results of outlet surveys 2014–2015 (59)**



**5.2.3. 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. Subtherapeutic drug dosage could be due to improper manufacturing, for example in the case of inadequate active pharmaceutical ingredient concentration; alteration, for instance due to poor storage and distribution conditions, in particular under tropical conditions; or plain falsification. Exposing parasites to subtherapeutic drug levels increases the risk of selection and spread of resistant parasites. Despite the measures put in place in the past, substandard and falsified drugs are widely available in Africa, especially in the private sector (60).

**Suggested interventions**

**Establish a stringent regulatory framework on product quality standards for both imported and exported ACTs:** stringent regulation can be achieved by empowering regulatory authorities within each country. Quality assurance of generic ACTs can be supported following WHO standards such as 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 (61).

**Monitor and promote the quality of ACTs:** robust national post-market quality surveillance programmes should be in place. The quality of ACTs should be monitored and managed along the supply chain, through sampling and testing at targeted locations, such as at customs, in storage locations, throughout the distribution network, and at points of sale in both public and private sector outlets. Sampling and testing activities should follow an approved protocol with well defined objectives and have a dedicated budget line (62). The post-market surveillance programme should be managed by a committee comprising representatives from the national regulatory authority, ministry of health, NMP, and other relevant partners and stakeholders.

Quality standards should be enforced to ensure concrete results. A clear list of sanctions for the manufacturing and wholesale purchase of substandard or falsified drugs (e.g. fines, shop closures, withdrawal of import licenses) 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 export (e.g. defining clear roles and responsibilities at borders, strengthening data-sharing processes between national authorities) in order to reduce the availability of substandard and falsified drugs in African markets. Political support and advocacy are key to ensure the successful enforcement of any quality standards.

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 incentivized to support government initiatives.

## **Pillar II – Intervention 4 | Remove non-recommended monotherapies and ensure that other monotherapies are used in accordance with WHO guidelines**

### ***Underlying issue***

Although WHO recommends the use of ACTs to treat children and adults with uncomplicated *P. falciparum* malaria, and the recommendations around the use of monotherapies should be strictly followed to support resistance management, non-recommended monotherapies remain an issue in Africa.

In 2007, WHO Member States called for the progressive removal of oral artemisinin-based monotherapies from markets, as these were identified as potential causes of resistance (63). 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 (64), weak capacity to enforce the bans and continued production and distribution by pharmaceutical companies have prevented the complete withdrawal of the remaining non-recommended monotherapies from markets. Additionally, non-pharmaceutical forms of *Artemisia* (e.g. *Artemisia* tea) are being used for the prevention or treatment of malaria (43). The varying artemisinin content of *A. annua* or *A. afra* herbal remedies means that widespread use of these remedies could lead to many people having subtherapeutic levels of artemisinin in their blood, increasing the risk of resistance developing and spreading. Current knowledge concludes that any potential weak antimalarial activity of compounds other than artemisinin in *A. annua* or *A. afra* would not be sufficient to protect artemisinin from resistance (44).

Parenteral or rectal monotherapies are recommended for treating severe malaria and when oral treatments are not tolerated. Overuse of these treatments in the absence of a clinical rationale, i.e. using injectable artesunate or artemether for uncomplicated malaria, has been reported in certain areas.

Likewise, using monotherapies for patients with severe malaria without completing the full recommended treatment (i.e. not administering a full ACT treatment following a parenteral or rectal antimalarial treatment) presents a risk for resistance by favouring de novo emergence and spread of resistant parasites.

Anecdotal evidence suggests that non-recommended monotherapies could also be more widely available and used in the private sector (65).

### ***Suggested interventions***

**Remove non-recommended oral monotherapies:** countries should intensify their ongoing efforts to remove non-recommended oral monotherapies from the market, including from the informal sector, in order to reach complete withdrawal. Remedial action should be considered at export, import 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. To this 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 non-recommended oral monotherapies from the market.

At the continental level, regional organizations could work with exporting stakeholders (e.g. governments, manufacturers). Strong collaboration among neighbouring countries can ensure 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 the use of these monotherapies.

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:** artemisinin-based monotherapies (injectable and rectal) are only recommended for use in severe malaria with specific follow-up care and treatment. These monotherapies should not be used for the treatment of uncomplicated cases. Countries will need to conduct activities that address the underlying root causes, including insufficient training and lack of supervision; insufficient health system financing that encourages the prescription of treatments that can be charged in full to the patient; wide availability and accessibility of the treatments; and perception of efficacy. HCWs should be trained to ensure broad knowledge of guidelines on the treatment of uncomplicated malaria (66). A communication plan could be developed to address communities' beliefs and personal preferences.

**Ensure complete treatment of severe malaria cases:** patients with severe malaria who do not receive the recommended ACT following the initial monotherapy may not be cured and could contribute to the de novo emergence and spread of resistance. To address this risk, HCWs

must be trained to follow the recommended treatment of severe malaria: a patient treated with injectable artesunate or artemether should subsequently receive a full ACT course, and 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 (54).

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

### ***Underlying issue***

Access to care can be affected by many factors, including geographical, financial, social and gender barriers (67). For instance, out-of-pocket expenditures faced by poor people can result in catastrophic health spending costs, use of non-recommended drugs, or choice to not use a service (including RDTs) or treatment. The lack of access to quality treatment can increase the risk of resistance by encouraging the use of substandard or falsified drugs, thereby increasing the number of parasites exposed to subtherapeutic drug levels. Among other characteristics, resistance has historically been observed to emerge first in areas and populations with poor access to quality malaria services (41). 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 (53). The private sector plays a prominent role in some parts of Africa, but often operates without sufficient government or regulatory oversight (68). The lack of alignment with national treatment guidelines can result in the distribution of lower quality or inadequate products.

### ***Suggested interventions***

#### **Increase access to quality health services for underserved communities and populations:**

the effect of the different barriers (e.g. geographical, financial, social, gender) on the access to and choice of treatment, 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 5**), efforts should be intensified to reach them. There are different ways of achieving this, for instance by leveraging community workers to provide quality diagnostics (see **intervention II-6**) and treatments to these specific groups. To minimize financial barriers, policies could be developed to drive down the cost of treatments for individual patients (e.g. private sector co-pay mechanisms, tax incentives on quality-assured medicines).

**Improve access to quality care in the private sector (53):** countries should ensure that only quality antimalarial drugs and diagnostic testing are available from private providers. This is achieved through adequate regulation and its enforcement by national and state regulatory authorities. To address the issue of limited resources, mechanisms such as the Affordable Medicines Facility for malaria programme, hosted by GFATM, should be explored. The Affordable Medicines Facility for malaria subsidized ACTs in the private sector and led to tangible results in improving access to quality-assured ACTs in that sector (with ACT availability increasing by at least 20 percentage points in six of the eight pilot countries), including among the poor (69). The programme also made ACTs more affordable (with full ACT treatment course prices in the private sector dropping by US\$ 1.28–4.82 in six of the eight pilots) (70,71). If considered, similar initiatives should be further extended to diagnostic testing.

Countries should promote private providers' adherence to national treatment guidelines. For providers to deliver quality case management in private health facilities, they must be supported by training, supervision and protocols that are tailored to them and the characteristics of the delivery channel. Engagement with community-based organizations and nongovernmental organizations can be effective in bridging the gap between the public and private sectors.

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

### ***Underlying issue***

Given the non-specificity of malaria symptoms, the accuracy of clinical diagnosis tends to be poor, which can lead to over-diagnosis and over-treatment of malaria; this in turn unnecessarily increases drug pressure and the risk of resistance. According to household surveys conducted in sub-Saharan Africa (2015–2019) among children under 5 years of age, only 38.5% of those with fever and for whom care was sought received a diagnosis for malaria (2). Malaria diagnosis should be made with either quality-assured malaria microscopy or WHO-prequalified RDTs. Microscopy must be performed by adequately trained HCWs with well maintained equipment. RDT performance depends on many factors – not only manufacturing quality, but also compliance with transport and storage requirements, and training and supervision of operators.

### ***Suggested interventions***

**Promote access to and use of quality RDTs:** WHO recommends parasitological confirmation of infection of all suspected cases of malaria prior to treatment. Countries should promote and assess adherence to the guidance on strengthening or setting up routine malaria diagnostic services provided in *Universal access to malaria diagnostic testing* (72). Based on a routine surveillance needs assessment, an adequate number of tests should be made available to the population, including in the private sector (73) (see **intervention II-5** and **Box 3**). The quality of RDTs should be monitored and assessed through the implementation of post-market surveys.

**Improve the quality of microscopy:** in 2016, WHO published the second version of the *Malaria microscopy quality assurance manual* (74), which details the key requirements of a malaria microscopy quality assurance programme. In parallel, WHO published a complete series of standard operating procedures 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 that includes competency standards that must be met before they can work in a clinical setting, leveraging the WHO Regional Office for Africa External Competency Assessment for Malaria Microscopists (75). The quality of processes and equipment should follow clear standard operating procedures, 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.

## Pillar II – Intervention 7 | Empower patients, HCWs 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 and/or to incorrect prescription or treatment of unconfirmed cases by care providers, contributes to drug resistance. In addition, safeguarding against antimalarial drug resistance risks being done at the expense of other life-saving treatments. The rationalization of use of antimalarial treatments could result in excessive use of other antimicrobial treatments (i.e. antibiotics).

### *Suggested interventions*

**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, adherence to policy, and good practices (76). The messaging needs to emphasize the importance of testing prior to administering antimalarial treatment, adherence to the full treatment course, and the need for correct and quality treatment, for instance by warning against the risk of using non-pharmaceutical forms of *Artemisia*. Specific stakeholders could also be targeted, for example by developing and distributing dedicated communication materials about regulatory policies to private sector outlets. If an ACT fails and a switch to a new treatment is required, public information and education will be needed to ensure understanding and compliance with the new guidelines. Empowering populations should go hand in hand with the development of incentives, such as financial ones, to address the barriers preventing patients from accessing adequate treatment (see **intervention II-5**).

**Provide training to HCWs:** training should be provided to HCWs to ensure full understanding of national treatment guidelines, such as when to use second-line treatment. HCW training should also cover ways to ensure that patients complete the full treatment course. HCW training could also include the benefit of synchronous intake of food to increase the treatment efficacy of artemether-lumefantrine. A treatment policy change, following for instance the failure of the existing first-line ACT, will require dedicated training. Continuous training and supervision should also be provided to HCWs on the use and interpretation of RDT and microscopy results and on the provision of antimalarial treatment only in the case of confirmed diagnosis (77). While limiting the use of antimalarial treatments to confirmed cases, public authorities should ensure that patients with suggestive symptoms who are found not to have malaria have access to appropriate alternative diagnostic and treatment options. Training should be considered from a holistic perspective through improved integrated community case management and integrated management of childhood illness in order to prevent the excessive use of other life-saving treatments, especially antibiotics (78).

#### 5.2.4. 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 on prioritizing optimal vector control and other preventive measures, such as chemoprevention and vaccines, in priority areas; containing transmission from recrudescing cases; and limiting any advantage that higher gametocyte carriage could potentially confer to resistant parasites. Although the risk linked to different areas and groups should be assessed and is likely to differ by population, country and region, additional resources and efforts should be mobilized towards areas where resistance is confirmed, border areas where there is evidence of resistance in neighbouring areas, and towards areas with significant inflows of mobile and migrant populations from areas with known resistance. Underserved areas and hard-to-reach populations (e.g. displaced populations, migrant population, forest goers) should not be omitted. 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 the availability and use of vector control interventions and preventive measures, and the risk of transmission from recrudescing cases.

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

#### *Underlying issue*

Limiting the onward transmission of resistant malaria parasites requires an efficient malaria vector control strategy, which will be influenced by different factors: timely deployment, high coverage and appropriate targeting.

