Area for Intervention:

Mitigating antimalarial drug resistance in Africa

*Malaria Programmatic Priority: Improve access to quality case management*
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1. **Purpose and context of this document**

At the Spring 2022 Joint Session of the Policy and Strategy Committee (PSC) and Finance and Accountability Committee (FAC), the Secretariat presented two-page summaries of new investment opportunities as alternatives to the existing Area for Intervention (AfI) document. The PSC/FAC showed support for a more streamlined narrative but recommended a modest expansion including more information on risk, partner landscape and fit with Unitaid’s existing portfolio. This pilot of streamlined documentation in support of an AfI aims to generate alignment on 1) the scope and level of detail of future AfI documentation, and 2) antimalarial drug resistance in Africa as a priority investment opportunity for 2023. As agreed at EB40, other investment opportunities for 2023 will be taken forward under existing AfIs.

2. **Introduction**

Mitigating antimalarial drug resistance in Africa is central to achieving the Programmatic Priority, *Malaria - Improve access to quality case management*. Unitaid’s Programmatic Priority in malaria case management is focused on improving the quality of diagnosis and treatment for *Plasmodium falciparum* (*P. falciparum*) and *Plasmodium vivax* (*P. vivax*) malaria, the two most common malaria parasites. In *P. vivax*, to improve case management in Asia and the Americas, new tests and treatments for radical cure are being introduced in Unitaid’s Vivaction grant. For *P. falciparum*, which causes most cases and deaths in sub-Saharan Africa, persisting challenges have limited the scale up of rapid diagnostic tests (RDTs) and artemisinin-based combination therapies (ACTs) needed for effective case management. These include a long history of presumptive treatment for fever, poor care-seeking behaviour and significant care-seeking in the private sector where the quality of treatments varies.

Against this backdrop, antimalarial drug resistance – specifically, resistance threatening the efficacy of WHO-recommended ACTs – has recently emerged in sub-Saharan Africa and is a key threat to our ability to deliver quality case management in the future. The seriousness of this threat has led global partners to mobilise rapidly before resistance leads to major setbacks. While ACTs remain effective in Africa, scaling up appropriate access to quality products is still a top priority alongside efforts to mitigate resistance. This is reflected in the Programmatic Priority which includes efforts to mitigate resistance as a near-term activity, and efforts to improve case management overall as a medium-term objective. In the later years of Unitaid’s Strategy, the Programmatic Priority includes an opportunity to support the introduction of non-artemisinin based drugs. The potential of new treatments depends on successful resistance management strategies, as the most advanced candidate in the research and development (R&D) pipeline includes a partner drug that is threatened by resistance. Together, these efforts are central to achieving the overall objectives of the Programmatic Priority.

3. **Public health challenge and commodity access issues**

The global malaria burden persists, with progress plateauing in recent years. In 2020, there were 241 million malaria cases and 627,000 deaths. Most cases occur in Africa (95%), and 77% of deaths affect children under five. Although malaria case incidence has reduced dramatically since 2000, from 2015 progress has plateaued and as a result the world is not on track to achieve global malaria targets.

Access to adequate quality malaria case management remains a significant challenge in low resource settings. Only two thirds (69.3%) of children under five seek treatment for fever. In the public sector, 71% of children seeking care received treatment and only 39% received a malaria test. Access to care is even lower
in the private sector (31% of children received treatment), where access to quality ACTs varies and substandard and falsified drugs are abundant.\(^1\)

**Antimalarial drug resistance in Africa is an urgent threat to the fight against malaria.** To treat malaria, WHO recommends six ACTs that combine artemisinin-based compounds with a partner drug. Artemisinin partial resistance\(^2\) has been confirmed for the first time in Africa, specifically in Uganda, Rwanda, and Eritrea, though experts believe that the problem is likely more widespread. Artemisinin partial resistance increases the risk of de novo emergence of partner drug resistance, and importantly, the spread of parasites less sensitive to the partner drugs, which can result in clinical treatment failures. Given the heavy reliance on ACTs in Africa where most cases occur, the threat of drug resistance must be addressed urgently. New non-artemisinin-based treatments will not be available before 2026, and as such, short-term strategies focus on scale-up and optimal use of ACTs while they remain effective. Resistance also poses a threat to the drug pipeline, as the most advanced candidate (ganaplacide-lumefantrine, in Phase 2b) shares a partner drug with artemether-lumefantrine (AL), the most widely used ACT. Preserving the efficacy of lumefantrine is therefore a high priority.