#### *Suggested interventions*

**Target deployment of vector control interventions:** intensified efforts to prioritize and optimize vector control interventions, with the intervention package depending on the specifics of the setting, should be considered to limit the transmission of resistant parasites. Such efforts should be both preventive (targeting areas and populations where resistance is deemed more likely to develop or spread) and reactive (targeting areas where resistance has been confirmed – be it artemisinin partial resistance or partner drug resistance). The feasibility and effectiveness of such efforts will depend on the availability of data, the ability to identify priority areas and populations, the capacity to tailor the interventions based on local epidemiological and entomological data, and market preparedness.

**Deploy vector control interventions in a timely manner:** recommended vector control interventions, such as the distribution of insecticide-treated nets and indoor residual spraying operations, should be made as efficient as possible to reduce onward transmission of resistant parasites and should be focused on priority areas when identified. Initiatives developed by



global partners to address some of the barriers affecting rapid scale-up of vector control interventions, such as the New Nets Project funded by GFATM and Unitaid, should be further encouraged and leveraged (79). The New Nets Project already procures and distributes two different dual active ingredient nets with the aim of supporting manufacturers and WHO while they evaluate the epidemiological efficacy of these products. Should one or both nets demonstrate impact, demand would, nevertheless, still quickly exceed current production capacity.

**Promote innovative deployment of vector control interventions:** leveraging new digital tools should be considered to further improve the efficacy of vector control interventions. One example is the use of geospatial technology for planning, implementing and targeting future indoor residual spraying campaigns. Geospatial generated maps could complement the existing manual process of collecting data on infrastructure and population, facilitating the identification and sizing of structures to be sprayed (80).

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

#### ***Underlying issue***

As stated in the GTS (1), 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. Chemoprevention interventions can be challenging in terms of planning and delivery, for example because of the need to use different drugs for chemoprevention and first-line treatment (81). However, the use of alternative drugs and the resultant decrease in cases needing treatment could limit the risk of emergence and further spread of resistant parasites. Evidence has shown that both school-aged children and individuals with asymptomatic infections are important contributors to the malaria infectious reservoir and could be targeted by malaria control interventions (82).

Malaria vaccines are another important means to reduce malaria cases, clinic visits and the use of antimalarial drugs. Currently, only one malaria vaccine is recommended for use, targeting young children to reduce malaria illness and death. Vaccines are generally well accepted public health interventions that can reach high coverage through routine distribution systems.

Although chemoprevention and vaccines are detailed under this section looking at their role in limiting the transmission of resistant parasites, both interventions could contribute to a decrease in the number of malaria cases, thereby decreasing the overall drug pressure, which relates to the objective of Pillar II.

#### ***Suggested interventions***

**Adequately plan and roll out chemoprevention strategies:** chemoprevention cures existing infections and prevents new infections. Its deployment should be targeted, closely monitored and in line with national treatment guidelines (i.e. using drugs that are not first- or second-line treatment). 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 currently include intermittent preventive

treatment of malaria in pregnancy, perennial malaria chemoprevention, seasonal malaria chemoprevention for children belonging to age groups at high risk of severe malaria, intermittent preventive treatment of malaria in school-aged children, post-discharge malaria chemoprevention and mass drug administration. These interventions (except for mass drug administration) are recommended in areas of moderate to high malaria transmission. Chemoprevention interventions should be adequately conducted.

**Intensify investments to enable the scale-up of the RTS,S/AS01 first-generation malaria vaccine (83):** vaccine introduction through routine childhood immunization programmes can substantially reduce clinic visits and the use of antimalarial drugs by increasing the immunity of the given population and decreasing the risk of emergence and spread of resistance. In October 2021, WHO recommended the expanded use of RTS,S/AS01 among children living in settings with moderate to high malaria transmission (84). Clinical trials showed that the vaccine reduced *P. falciparum* malaria cases presenting to health facilities by 55% in the first year after vaccination, and by 39% over four years (85). Pilot introductions of the vaccine in Ghana, Kenya and Malawi through routine child immunization clinics have resulted in substantial reductions in children admitted with deadly severe malaria (30%) and hospitalizations with a positive malaria test (21%) (86).

### **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, in a recrudescence case, parasites are more likely to have reduced drug sensitivity and increased gametocyte carriage. Finally, some resistant parasites may have intrinsically higher gametocyte carriage.

#### ***Suggested interventions***

**Promote good case management, including early diagnosis and treatment to 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.

**Limit the risk of transmission from recrudescence cases:** to limit the risk of transmission from recrudescence cases, patients and caregivers must be informed of the need to take the full treatment course and to seek immediate care if symptoms return. 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 depending on the ACT administered). Providers should routinely ask questions on patients' previous treatment history to facilitate the switch to a second-line treatment when needed. In addition, patients should be encouraged to use insecticide-treated nets where available.

**Limit gametocyte carriage for artemisinin partially resistant cases:** a single low-dose of primaquine with ACT treatment has been proven to be safe and potentially impacts parasite transmission. To reduce transmission, WHO currently recommends that a single dose of 0.25 mg/kg body weight primaquine be given with an ACT to patients with *P. falciparum* malaria in low-transmission areas, except for pregnant women, infants under

6 months of age and women breastfeeding infants under 6 months of age (54). Depending on the national treatment guidelines, the addition of single low-dose primaquine should also be considered in areas of confirmed or suspected artemisinin partial resistance and in the case of suspected recrudescence.

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

#### ***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 in case of inflows of mobile and migrant populations from areas where resistance has emerged.

#### ***Suggested intervention***

**Facilitate and encourage country collaboration:** building on 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 coordinate to rapidly deploy 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. Multilateral organizations such as WHO, regional organizations, funding agencies and donors can play an important role in supporting cross-country coordination. The coordinating role of supranational agencies becomes even more fundamental in areas where political tensions, cross-border conflicts, competing priorities, and lack of resources or infrastructure undermine malaria control activities (87).

#### **5.2.5. Pillar IV: Stimulate research and innovation to better leverage existing tools and develop new tools against resistance**

An effective response to the threat, limiting the potential impact of antimalarial drug 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 reached just over US\$ 619 million in 2020 (2). Between 2021 and 2030, it is estimated that an average annual investment of US\$ 851 million in research and development is needed.

This pillar calls for innovative approaches to better use current tools, for the development of new tools, and for increased modelling and research to characterize resistance, its impact, drivers and how corrective interventions might address those 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 in order to test new approaches and improve the overall knowledge on malaria drug resistance.

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

### *Underlying issue*

With new treatments years away, preserving the therapeutic lifespan of current ACTs is critical. The existing malaria armamentarium could potentially be used in innovative ways. Additional evidence needs to be generated to demonstrate the impact of these innovative approaches on resistance.

### *Suggested interventions*

#### ***Potential innovative ways to increase demand for different drugs and ensure matching supply***

**Explore new schemes in the use of treatments at national level:** currently, a treatment is recommended until the failure rate reaches 10%. Deploying the currently available treatments differently, for instance by rotating drugs before high failure rates are detected or by 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. using different ACTs for different age groups or geographies, or rotating ACTs, in particular if they exert opposing selective pressures on local parasite populations). The operational feasibility of such approaches should be further studied to understand the logistical challenges, cost and acceptability by countries (88). Modelling supported by research should also be pursued to assess the impact of multiple first-line therapies on drug resistance (89).

**Evaluate initiatives to build a healthy marketplace:** market-related interventions, such as diversifying the portfolio of currently available drugs or enabling timely deployment of alternative treatments or vector control interventions, require proactive and deliberate market shaping. Market challenges should be comprehensively studied, and the merits of various market interventions, such as volume guarantees and co-pay mechanisms, should be assessed for individual products, with an overall objective of increasing their availability and affordability. Based on the output of such assessments, market interventions should be implemented at a global scale, if appropriate, or through pilots combining both economic research and procurement operations, if necessary.

#### ***Further considerations to limit the spread of resistant parasites***

**Assess transmission-blocking interventions:** the lack of understanding of *PfKelch13* mutants' gametocyte carriage and transmissibility in Africa is an important knowledge gap. The deployment of transmission-blocking interventions, such as single low-dose primaquine given together with an ACT in areas where resistant parasites are prevalent, depends on research showing that such parasites have a transmission advantage in African settings. Furthermore, additional modelling is needed to explore whether transmission-blocking interventions is likely to have a significant impact in settings where coverage of these interventions is expected to be lower than in areas where the provision of single low-dose primaquine is currently recommended.

**Consider extended treatment regimens:** extending the duration of treatment beyond the current three days may also be relevant and should be further investigated in order to build the evidence needed before considering a new global policy. Such research should include an

assessment of the potential risks, including safety, and solutions, especially with respect to the expected adherence of patients to the extended regimen.

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

### ***Underlying issue***

Adequate information on the biological, environmental, economic and social factors driving resistance remains scarce, but is needed to help inform the design of interventions and where to deploy them. The identification of areas and populations where resistance is more likely to develop or spread in Africa is hindered by the limited understanding of these factors. Historically, resistance has first emerged in areas of low endemicity where there is an influx of populations with limited immunity and limited access to quality diagnosis and treatment, and where there is high unregulated use 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:** information should be collected to identify the areas and populations where resistance is more likely to develop and spread, and the implementation of interventions should be tailored accordingly. The information collected could include information on the results of efficacy studies, treatment rates, patterns of drug use (symptomatic vs. asymptomatic, private vs. public sector), the proportion of patients adhering to treatment guidelines, delay between symptoms and treatment, population movements and migration patterns, age- and gender-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 and spread.

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

### ***Underlying issue***

As clearly stated in the GTS (1), the long-term usefulness of any medicine or combination is threatened by resistance. Additionally, the formulation and dosage for certain population groups, and treatment regimens for some available treatments are suboptimal and may need to be revised. Finally, patients with symptoms suggestive of malaria might receive malaria treatment despite a negative test result, due to the lack of tools to perform differential diagnosis at point of care.

### ***Suggested interventions***

**Improve the formulation, dosage and regimen of currently available treatments:** for ACTs, the focus should be on improving formulations for specific population groups (e.g. young children, pregnant and lactating women, malnourished populations). The development of a paediatric formulation for primaquine should be accelerated. Newer drugs with regimens that are simpler and require less frequent dosing should be further explored.

**Explore the potential benefit of triple artemisinin-based combination therapies (TACTs):** TACTs, which combine an artemisinin component with two of the currently used ACT

partner drugs, have been explored. The partner drugs most frequently proposed in TACTs are piperazine plus mefloquine and lumefantrine plus amodiaquine (90). Other triple combination therapies being tested combine an ACT with atovaquone-proguanil.

Part of the rationale behind combining piperazine and mefloquine or amodiaquine and lumefantrine is the potential antagonistic resistance mechanism between these drugs. However, in the context of artemisinin partial resistance, parasites resistant to both mefloquine and piperazine have already been reported in Cambodia and Viet Nam. In the absence of known, validated markers of resistance for amodiaquine and lumefantrine, it is not possible to predict whether a similar situation might occur with the emergence and spread of parasites resistant to both amodiaquine and lumefantrine (91).

Modelling and research are needed to explore how the combination of two long-acting partner drugs in a TACT impacts the risk of emergence and spread of resistance in Africa, compared to partner drugs given individually as ACTs. Artemisinin partial resistance has emerged in Africa despite the high efficacy of the partner drug within the ACT. Shifting to a TACT where a significant level of resistance to one of the partner drugs has already developed could limit the potential benefits of the combination in terms of resistance management, in particular in areas where artemisinin partial resistance has already been reported.

Adding another drug to established regimens would require studies on tolerability, toxicity and drug interactions. Potential delays in resistance benefiting future patients would need to be balanced against any potential increased risk for current patients caused by receiving an additional drug and challenges in achieving full adherence to the treatment if the combination is given twice a day.

**Develop new treatments:** for alternative treatments, the focus should be on non-artemisinin-based combinations, such as ganaplacide-lumefantrine, and innovative multiple combinations with existing or novel agents, such as medicines with better matching pharmacokinetic profiles and different modes of action. Additionally, global stakeholders should increase efforts and coordination to establish target product profiles that list the minimum requirements that new medicines have to meet across different dimensions. Such target product profiles should focus on novel compounds for treatment and prevention, beyond ACTs.

**Develop new tests allowing for differential diagnosis at point of care:** patients seeking care for symptoms suggestive of malaria should be tested for alternative causes in the case of a negative malaria test. Multi-pathogen tests at point of care would guide HCWs in providing the correct treatment. Research should focus on improving the sensitivity and specificity of these platforms.

Once next-generation therapeutics and diagnostics are available, concerted efforts to introduce these new products will be crucial to ensure their rapid and wide uptake.

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

### ***Underlying issue***

While the current malaria armamentarium needs to be optimized, there is also a need to develop more effective tools, both pharmaceutical and non-pharmaceutical, to reduce malaria infection and transmission, and therefore decrease the likelihood of resistance emerging and spreading.

### ***Suggested interventions***

**Pursue investments in the research and development of pharmaceuticals and vaccines:** second-generation vaccines (92) and monoclonal antibodies (93), for example, could represent promising tools to limit malaria infection and transmission.

**Encourage innovation in the area of vector control and vector surveillance (94):** the improvement of existing vector control interventions – insecticide-treated nets and indoor residual spraying – and rigorous evaluation of these improvements is a priority area that requires further attention, as stated in the GTS (1). Regarding nets, the priority should be to make them more efficacious, particularly with regard to addressing resistant vector populations, and to improve their quality. More efficacious nets should be developed and deployed, in particular in areas with pyrethroid resistance. Efficacious nets could include dual active ingredient nets and nets with an added synergist such as piperonyl butoxide or other chemicals. Ensuring the quality of nets should be a primary focus, and the search for lower prices should not be to the detriment of quality. Higher quality nets should ensure both physical quality and residual activity of insecticides on the nets. New types of indoor residual spraying and/or longer lasting formulations would also be helpful. Innovative methods of delivering indoor residual spraying in areas where housing is becoming increasingly modernized should also be considered.

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

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

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

### ***Underlying issue***

Many unknowns remain in terms of resistance mechanisms, the health impact of resistance and how interventions can address drivers of resistance. Tailoring interventions to specific settings, including the local specificities of hosts, vectors and parasites, will require advanced research

on background drivers, such as the identification and confirmation of genetic determinants, the definition of the impact of different genetic backgrounds on the gain and degree of resistance, the role of different vector species, the impact of transmission intensity, and importation risks.

### ***Suggested intervention***

**Foster advanced research on resistance at the global, regional and national levels:** Priority topics could include:

- gametocyte carriage and transmissibility in Africa among parasites with mutations associated with artemisinin partial resistance;
- identification and validation of new molecular markers for artemisinin partial resistance and partner drug resistance to better monitor the emergence and spread of resistance to each ACT component compound; this can include the use of genetic crosses using custom mouse models that support *P. falciparum* infections and gene editing techniques such as CRISPR/Cas9, as well as genomic and phenotypic studies to map and confirm resistance mediators;
- assessment of the degree of clinical and in vitro 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 outcomes in patients with severe malaria infected by parasites carrying *PfKelch13* mutations compared to outcomes in patients with severe malaria infected by parasites carrying wild-type *PfKelch13*, and the potential need to modify treatment, for example by adding quinine to artesunate;
- measurement of drug levels in the blood to understand the pharmacokinetic behaviour of the different drugs in different age groups;
- assessment of the role of weakened immune status (for instance due to HIV infection or other factors) in the emergence and spread of drug-resistant parasites;
- investigation of the impact of mass drug administration and chemoprevention on the reduction of transmission among asymptomatic carriers.



# 6. Role of stakeholders and enabling mechanisms

## 6.1 Role of key stakeholders

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

The section below provides an overview of eight categories of stakeholders that should be involved to ensure that this Strategy is successfully implemented. The roles and responsibilities of each stakeholder are detailed in **Annex 6**.

**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 define a national strategy suitable to their specific situation and be empowered to implement it efficiently by the ministry of health. NMPs should assess the country's priorities based on factors that are likely to be relevant drivers of resistance and allocate resources accordingly, with support from regional and global stakeholders. They should provide adequate training and supportive supervision to health care providers (public and private) on new guidelines and approaches. NMPs should act as a connector, involving other government agencies along with the key stakeholders presented below. NMPs are in charge of consolidating the data retrieved from the field in order to take appropriate actions, disseminating data through regional networks and ensuring strong collaboration with global stakeholders.

**National regulatory authorities** should further harmonize and strengthen quality assurance and quality control 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. Regional organizations should use their supranational influence to provide advice and ensure coordinated implementation of consistent strategies throughout the continent. Regional organizations should further contribute to shaping a viable and sustainable market, for instance by establishing harmonized continent-wide standards and processes or by supporting the rapid uptake of innovative technologies.

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

**Funding agencies and donors** should advocate for and respond to the call to action, seeking to ensure adequate levels of financing and technical support for regional and local

implementation of the interventions. Beyond supporting countries and regional organizations in the operational implementation of the Strategy, funding agencies and donors 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, and support the implementation of strong surveillance capacities in Africa.

**Academia and research organizations** (e.g. academia, research centres, drug developers, including research and development units of pharmaceutical and biotechnology companies, product development partnerships and public–private partnerships, and other research-based organizations) play pivotal roles in strengthening resistance surveillance. They also play a key role in training health care professionals. They should also foster cross-sectoral collaboration. In addition, academia and research organizations should work to advance research on resistance and on innovative products and strategies. Modelling supported by research is key to continuing 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 and community-level networks** should mobilize resources, support advocacy efforts and foster engagement around the Strategy at community level. Civil society organizations should liaise with different stakeholders, for instance with the public and private sectors, and support the adoption of national strategies by care providers. Community networks should be strongly engaged to disseminate and implement the Strategy across the communities, for instance through improved access to and uptake of malaria services.

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

The stakeholders mentioned above are considered to be the most relevant in the response to antimalarial drug resistance, but this Strategy calls for broader action. As highlighted by the *Multisectoral action guide to end malaria (95)*, all sectors have an important role to play in promoting and protecting community health from the burden of malaria. Although the specific elements of a successful multisectoral action plan will vary by country, the partner landscape could further include national and local government ministries (e.g. urban planning and housing, water and sanitation, forestry and mining), private companies (e.g. manufacturers, forestry and mining companies) and local faith-based organizations, among others.

## 6.2 Ensuring that key enabling mechanisms are in place

Transversal conditions – “enablers” – are needed in all settings and at all levels to ensure the feasible, impactful and sustainable implementation of each intervention. 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.

## 6.2.1 Five transversal enablers to ensure successful implementation of the 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 in order to ensure that interventions are implemented efficiently. A periodical assessment should be put in place to ensure the accountability of all stakeholders, measure progress and identify areas for improvement.
- **Financing:** implementing these activities will require a significant financial effort. Ministries of health will have to mobilize domestic budgets. Funding agencies and 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. Resistance should be a consideration when planning and implementing any malaria activity. Advocacy should focus on increasing awareness to ensure buy-in from global partners to grassroot stakeholders, and to ensure that efforts and resources are targeting priority areas.
- **Strong regional coordination:** this Strategy provides a regional approach for 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 and response system:** optimizing the response to resistance will require an overall routine surveillance system to monitor the local specificities of each setting and further develop locally driven research.

## 6.2.2 Core requirements for the design and establishment of a robust routine malaria surveillance system

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

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 must include:

- 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, harnessing the power of digital solutions to develop such integrated systems;
- front-line staff involved in the detection, recording and reporting of cases and as the first users of data; staff at different levels should be trained in the examination and evaluation of 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 enable 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.

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

Building on the recommendations laid out in the GTS (1) and in *Malaria surveillance, monitoring and evaluation: a reference manual (96)*, the paragraphs below highlight the areas where good-quality data are needed to adequately and continuously adapt the interventions detailed in **section 5.2**.

1. **Information on malaria burden:** understanding the burden of malaria is the first step to planning, implementing, monitoring and evaluating malaria programmes, and implementing interventions targeted at addressing gaps that increase the risk of resistance. Good-quality data on the burden of malaria provide the basis for directing resources to those in need.

The data should be disaggregated by gender and age group and be analysed at the lowest administrative level possible. Required information on malaria burden includes:

- reporting the 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 available administrative level;
- standardized and continuous 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)
  - cases treated clinically (presumed cases)
  - severe malaria cases
  - cases in specific groups (e.g. children under 5, pregnant women)
  - deaths.

2. **Information on quality of care:** data on prescription and consumption need to be interpreted based on an understanding of factors such as the availability of commodities, seasonal trends, patient preferences and patient non-compliance. Conducting routine surveillance of treatment through national surveillance or surveys and detailed records will help in selecting which interventions to deploy.

Countries should aim at progressively increasing the level of granularity of the data collected in order to ultimately be able to disaggregate data by gender, age group and provider type (e.g. public, private) and conduct analyses at the lowest administrative level possible. Important information on the quality of care includes:

- compliance with national guidelines for case management:
    - proportion of suspected cases tested
    - proportion of cases confirmed positive
    - proportion of cases treated (with any first-line treatment, with ACTs);
  - monitoring indicators over time and by geography related to care-seeking patterns, access to care and hospitalization:
    - all-cause outpatients
    - all-cause inpatients
    - all-cause deaths
    - malaria proportion of all outpatients
    - malaria proportion of all inpatients
    - malaria proportion of all inpatient deaths
    - malaria case fatality rate.
3. **Supply chain management and post-market surveillance:** routine monitoring of drug quality through outlet surveys and other post-market surveillance activities will help to quantify the issue of substandard drugs, falsified drugs, degraded stocks, non-recommended monotherapies, stockouts, and so on. This monitoring can include:
- structured and comprehensive post-market 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;
  - stockout reporting;
  - continuous monitoring of the availability and use of monotherapies across the country to identify outliers (e.g. through procurement data).
4. **Surveillance of parasitological changes affecting the ability to detect and treat malaria:**
- *Surveillance of antimalarial drug efficacy:* 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 drugs so that the most appropriate treatments can be selected for national policies.

- *Surveillance of Pfhrp2/3 deletions:* diagnostic accuracy is under serious threat as a result of the emergence of parasites not expressing the HRP2 protein due to genetic mutations. Consequently, RDTs that are HRP2-based only may be unable to detect infections with such parasites. This issue can have a significant impact on public health, putting patients at risk of misdiagnosis, significantly increasing morbidity and potentially mortality. Additionally, if some parasites with *Pfhrp2* deletions were reported to also carry *PfKelch13* mutations, this would represent a threat to drug resistance management. Surveillance for *Pfhrp2/3* deletions and their impact on RDT results is essential to inform RDT procurement and to avert missed or delayed diagnosis. Should the local prevalence of *Pfhrp2/3* deletions causing false-negative results with HRP2-based RDTs be over 5%, a different testing strategy should be implemented immediately, as called for by the Malaria Policy Advisory Group in 2021 (97). Changing the testing strategy will avoid missing cases that could further transmit infection by resistant parasites.

Understanding the other mutations carried by these parasites may provide clues to their expansion beyond selection pressure from HRP2-based RDTs. Therefore, surveillance of *Pfhrp2/3* deletions should be integrated into other molecular surveillance efforts wherever possible, such as those targeting markers of drug resistance. TESs offer such opportunities, but they are not a replacement for representative surveys for *Pfhrp2/3* deletions.

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. The following are essential:
  - identification of the major *Anopheles* malaria vector(s) competent for *Plasmodium* transmission and of the vector rates of infection with the malaria parasite (sporozoite rate, oocyst rate);
  - 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.

Routine surveillance can be challenging, especially in terms of logistics. For it to be effective, in the short term, stakeholders should share data transparently and in a timely manner and communicate effectively (e.g. periodical meetings among NMPs, 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. Countries can ensure that routine surveillance systems are adequate by carrying out systematic and standardized surveillance system assessments using the WHO Malaria Surveillance Assessment Toolkit (98).

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# Annex 1.