Despite multiple quality ACT options, the market is dominated by a single ACT – AL, which is potentially driving resistance in Africa. The current ACT market is not optimally structured to limit drug pressure. Most African countries rely on AL as their first line treatment, and 30 African countries use AL exclusively. This is despite several countries including other ACTs in their treatment guidelines as possible first line options. As a result, AL’s share of donor-funded ACT procurements is over 80%. With such heavy reliance on AL, artemisinin partial resistance could instigate an emergency and trigger the rapid spread of lumefantrine resistance, causing a rise of cases and deaths, and potentially derailing the most advanced pipeline candidate. Reliance on AL is attributed to the fact that it was the first ACT to become available and has good user acceptability, a large supplier base and low pricing. In addition, unlike other disease areas such as HIV, WHO’s malaria treatment guidelines do not explicitly encourage diversified ACT use, but they do not explicitly limit diversification either.

4. **Potential opportunities to mitigate antimalarial drug resistance in Africa**

WHO is finalising a strategy that will guide the response to antimalarial drug resistance in Africa, which will be launched during World Antimicrobial Awareness Week in November 2022. The draft strategy\(^3\) proposes that countries, regional bodies and global partners address the threat through four pillars: (I) strengthen the surveillance of antimalarial drug efficacy and resistance; (II) optimise the use of diagnostics and therapeutics to limit drug pressure; (III) react to resistance by limiting the spread of antimalarial drug resistant parasites; and (IV) stimulate research and innovation.

In Pillar II WHO recommends quickly diversifying ACT markets in countries to reduce drug pressure. This will require both supply and demand side interventions, the latter closely linked to closing evidence gaps related to the impact and feasibility of approaches like multiple first line ACTs in mitigating drug resistance (Pillar IV).

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2 A delay in the clearance of malaria parasites from the bloodstream following treatment with an ACT. As a result, the artemisinin compound is less effective in clearing all parasites within a 3-day period among patients who are infected with artemisinin partially resistant strains of malaria.
3 https://cdn.who.int/media/docs/default-source/malaria/who-antimalarial-drug-resistance-strategy-for-consultation.pdf?sfvrsn=9d4eaa0_6
In Pillar II WHO also recommends expanding chemoprevention and scaling-up vector control tools, already key focus areas of Unitaid’s malaria portfolio.

4.1. Opportunities to diversify ACT markets

A near-term opportunity exists to limit antimalarial drug pressure by diversifying ACT markets through interventions that address supply barriers, generate demand for underutilised ACTs, and evaluate the impact and feasibility of strategies such as multiple first-line treatments (MFTs) to mitigate resistance. In light of challenges with older ACTs e.g., tolerability due to side effects, partner drug resistance, and the fact that artesunate-amodiaquine (ASAQ) cannot be used as treatment in areas implementing seasonal malaria chemoprevention, diversification efforts will focus primarily on artesunate-pyronadine (ASPY) and dihydroartemisinin-piperaquine (DHA-PPQ). ASPY became available in 2019, but despite having the advantage of once daily dosing, its uptake is low primarily due to its high price (three to four times the AL price), dosing by specific weight bands, and initial but now resolved safety concerns. ASPY’s price is driven by low volumes/poor demand, lack of competition, and high costs of the pyronadine active pharmaceutical ingredient (API). DHA-PPQ also has a reduced pill burden and its market share has recently grown, however there is only one quality-assured supplier of the child-friendly formulation and prices are also three times that of AL. While it is susceptible to resistance due to the long half-life of PPQ, close monitoring can ensure early detection and follow-on action.

Supply side market shaping work is therefore needed to improve the affordability of ASPY and DHA-PPQ and increase suppliers/production capacity. Market interventions could include a volume guarantee with a co-payment that offsets higher prices. Other interventions being explored include reducing the pyronadine API price through manufacturing efficiencies and increasing the number of finished pharmaceutical product (FPP) suppliers. Longer-term work could include expanding production capacity through local manufacturing. Further evaluation of the benefit of this approach is needed, considering challenges such as higher costs (e.g., lower volumes, tariffs on imported APIs, export taxes, limited infrastructure) and the need to meet international quality standards.

Accelerating the demand and adoption of ASPY and DHA-PPQ is also needed alongside supply side interventions. This can be achieved through multi-country implementation pilots that create early volumes and grow the market, while also addressing key evidence gaps to support policy change and sustain demand over time. This includes operational evidence on how to implement ASPY and how to deploy MFTs (e.g., regionally, by age group etc.), as well as evidence on the impact of MFTs on reducing drug pressure.

4.2. Partner engagement

WHO’s global strategy on antimalarial drug resistance in Africa has included a public consultation as well as engagement with country programmes and a workstream to inform market shaping interventions. Unitaid is a key thought partner in this area and is working closely with the Bill and Melinda Gates Foundation (BMGF), the Global Fund, MedAccess, the Medicines for Malaria Venture (MMV), the US President’s Malaria Initiative (PMI) and others to ensure harmonised efforts.

MedAccess is actively scoping a volume guarantee for ASPY and launched an Expression of Interest targeting manufacturers with capacity to supply both ASPY granule sachets (the paediatric formulation) and tablets, from initial industry engagement led by MMV, it is likely that additional manufacturers are interested in developing and supplying ASPY.
to understand their potential to achieve lower prices with increasing sales volumes. BMGF is also working with partners on a market shaping initiative (price optimization) to support the uptake of ASPY.

Both the Global Fund and PMI are developing interventions to support ACT diversification. The Global Fund is scoping market shaping interventions that could be funded through the NextGen Market Shaping initiative such as a co-payment for ASPY and DHA-PPQ, leveraging the volume guarantee being scoped by MedAccess and BMGF, to overcome price premiums. The details of the co-payment, including the countries and volumes to be supported and the resulting funding requirements, are currently under development. Other Global Fund efforts to respond to resistance include supporting malaria surveillance systems including surveillance of antimalarial drug efficacy and resistance, continued support for the Regional Artemisinin-resistance Initiative (RAI), and additional efforts to address biological threats in malaria case management in Africa via the Strategic Initiative. PMI placed a large spot purchase of ASPY (approx. 1.5 million units) to boost the market and is tracking potential demand for ASPY and DHA-PQP in the countries it is supporting. It also is continuing to support robust resistance surveillance efforts at the country level.

MMV has supported MFT pilots in Burkina Faso and Kenya to assess real world implementation and inform countries that are considering MFT as part of their resistance mitigation toolkit. There is strong agreement among partners that additional, large-scale pilots are needed to generate strong evidence and guidance for both MFT and ASPY scale up, and generate the volumes needed to enable the supply-side interventions described above.

Unitaid has engaged countries by presenting at the RBM’s National Malaria Programmes and Partners Annual Meetings 2022 across four African regions. Nigeria accounting for a large portion of malaria case and being a key driver of the ACT market, the Malaria Technical Director at National Malaria Elimination Program of Nigeria was also consulted. The Secretariat held a dialogue with the Executive Board Communities Delegation and held an additional dialogue with the Civil Society for Malaria Elimination (CS4ME) and their partner organisations. Advice will be incorporated into the call for proposals. Advocacy, community and civil-society groups will continue to remain engaged through implementation and scale up, such as increasing health literacy and generating demand at the grass-roots level. Support for these groups will also be considered during project development.