## Strategy development process

A project team including Charlotte Rasmussen and Pascal Ringwald, with the direct support of Boston Consulting Group (Guervan Adnet, Francesca Bona, Hamza Haloui, Raphaelle Kemoun) oversaw the technical discussions, consolidated findings, conducted a broad literature review and wrote the document.

A leadership team comprising WHO and the chair of the Malaria Policy Advisory Group (MPAG)<sup>1</sup> provided guidance and oversight during the Strategy development process.

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An initial technical fact base on antimalarial drug resistance in Africa was developed with the support and expertise of five workstreams focused on i) drug resistance, ii) market shaping, iii) quality of care, policy and private sector, iv) surveillance and modelling, and v) vector control. These workstreams were led by WHO staff, who leveraged inputs from global health partners and malaria experts in order to inform the WHO perspective. These global health partners and malaria experts did not sign a declaration of interest.

<sup>1</sup> The MPAG was established in 2011 to provide independent advice to WHO to enhance the control and elimination of malaria. The MPAG provides strategic advice and technical input to WHO, and extends to all aspects of malaria control and elimination, as part of a transparent, responsive and credible process.

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The core document underwent a 28-day public consultation in June and July 2022.

The MPAG reviewed and endorsed the final document in a dedicated meeting on 24 August 2022. All MPAG members participating in the meeting updated their declarations of interest in advance of the meeting, which were assessed by the WHO Secretariat. Eleven members reported conflict of interests, but no MPAG members have reported specific interests regarding agenda topics for decision. It was assessed that all members could fully participate in all sessions.

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Figure A1.1. Summary of the development process of the Strategy

1

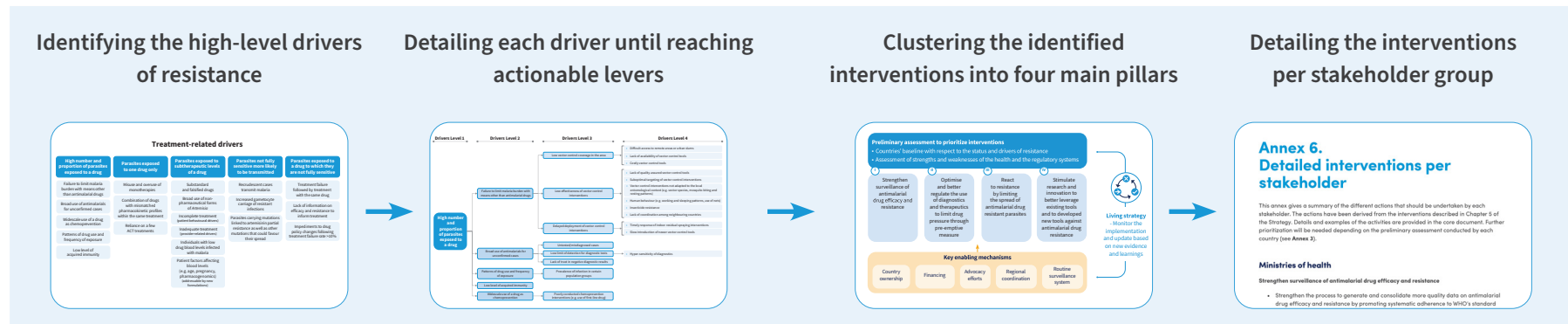
Problem statement:  
Drivers of resistance

2

Potential solutions:  
Interventions to respond to resistance

- List **all drivers that favour the emergence or spread** of antimalarial drug resistance.
- Focus on drivers that are **related to treatment** and that can be addressed with current tools and knowledge
- Detail out drivers to reach **actionable levers** (level 1 to level 4 drivers, see **Annex 4**)
- Collect **relevant data and underpinning evidence**

- List **activities** that can be leveraged to address drivers at the lowest level of detail (i.e. level 4 drivers – see **Annex 4**)
- Collect **data, evidence and expert opinion** to further flesh out activities
- Cluster activities into **core areas of interventions** (i.e., **20 interventions clustered into 4 pillars**)
- For each intervention, detail the **level of implementation and responsibilities for each key stakeholder group**



## Annex 2.

# Definitions of resistance

**Antimalarial drug 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.

**Multidrug resistance** 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.

**Treatment failure (≠ resistance)** is the inability to clear parasites from a patient's blood and to prevent their recrudescence (i.e. recurrence of asexual parasitaemia of the same genotype(s) that caused the original illness) after the administration of an antimalarial drug. Many factors can contribute to treatment failure, including incorrect dosage (i.e. weight–dose mismatch), poor patient compliance, poor drug absorption, poor drug quality, and drug interactions and resistance. Most of these factors are addressed in TESs.

**Artemisinin partial resistance** can be defined as delayed clearance after treatment with a drug containing an artemisinin derivative of a parasite strain carrying a particular mutation or set of mutations that are validated as associated with this delayed clearance, 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.

The presence of artemisinin partial resistance in an area must be confirmed using a quality-controlled study. At present, only *PfKelch13* mutations have been validated as markers of artemisinin partial resistance. 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-validated mutations and with delayed clearance as shown either by persistent parasitaemia detected by microscopy at 72 hours ( $\pm 2$  hours, i.e. day three) or a parasite clearance half-life  $\geq 5$  hours. A list of validated *PfKelch13* mutations (i.e. significantly associated with delayed parasite clearance and identified as having reduced susceptibility using RSA) and candidate markers (i.e. significantly associated with delayed parasite clearance or identified as having reduced susceptibility using RSA) is kept up to date on the WHO Global Malaria Programme website (1).

Although sensitivity to artemisinin could decrease further, it should be emphasized that, to date, there have been no observations of a change from delayed clearance towards artemisinin full resistance. It is difficult to create artemisinin full resistance *in vitro* and the biological chances of seeing its emergence are small. Therefore, using the term **artemisinin resistance** is not accurate based on currently available data. Using the terminology partial resistance or tolerance would allow for a change in the messaging should the situation worsen.

The term **artemisinin tolerance** was used in WHO's first document on this topic in 2008 (2). The word tolerance has been used to describe antibacterial delayed clearance (3), which from a biological perspective is in line with current *PfKelch13* observations in the GMS and Africa. However, the targeted audience, not exclusively comprising scientific experts, might

not embrace the nuance of tolerance being more scientifically accurate. As a result, **partial resistance** should be used.

The major threat correlated to artemisinin partial resistance is a potential increased risk of de novo emergence of resistance or 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. Delayed clearance linked to *PfKelch13* mutations does not necessarily predict treatment failure for ACTs, and delayed clearance alone does not lead to a significant increase in ACT treatment failure rates. However, in combination with partner drug resistance, very high failure rates have been reported.

The term **ACT resistance** was not endorsed by the Technical Expert Group on Drug Resistance in 2015 and was replaced by **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.

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## Annex 3.

# Threat and potential impact of resistance

The implications of antimalarial drug resistance are numerous and complex to estimate. For a given country, the consequences of resistance spreading will depend on the transmission setting, strength of the health system, type of drug resistance, and availability of alternative drugs. The following list describes some possible consequences of resistance, partly based on experiences from other regions or previous development of resistance to antimalarial treatment in Africa. Possible consequences include:

- an increase in transmission due to artemisinin partial resistance if artemisinin partial resistance is shown to increase gametocyte carriage;
- an increase in transmission due to recrudescence caused by partner drug resistance;
- an increase in morbidity and mortality; although this has not been observed in the GMS, it could be a consequence of increased transmission in Africa;
- underlying economic costs due to both the repeated care required to treat patients infected by resistant parasites and the productivity losses resulting from the increased morbidity (e.g. absenteeism in the workplace due to disease burden or the need to care for a sick child, loss of school days) and mortality (i.e. years of productive life lost due to premature death);
- a need to rapidly rotate to another ACT if there is evidence of partner drug failure, with operational implications such as policy changes, training requirements and review of supply chains, as well as a potential incremental cost linked to the new commodity;
- a specific risk borne by lumefantrine, as artemether-lumefantrine is the most widely used ACT in Africa to date; resistance to lumefantrine would also represent a major setback in recent research and development efforts, as the most promising non-artemisinin combination – ganaplacide-lumefantrine – in the patient exploratory phase (Phase IIb) relies on lumefantrine (1);
- a risk that TACTs based on the currently available drugs (artemether-lumefantrine-amodiaquine) may no longer be an option should artemisinin partial resistance spread further and partner drug resistance be observed;
- a disproportionate risk that is likely to be borne by the most vulnerable people, such as children under 5 years of age and pregnant women, especially in the poorest populations, thereby hampering social justice and increasing the inequity gap.

The impacts that are estimated in this section are listed in **Table A3.1**.

**Table A3.1. Health and economic impacts assessed**

Type of impact	Impact	Description
Health impact	Additional malaria cases	Estimated number of additional cases compared to a scenario with no resistance <i>Note: direct output of the Imperial College London model</i>
	Additional severe malaria cases	Estimated number of excess severe cases solely derived from the increased transmission <i>Note: <b>hospitalized cases only</b>, direct output of the Imperial College London model</i>
	Excess deaths	Estimated number of total excess deaths solely derived from the excess severe cases
Economic impact	Cost of care for uncomplicated malaria cases	Cost of an RDT and an ACT, and cost of outpatient care delivery
	Cost of inpatient care for severe malaria	Cost of treating patient with severe malaria (e.g. cost of antimalarial drug, bed occupancy, etc.)
	Cost of introduction of new first-line treatment <i>Note: only the incremental cost of a new commodity has been estimated</i>	Incremental cost of a new commodity <i>Note: one-off cost, as elements such as policy change, training and implementation costs are not factored in</i>
	Productivity losses	Losses due to absenteeism in the workplace due to sickness, due to adults needing to care for their sick children and due to premature mortality

There are many unknowns around the health impacts associated with antimalarial drug resistance. The scenarios described below are hypothetical ones. The aim of this section is to give an idea of the health impacts (see **Table A3.2**) and economic costs (see **Fig. A3.1**) that would arise if antimalarial drug resistance were to further emerge and spread in Africa. The estimates presented below build on existing mathematical modelling studies and data. The results should be interpreted in the context of other evidence and broader research and complemented by field intelligence to refine predictions.

## Scenarios for resistance in Africa

In 2016, researchers at Imperial College London built an African model simulation to estimate the potential impacts of artemisinin and/or partner drug resistance in Africa (2). Two forms of resistance are considered in this study: i) artemisinin partial resistance, which results in a proportion of treated individuals with delayed parasite clearance, and ii) partner drug resistance, which results in a proportion of individuals initially appearing to clear the infection before recrudescing to either symptomatic (clinical) or asymptomatic (parasitological) infection.

The call to action for this Strategy is built upon three of the scenarios included in the paper:

1. **Scenario 1: Widespread artemisinin partial resistance, partner drug still efficacious:** In this scenario, 48% of infected individuals experience delayed clearance. The partner drug is still effective, with 6% of treated patients recrudescing.
2. **Scenario 2: Medium artemisinin partial resistance and moderate partner drug resistance:** In this scenario, 32% of infected individuals experience delayed clearance. The partner drug is moderately effective, with 13% of treated patients recrudescing.
3. **Scenario 3: Widespread artemisinin partial resistance and high partner drug resistance:** In this scenario, 54% of infected individuals experience delayed clearance. The partner drug is no longer effective, with 45% of treated patients recrudescing.

The levels of artemisinin partial resistance and partner drug resistance used in the original study are taken from studies in South-East Asia. These levels are used to parameterize the model and define the three scenarios. The model simulates the impact of these scenarios in different African settings, considering local data from the first administrative unit across Africa, namely the underlying population demographics, parasite prevalence, seasonal patterns of transmission and coverage of insecticide-treated nets. Scenarios are considered with some fixed level of resistance, assuming no mitigation efforts are undertaken during the timeframe studied.

## The health impact in Africa

The estimate of additional malaria cases is a direct output of the model built by Imperial College London (2). The estimate is based on the following assumptions:

- All antimalarials in use are ACTs (this model does not consider other drug-based interventions such as seasonal malaria chemoprevention).
- Resistance to the artemisinin component or partner drug is uniform and fixed across Africa.
- Resistance is constant over the five-year period to the levels described in the scenarios (i.e. resistance is already at a steady state from the first year; a ramp-up period is not factored in).
- A recrudescing individual in a high-prevalence area has a higher probability of developing asymptomatic infection than an individual in a low-prevalence area due to greater acquired immunity.

The number of excess severe malaria cases is derived from the same study conducted by Imperial College London (2). One important note is that only hospitalized severe cases are considered in the Imperial College London model. The model underestimates the total number of excess severe cases by not factoring in the severe cases that would not reach hospital; at the same time, it overestimates the number of hospitalized severe cases as per the strict WHO case definition. Additionally, as the extent to which drug resistance affects the risk of an infection developing into a severe case is unclear, the additional severe malaria cases estimated in the model are only due to the increased transmission and the additional cases



resulting from treated individuals recrudescing to clinical infection. Therefore, the model takes into consideration symptomatic cases, although parasitological failures causing asymptomatic cases can also have severe clinical manifestations, potentially leading to death (3).

The number of excess deaths has been calculated separately. A 2003 study observed an association between the spread of chloroquine resistance in Africa in the 1980s and increased mortality in East and Southern Africa (4). Additionally, several studies have highlighted the correlation between treatment failure and increased severe anaemia and mortality (5), and the correlation (at least among children) between the need for transfusion and the risk of transfusion-transmitted HIV (6). Yet, the impact of antimalarial drug resistance on public health is likely to be less severe today than it was in the 1980s and 1990s.

The estimate presented below is derived from the additional malaria cases leading to severe cases and ultimately death. The underlying assumptions of another mathematical modelling study were leveraged (7). In this study, it is assumed that the overall mortality due to malaria is proportional to the incidence of hospitalized severe malaria. To predict the overall mortality due to malaria, the incidence of hospitalized severe malaria is multiplied by 0.215. The same multiplier was applied here to the number of hospitalized severe cases. This methodology generates a high-level estimate of the number of overall deaths that would be derived from the additional malaria cases. Nonetheless, this multiplier has its limitations, as it ignores the differences in case fatality resulting from variations in access to care (8). Further research grounded in field intelligence is required to determine the impact of resistance on mortality.

**Table A3.2. Health impact due to artemisinin partial resistance and partner drug resistance in Africa per year**

	Scenario 1	Scenario 2	Scenario 3
	Widespread artemisinin partial resistance, partner drug still efficacious	Medium artemisinin partial resistance, moderate partner drug resistance	Widespread artemisinin partial resistance, high partner drug resistance
<b>Excess malaria cases<sup>a</sup></b>	+2m	+5m	+16m
<b>Excess severe cases<sup>b</sup></b> <i>(Hospitalized cases only)</i>	+44k	+122k	+364k
<b>Excess deaths<sup>b</sup></b>	+9k	+26k	+78k

Notes: **a.** numbers have been rounded to the nearest million, **b.** numbers have been rounded to the nearest thousand

**Table A3.2** shows numbers **per year**, assuming a linear distribution of the estimated additional cases calculated over a five-year period (2016–2020) by the Imperial College London model, i.e. the output of the model was divided by 5, which is consistent with the model’s assumption of a steady state reached from year one.

Partner drug resistance represents a major threat. There is a pressing concern to respond to the emergence and spread of artemisinin partial resistance, especially due to the lack of viable alternatives. However, the model shows that a failing partner drug would result in an increase in malaria cases and morbidity greater than what would be observed with artemisinin partial resistance only.

## The economic impact in Africa

The economic burden of antimalarial drug resistance includes two cost categories (9):

- the direct cost of accessing<sup>1</sup> and delivering malaria testing and treatment services from the perspective of the patient and the provider (health care system), respectively;
- the indirect cost, including elements such as lost productivity due to time spent out of work because of a patient's own sickness or time spent caring for another sick individual.

Cost is considered from a country perspective and includes the cost borne by all relevant stakeholders involved in malaria care, including patients and caregivers (out-of-pocket expenses for an RDT and an ACT or during hospital admission, loss of income due to time spent away from work), and health care providers (cost of commodity procurement, cost of outpatient and hospital inpatient visits). The total cost was estimated for the entire African continent over a one-year period.

### Direct cost

The total cost of treating the additional uncomplicated malaria cases, resulting from either increased transmission or treatment failures transitioning to symptomatic cases, was calculated as the sum of the commodity cost (cost of an ACT plus an RDT) and the cost for outpatient health service delivery multiplied by the number of additional malaria cases accessing care. The number of additional malaria cases accessing care was calculated using the total number of additional malaria cases multiplied by the percentage of children under 5 with fever in the past two weeks for whom advice or treatment was sought as a proxy (based on the most recent household surveys in sub-Saharan Africa (10)). For simplicity, it was assumed that all people seeking care would receive an RDT and an ACT. The total average cost used for an RDT plus an ACT was US\$ 0.70 per case<sup>2</sup> and a mean value of US\$ 5.50 was used for the cost of outpatient health service delivery (average calculated with WHO-CHOICE data across all levels of health facilities for the WHO African Region (11)), which led to a total cost of treating one uncomplicated malaria case of US\$ 6.20.

The total cost of treating the additional severe malaria cases was calculated by multiplying the unit cost of inpatient care for severe malaria by the number of inpatients from the Imperial College London model. An average cost of US\$ 30.50 per inpatient bed day for inpatient health service delivery (average calculated with WHO-CHOICE data across all levels of health facilities for the WHO African Region (11)) was multiplied by an average hospital stay of 7.8 days (12). This was then added to the cost of an injectable artesunate course, US\$ 1.35 per 60 mL vial, times three injections, which led to a total cost of treating one severe malaria case of US\$ 242 (13).

The introduction of a new first-line treatment includes a one-off cost due to elements such as policy changes, training and implementation costs, and also a recurring cost linked to the incremental cost captured by the price of the new commodity (assuming that the new product is more expensive than the product it replaces). Only the latter is estimated here, considering a new ACT weighted average price of US\$ 2 (14).

1 Excluding transportation cost.

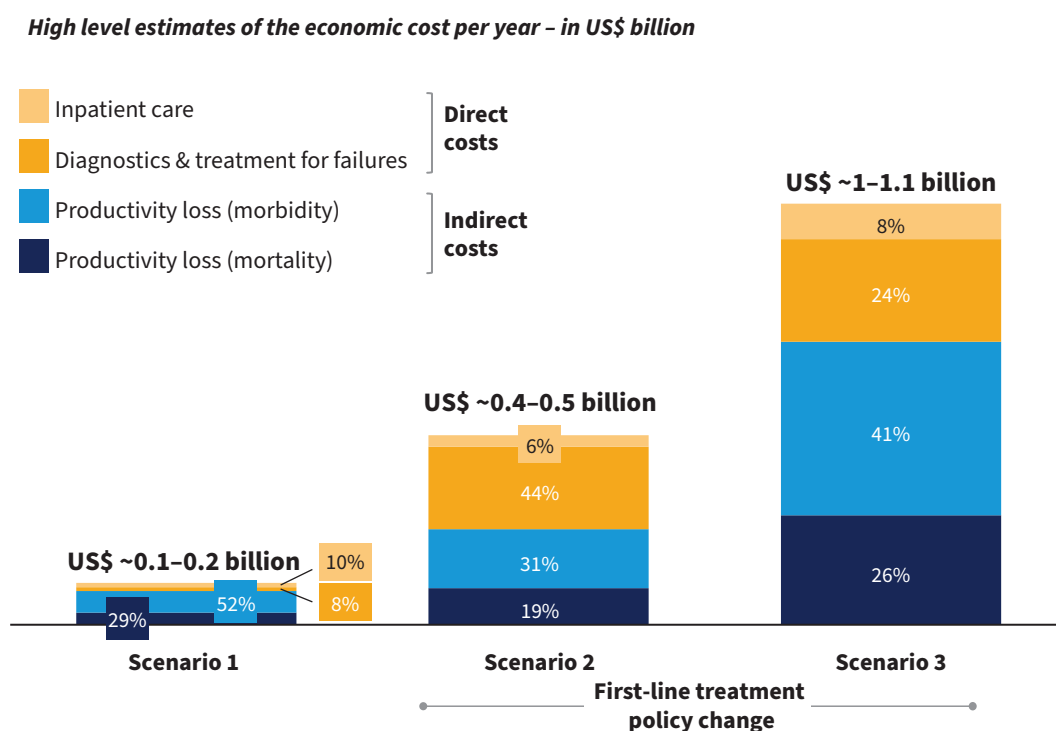
2 Global Fund Pooled Procurement Mechanism weighted average price for an ACT and an RDT in 2020.

## Indirect cost

Lost productivity considered in this document results from excess morbidity and mortality. Lost productivity due to adults needing to care for their sick children or due to absenteeism in the workplace because of sickness was estimated assuming that each treatment failure and uncomplicated malaria case results in one week of lost productivity<sup>1</sup> and that severe cases result in three weeks of lost productivity (15). These losses were valued using gross domestic product (GDP) per capita<sup>2</sup> for each country (16). Lost productivity due to premature mortality was calculated based on the human capital approach,<sup>3</sup> as estimated in a study in the United Republic of Tanzania covering the 2006–2015 period (17).

The estimate of lost productivity has some limitations. Among them, the adopted methodology uses a similar calculation approach across age groups, applying undifferentiated assumptions for adults and for younger age groups. Further research is needed to understand how malaria in young age groups impacts their caregiver’s productivity. In addition, lost productivity due to premature death is sensitive to the discount rate adopted in the calculation. Other limitations in the use of GDP, for instance, should be further considered. An aggregated cost per year is presented in **Fig. A3.1** below.

**Figure A3.1. Total economic cost of inaction from the perspective of both the provider and the patient/household due to artemisinin partial resistance and partner drug resistance per year, in US\$ billion, by scenario**



1 For treatment failure, only the additional week of lost productivity is considered in order to estimate the excess cost caused by resistance.

2 Applying a pro rata share to the annual GDP: number of cases (uncomplicated/severe) \* number of weeks of lost productivity \* country GDP per capita/52 (source: (16)) based on the number of weeks lost.

3 Lost productivity caused by premature mortality due to malaria, adjusted by a discount rate to get the present value of the future cost. Based on the article, a rate of 2.5 is used per death \* GDP per capita \* number of deaths.

Although lost productivity accounts for the highest share of the economic impact of antimalarial drug resistance, estimated as per the methodology described, inaction could result in a recurring direct cost for individuals, their families and health care providers, especially in the case of an ACT policy change.

The assumptions and parameters considered here are relatively conservative. They do not factor in the impact of resistance in other areas where it could have dramatic consequences, including social welfare, equity, well-being and other health conditions associated with malaria. Children, who are the most affected by malaria, are likely to learn less at school because they are often absent or unable to concentrate and may develop longer term disabilities (18, 19). If individuals expect to live a shorter life, their savings and investment in human capital, such as in developing skills, knowledge and experience, will likely be limited. Additionally, antimalarial drug resistance is a biological threat to malaria eradication, further postponing the vast economic and social benefits that could be attained through eradication (20).

These health and economic impacts represent the cost of inaction against resistance. Their magnitude justifies a call to action for leaders and decision-makers to act in a timely and effective manner against the threat and potential impact of artemisinin partial resistance and partner drug resistance.

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# Annex 4.

## Detailed resistance driver tree

The drivers are presented as an issue tree with four levels of granularity, from a macro level (level 1) to level 4, corresponding to the root causes of these drivers. The issue tree was developed through a broad literature review and consultation process.

Figure A4.1. Detailed resistance driver tree

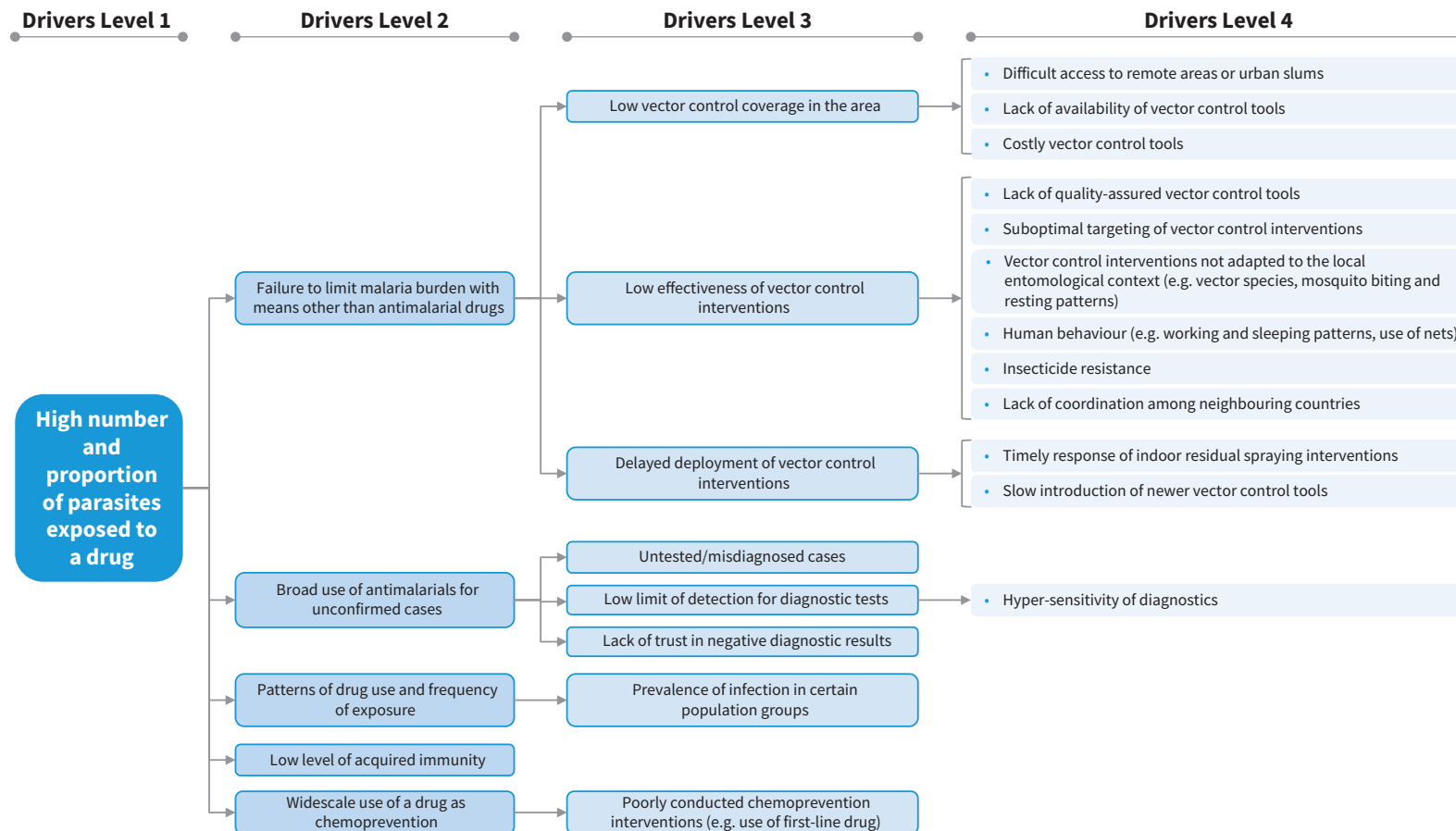


Figure A4.1. Detailed resistance driver tree (continued)

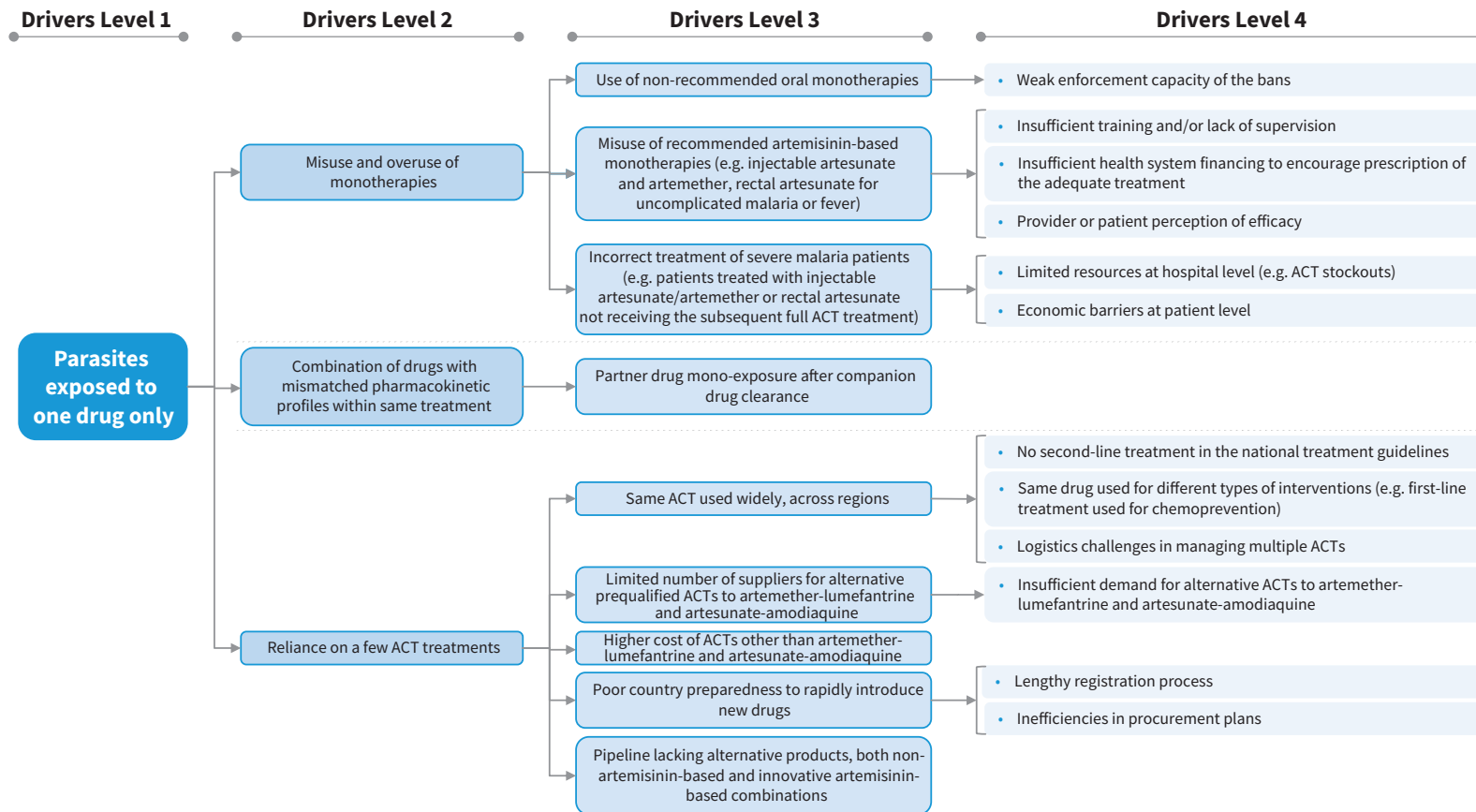


Figure A4.1. Detailed resistance driver tree (continued)

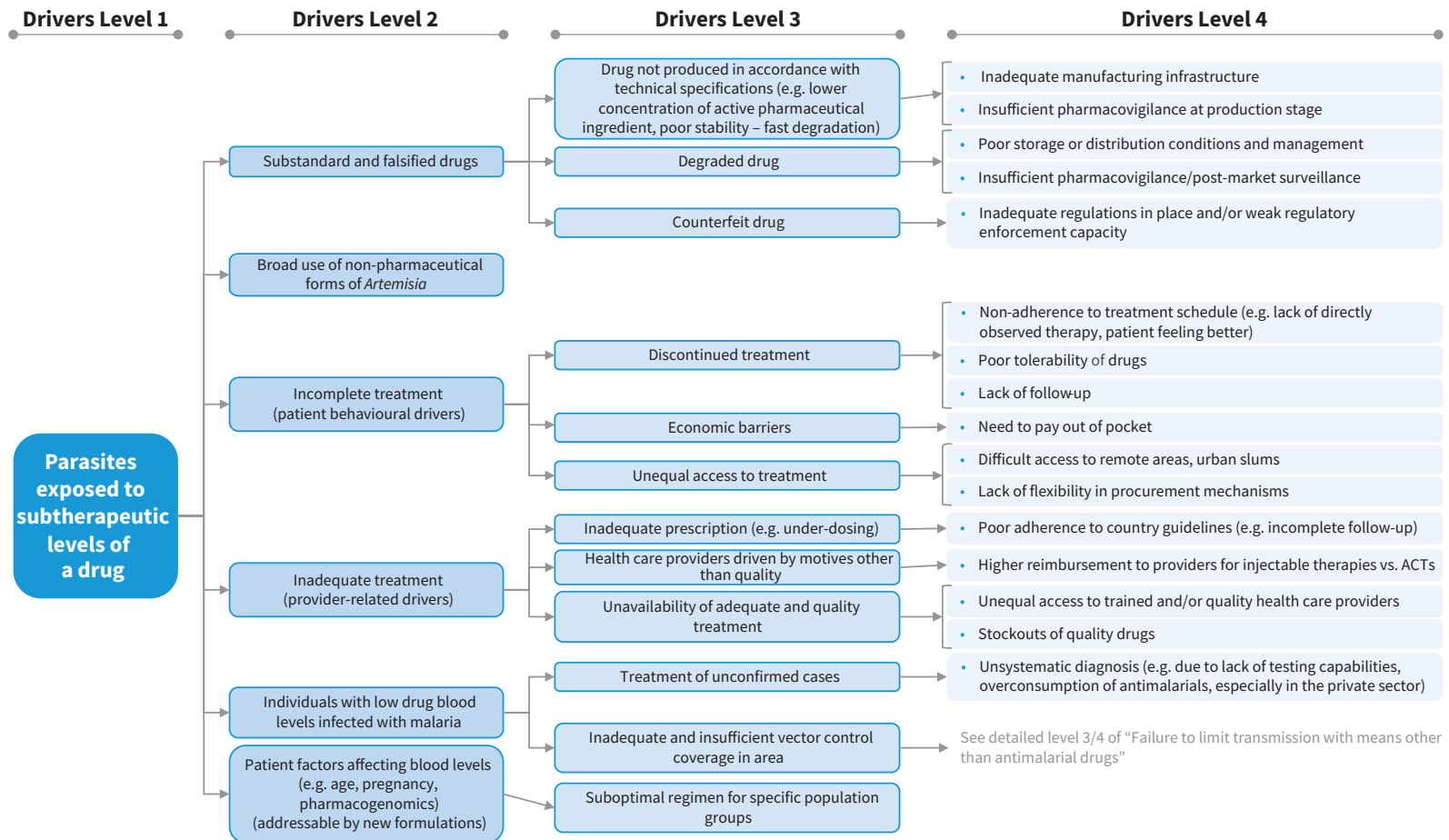




Figure A4.1. Detailed resistance driver tree (continued)

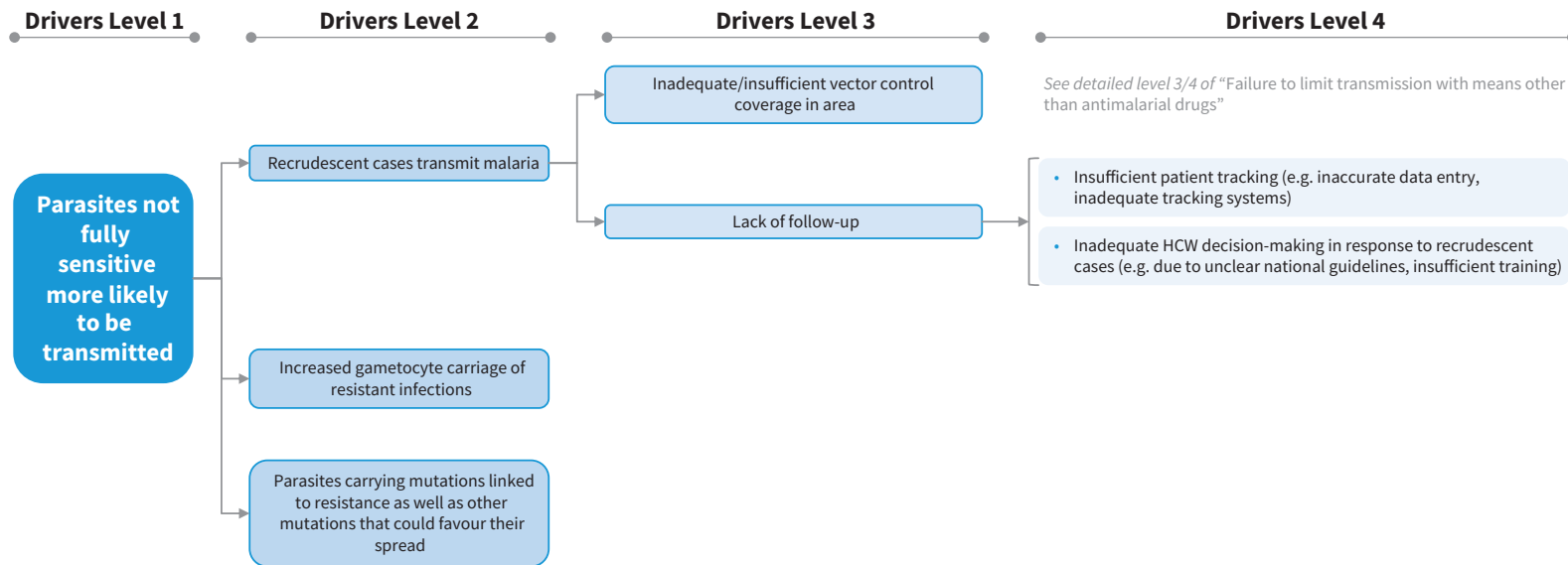
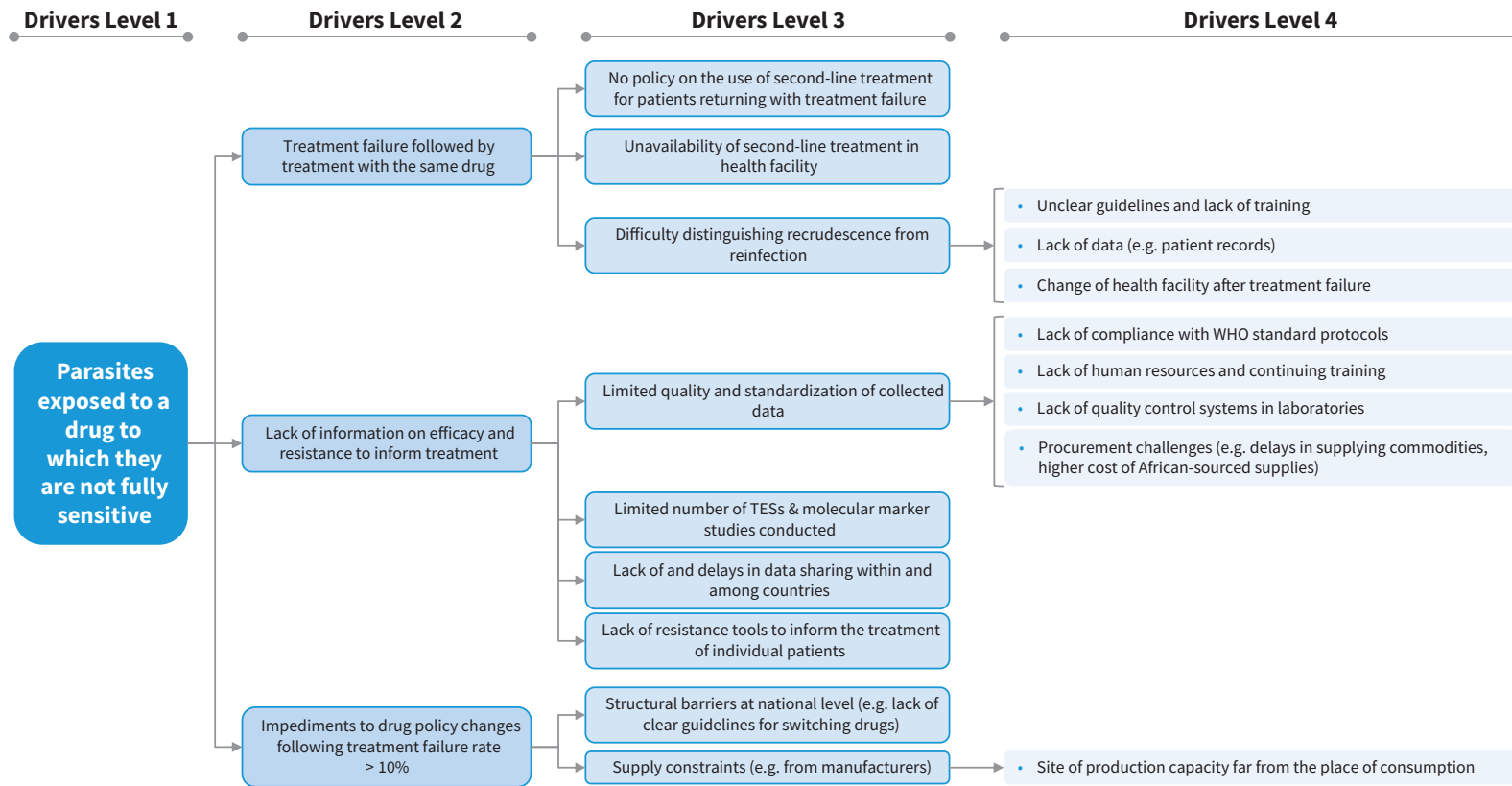


Figure A4.1. Detailed resistance driver tree (continued)



# Annex 5.

## Preliminary country assessment to prioritize interventions

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

This annex lists the main aspects that could be included in the assessment, acknowledging that some data might not be readily available and thus would be quite onerous to collect. The annex highlights a core set and an extended list of elements that can be included in the assessment if there are sufficient resources. Additionally, countries should leverage existing or ongoing assessments to consolidate already available information, thereby reducing the data collection burden.

The assessment should focus on three main areas: status of resistance and epidemiology, drivers of resistance, and overall health and regulatory systems.

### Priority elements to assess

If resources to conduct the baseline assessment and data availability are limited, the following areas should be prioritized for the assessment.

#### 1. Status of resistance and epidemiology

- **Review of efficacy data in the country and region:** An overview of efficacy data for first- and second-line treatments and chemoprevention regimens used in the country, as well as evidence for other ACTs. Data should be examined to detect 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.
- **Main characteristics of in-country malaria epidemiology:** Examples include the patterns of malaria transmission, parasite species, vector species and characteristics of the human population (e.g. level of immunity).
- **Human population movements and migration patterns:** Size, movements, behaviours and preferences of mobile and migrant populations, as, in the past, one commonality of the areas where resistance was suspected was the high number of migrant and mobile populations (1).

## 2. Drivers of resistance

- **Drug availability in-country:**
  - antimalarial drug(s) recommended in the national malaria treatment guidelines
  - antimalarial drug(s) approved by the national regulatory authority
  - antimalarial drug(s) produced in-country
  - main procurement mechanisms of drugs imported into the country
  - antimalarial drug(s) available to patients by sector (public, private formal, private informal)
  - antimalarial drug(s) used in chemoprevention
  - availability of non-recommended monotherapies such as oral artemisinin treatments
  - availability of non-pharmaceutical forms of *Artemisia* (e.g. *Artemisia* tea).
- **Drug use:** Review available information on which treatments are used by patients, including the use of non-pharmaceutical forms of *Artemisia*
  - (mis)use of monotherapies (injectable or rectal).
- **Adherence to treatment guidelines – reference materials:** access to key resources for malaria case management by public and private care providers, such as national treatment guidelines.
- **Adherence to treatment guidelines – knowledge and understanding:** should include knowledge of symptoms, prevention, and the need for parasitological diagnosis and adherence to treatment guidelines.

## Extensive list to be progressively considered

The priority elements listed above may be completed along with the below elements to get a more comprehensive picture of a country's starting point.

### 1. Status of resistance and epidemiology

#### 1.1. Assess the current status of antimalarial drug efficacy and resistance and data availability.

- **Map of data coverage:** Efficacy studies are resource-intensive and a limited number of studies can be conducted each year. However, where data are only available from a few geographical provinces or transmission settings, these gaps need to be recognized and addressed.
- **Capacity and quality:** Highlight issues and challenges in terms of the capacity to perform TESs, surveys and laboratory analysis.
- **Processes of data sharing in-country and with neighbouring countries:** Review the current process and identify challenges in data access and sharing.

## 1.2. Identify the areas and populations where the risk of resistance developing and spreading is high.

- **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, military personnel, and populations in conflict areas.
- **Vulnerable populations with relatively little immunity against the disease:** These groups include children under 5, pregnant women, people living with HIV/AIDS and populations with low immunity moving to areas with high transmission. The poorest and most marginalized populations, also at great risk of malaria, should be identified.
- **Data gaps:** Identify areas and populations from which no information is available, for instance areas and populations not covered by surveillance systems. This could include groups such as migrants or military personnel.
- **Demographic and social patterns of access to services and vector control interventions:** This can include disaggregation by geography, gender, age, occupation and ethnicity.
- **Demographic and social patterns of overuse and misuse of treatment:** This can include disaggregation by geography, gender, age, occupation and ethnicity.
- **Burden and transmission:** This includes the geographical, demographic and social distribution of the malaria burden.

## 2. Drivers of drug resistance

### 2.1. Understand the access to, availability and use of diagnostics, drugs and vector control interventions.

- **Treatment-seeking patterns:** Review available information on where patients seek and receive treatment for malaria (e.g. in the public vs. private sector).
- **Regulation of private sector:** Review existing regulation in place for the private sector.
- **Groups with use of treatment diverging from national treatment policy:** In some countries, large risk groups, such as the military, could have supplies and treatment policies that differ from those promoted by the ministry of health. The policy and impact of this need to be assessed.
- **Supply chain:** Map out in-country supply chains, including the main distribution channels and storage; assess stockouts in the public sector as a priority (frequency and root causes).
- **Quality of drugs throughout the supply chain:** Review available data on the quality of drugs throughout the supply chain, key potential factors of drug degradation (e.g. heat in facilities), and the systems in place to monitor this.
- **Diagnostics availability, use and quality:**
  - data on the availability and use of diagnostics by sector, including what proportion of patients treated with antimalarials receive a parasitological diagnosis
  - quality of diagnostics, including a list of key challenges around diagnostics quality, and availability of information on the presence and prevalence of *Pfhrp2/3* gene deletions.

- **Vector control interventions availability and use:**
  - availability of entomological data on species, biting patterns and insecticide resistance to ensure good targeting of vector control interventions
  - availability and coverage of vector control interventions by type
  - use of vector control and main challenges encountered in increasing coverage and use.
- **Chemoprevention interventions coverage and delivery:**
  - coverage of chemoprevention interventions
  - drugs used during chemoprevention interventions
  - adherence to *WHO Guidelines for malaria (2)* in the planning and delivery of chemoprevention interventions.
- **Background drivers of resistance:** Depending on a country's situation, specific research and assessment could be targeted at the most context-relevant background drivers, especially environmental ones.

## 2.2. Understand the current behavioural drivers of care provider and patient choices.

- **Care providers:** Review information on the knowledge, attitudes and practices of care providers (by provider type as available):
  - *Practices:* This should include patterns of diagnosis, prescription and communication to patients, including the role of traditional healers.
  - *Felt needs and preferences:* This should include the preference for prescribing certain types and dosages of treatment, perceived benefits of parasitological diagnosis and malaria treatments, and perceived value in spending time to ensure that patients understand the importance of taking the full treatment.
  - *Barriers and incentives that could affect the effectiveness of interventions:* This should include barriers to treating patients as per the national treatment guidelines (e.g. availability of drugs), as well as incentives for providing non-recommended treatments (e.g. financial).
- **Patients:** Review information on the knowledge, attitudes and practices of patients.
  - *Practices:* This should include when and where treatment is sought, compliance to prescribed treatment and use of vector control interventions.
  - *Knowledge and understanding:* This should include knowledge of symptoms, prevention, and the need for parasitological diagnosis and completion of the correct treatment.
  - *Communication:* This should include the main sources of information on malaria prevention and treatment, and key challenges in communication (e.g. language).
  - *Felt needs and preferences:* This should include the preference for certain sources, types and dosages of treatment, perceived benefits of parasitological diagnosis and malaria treatments, perceived value in taking the full treatment, and key perceived challenges in accessing quality treatment and vector control interventions.
  - *Barriers and incentives that could affect the effectiveness of interventions:* This should include barriers making it difficult to seek treatment, as well as incentives, for instance for taking the full treatment.

### 3. Strengths and weaknesses of the health and regulatory systems

#### 3.1. Assess the strengths of the health and regulatory systems.

- **Health care funding mix:** Examples include the mix between donor-provided funds, domestic public funding, private health insurance and out-of-pocket payments.
- **Structure of care provision:** This includes assessment of the role and importance of the different sectors of care (e.g. public, private formal and informal sectors).
- **Integrated delivery of care:** Examples include the level of integration of care delivered throughout the patient journey (e.g. referral to inpatient care) and across different diseases (e.g. integrated community case management).
- **Quality of care:** Examples include indicators measuring coverage (e.g. universal health coverage index), infrastructure (e.g. number of operating rooms) and health outcomes (e.g. neonatal mortality).
- **Human resources:** Examples include the availability of resources (e.g. number of nurses per 1000 people), distribution of HCWs across the country and their level of training.
- **Health information systems and monitoring:** Examples include assessment of the systems and processes in place to monitor, analyse and evaluate ongoing programmes.
- **Procurement and supply management systems:** Examples include planning and projecting a country's health resource needs, the availability of pharmaceuticals and supply of products to the facilities.
- **National treatment guidelines and registration of essential medicines:** Examples include the inclusion of an ACT as a second-line treatment.
- **Enforcement capacity:** Examples include the capacity to assess and proactively monitor the quality of drugs and enforce sanctions.

#### 3.2. Understand the gap between the plans developed by the NMP and their effective implementation.

- Countries should rely on existing monitoring and evaluation frameworks and on interviews with 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).

#### 3.3. Identify synergies with other strategies and global plans.

- Identify interventions already being deployed within the framework of other strategies that could be beneficial and further leveraged to respond to antimalarial drug resistance, e.g. training and awareness campaigns suggested in the *Global action plan on antimicrobial resistance (3)*.

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# Annex 6.

## Detailed interventions per stakeholder

This annex gives a summary of the different actions that should be undertaken by each stakeholder. The actions have been derived from the interventions described in Chapter 5 of the Strategy. Details and examples of the activities are provided in the core document. Further prioritization will be needed depending on the preliminary assessment conducted by each country (see **Annex 3**).

### Ministries of health

#### Strengthen surveillance of antimalarial drug efficacy and resistance

- Strengthen the process to generate and consolidate more quality data on antimalarial drug efficacy and resistance by promoting systematic adherence to WHO's standard protocols, providing continuing training, establishing a supervision and quality control system for TESs.
- Increase the frequency of TESs and, if necessary, the capacity to conduct them. Provide support in increasing the capacity to conduct genomic and pharmacokinetic studies and provide training.
- Consider collecting a broad spectrum of samples (smears, filter paper, whole blood) at select sites and monitor trends over time. Sign agreements with academic institutions to secure their support and leverage their knowledge, expertise and capabilities.
- Engage with other countries and with regional and global stakeholders to consider the development of a robust subregional network of surveillance for antimalarial drug efficacy and resistance, including regional reference centres, a harmonized regional framework for data sharing and a systematic quality control system.
- Establish a clear process to improve data dissemination among all stakeholders (internally and with other countries) by leveraging existing groups or building dedicated ones.

#### Optimize and better regulate the use of diagnostics and therapeutics to limit drug pressure

- Review national treatment guidelines based on the *WHO Guidelines for malaria (1)* and regularly update them based on the latest evidence on local antimalarial drug efficacy.
- Investigate and revise policies to support appropriate case management across health sectors, with an intensified effort towards the private sector, and to drive down the treatment cost for individual patients in certain population groups.
- Collaborate with the national regulatory authority to enforce a stringent regulatory framework for quality standards for antimalarial drug and diagnostic tools, to withdraw non-recommended oral monotherapies from markets and to reach the private sector.

- Promote the availability of a diversified portfolio of antimalarial drugs and diagnostic tools by optimizing the process of including new ACTs in the national treatment guidelines and working with global partners to ensure the availability of different ACTs as second-line treatment in the country and diagnostic tools across health sectors.
- Promote efficient and flexible national procurement plans by assessing local needs, consolidating them at national level, improving demand forecasting, and assessing opportunities to increase the availability of antimalarials and diagnostic tools through complementary procurement mechanisms.
- Increase access to quality health services for underserved communities and populations by developing initiatives to address barriers, such as financial ones, and by engaging with communities.
- Engage with the private sector to bridge the gap between public and private care by regularly assessing adherence to national treatment guidelines and working through private sector channels (pharmacies and distributors) to ensure broad-based availability of high-quality ACTs and diagnostic testing.
- Raise awareness of populations and key stakeholders on antimalarial drug resistance and treatment guidelines.
- Allocate resources for the training of HCWs to promote adherence to treatment guidelines and WHO protocols.
- Collaborate with neighbouring countries by enforcing systematic monitoring of the circulation of drugs at borders, taking coordinated measures to stop the production and export of substandard or falsified drugs and non-recommended monotherapies.

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

- Intensify efforts to prioritize and optimize vector control interventions in priority areas, address potential barriers to the rapid scale-up of vector control interventions and complement existing tools with innovative ones.
- Promote the targeted deployment of chemoprevention and vaccination campaigns in accordance with WHO guidelines.
- Develop actionable standard operating procedures for recrudescence cases.
- Depending on the national treatment guidelines, consider the use of single low-dose primaquine in areas of confirmed or suspected artemisinin partial resistance and in cases of suspected recrudescence.
- Communicate early warning signals of resistance to neighbouring countries and promote coordinated actions at borders.

#### **Stimulate research and innovation to better leverage existing tools and develop new ones against resistance**

- Consider, with the support of global partners, the implementation of pilots to test alternative approaches to using current treatments.
- Collaborate with academia and research institutes to conduct setting-specific modelling supported by research.

## National regulatory authorities

- Establish a stringent regulatory framework for quality antimalarial drugs and diagnostic tools and collaborate with the ministry of health to enforce it.
- Intensify efforts to regulate and collaborate with the ministry of health to enforce complete withdrawal of non-recommended oral monotherapies from markets.
- Increase monitoring of antimalarial drug and diagnostic quality, especially in the private sector, as part of post-market surveillance activities.
- Promote the availability of a diversified portfolio of antimalarial drugs and diagnostic tools by optimizing the registration process.
- Collaborate with neighbouring countries by promoting the adoption of a harmonized regulatory framework.

## Regional organizations

- Raise overall awareness on antimalarial drug resistance.
- Advocate to malaria-endemic countries to produce quality data on antimalarial drug efficacy and resistance and adhere to WHO standard protocols.
- Support the development of robust antimalarial drug efficacy and resistance surveillance networks across Africa, for instance by supporting countries in addressing procurement challenges for surveillance supplies.
- Advocate for a diversified portfolio and diversified sources of supply of antimalarials and diagnostic tests.
- Contribute to the establishment of a viable and sustainable marketplace by supporting the development of continent-wide harmonization of regulatory standards and processes; facilitating the uptake of innovative technologies; coordinating joint safety monitoring and assessments of medical products; and providing advice on local pharmaceutical industry development.
- Advocate for the inclusion of drug resistance management actions in the mandate of regional organizations.
- Support countries in accessing and rapidly mobilizing resources, and optimizing the deployment of preventive measures.

## World Health Organization and other multilateral organizations

- Raise awareness on the threat of antimalarial drug resistance and on the need to act, through targeted communication at the global, regional and local levels.
- Lead and coordinate the response to antimalarial drug resistance by consolidating data from all relevant stakeholders and by recommending the appropriate course of preventive and reactive actions.

- Provide technical support to countries and partners, for example to build strong and sustainable networks of surveillance, to review treatment guidelines and to optimize deployment of vector control interventions.
- Advocate for and support country coordination, for instance in the establishment or strengthening of subregional networks for antimalarial drug efficacy and resistance surveillance
- Advocate for a continued effort to conduct research on antimalarial drug resistance.

## **Funding agencies and donors**

- Advocate for the need to respond to antimalarial drug resistance.
- Provide financial and technical support to strengthen surveillance networks at country and regional levels.
- Support countries in diversifying their portfolio of antimalarial drugs and diagnostic tools.
- Provide a coordinated effort to address market failures and develop a viable and sustainable marketplace by engaging with manufacturers and defining market interventions to ensure the availability and affordability of quality ACTs and diagnostic tools.
- Advocate for key actions, such as the withdrawal of the remaining non-recommended oral monotherapies from the market and the monitoring of at-risk areas by countries and regional organizations.
- Provide technical and financial support to countries to improve access to quality care, especially in the underserved populations and in the private sector.
- Support countries in rapidly mobilizing resources, for instance for vector control interventions.
- Provide adequate funding to advance research and develop pilots on priorities identified in the Strategy.

## **Academia and research institutions**

- Strengthen the surveillance of antimalarial drug efficacy and resistance by generating and consolidating more quality data, increasing the frequency of TESs, and increasing capacity to conduct genomic and pharmacokinetic studies.
- Support the NMP in the training of health care professionals, including through continuing professional development and additional courses, such as microscopy and leadership training.
- Foster cross-sectoral collaboration.
- Systematically and rapidly make the outputs of studies available to NMPs and other relevant stakeholders.

## Civil society organizations and community-level networks

- Raise awareness and foster community engagement around the response to antimalarial drug resistance.
- Coordinate with the NMP to implement interventions at community level, with an increased focus on bridging the gap between public and private sectors and increasing efforts to reach underserved communities.
- Support the NMP in developing and conducting targeted training for health care providers.
- Collaborate with the NMP to communicate to and raise awareness among patients.

## Care providers (public and private)

- Adhere to national treatment guidelines.
- Promote adherence to guidelines.
- Coordinate with the NMP by sharing information on storage, stock management and patient use.

The stakeholders mentioned above are considered the most relevant in the response to antimalarial drug resistance, but this Strategy calls for broader action. As highlighted in the *Multisectoral action guide to end malaria (2)*, all sectors have an important role to play in promoting and protecting community health from the burden of malaria. Multisectoral collaboration should target multiple objectives. First, it should ensure that both pre-emptive and reactive measures are adequately and efficiently implemented in a timely manner in all sectors, including those that are harder to reach, such as the military or workers hired by private companies in remote areas. Second, it should prevent actions being taken outside of the health sector that unwittingly hinder the response to resistance, for example actions that promote work-related mobility of populations into malaria-endemic areas without ensuring adequate access to malaria prevention, diagnosis and treatment. And third, it should foster coordination among different sectors to maximize the impact of the response to resistance.

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