5. Opportunities for Unitaid investment

5.1. Pilots to accelerate demand and adoption of underutilized ACTs, and evaluate the impact of multiple first line ACTs as part of national resistance management strategies

Large scale, multi-country implementation pilots are needed to support ACT diversification. They would serve to increase demand for underutilized ACTs, create early volumes needed to support supply-side efforts, and address key evidence gaps. The latter includes demonstrating how to implement ASPY alongside other ACTs while adhering to the specific dosing weight bands, as well as evaluating the impact, feasibility, and cost-effectiveness/willingness to pay for multiple first-line treatments. Strategies can include rotating ACTs, “mosaic” models, or diversifying ACTs by region or age group. Other innovative strategies that consider sub-national tailoring or implementing multiple first-line treatments across the public and private sectors could also be considered. WHO has indicated that additional evidence is needed on the impact of these strategies prior to issuing a global policy recommendation. At the same time, generating evidence on the operational feasibility, acceptability, and cost-effectiveness of these strategies is needed to strengthen the case for ACT diversification and inform the development of resistance management operational guidance. Data generated
from implementation pilots would therefore be important inputs into WHO policy recommendations and operational guidance, as well as generating evidence to support country-level scale-up. Pilots are also needed to create early market volumes needed to support the planned supply-side interventions described in Section 4.2. The proposed opportunities for Unitaid fit primarily within Strategic Objective 1 of Unitaid’s Strategy 2023-2027.

6. **Assessment of the opportunity**

6.1. Impact potential, including public health value of the solution, potential to improve equity, and the transformative potential of the solution

ACT treatment failures could result in an increased number of cases, additional severe cases, and excess deaths. Across Africa, estimates show that widespread artemisinin partial resistance and partner drug resistance could result in an additional 78 million cases over a 5-year period, a 7% increase in cases compared to a scenario with no resistance, and an estimated US$ 5.9 billion additional costs. Women, children, poor, mobile, and rural populations would be disproportionately affected, further widening the gap.

Improving equity is a key impact criterion and given that malaria disproportionately affects children under five, work should focus on meeting their needs. As such, child-friendly formulations of ASPY and DHA-PPQ exist giving caregivers a suitable alternative to dispersible AL. Thus, planned efforts have the potential to quickly expand access to at-risk children.

Beyond the 5-year impact estimates, preserving ACTs by scaling-up underutilised drugs with the aim of protecting the efficacy of lumefantrine, is essential for long-term resistance management strategies that will rely on non-artemisinin based chemical compounds in combination with lumefantrine.

From previous examples, malaria treatment used to rely on chloroquine (CQ) but the widespread use, misuse, and very low cost of CQ led to the rapid emergence of resistance in Africa. CQ resistance was a major contributor to global malaria resurgence in the 1990s and is credited for the doubling of malaria-attributed child mortality in eastern and southern Africa. In the Greater Mekong Subregion, ACT treatment failures have been observed due to partner drug resistance (e.g., piperaquine, mefloquine). By the time treatment failures were reported, resistance was already widespread.

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5 where there is artemisinin partial resistance for 50% of cases
6 where 25% of ACTs are failing
6.2. Ability to make a difference, including fit Unitaid’s comparative advantage, maturity and feasibility of the solution and readiness of partner ecosystem

Unitaid is strongly positioned to make a difference and planned efforts strongly fit Unitaid’s comparative advantage i.e., Unitaid has extensive experience funding multi-country implementation pilots for malaria and fever management. The timing is optimal as WHO’s strategy will be launched soon, and partners are mobilized to address supply-side access barriers. Bringing forward the AfI now will allow Unitaid to act as soon as WHO’s strategy is launched. The timing also aligns with the short-term interventions included in the Programmatic Priority, fitting with Unitaid’s overall planned investments in improving malaria case management. This work builds on Unitaid’s previous investments i.e., the VivAction grant focusing on malaria case management in Asia/the Americas. As this new investment focuses on Africa it would bring geographical diversity to Unitaid’s case management efforts. Other portfolio links include work on severe malaria in Africa by piloting the appropriate use of antimalarials for prerereferral treatment.

6.3. Risk

The opportunity has a low – moderate risk profile. Strategic risks are low given the high public health relevance of the opportunity. Mitigating antimalarial drug resistance has also been raised as a priority across stakeholders, there are strong links with Unitaid’s existing portfolio, and Unitaid has a clear comparative advantage to support large scale implementation pilots. There is a moderate strategic risk that treatment failures to ACTs emerge during pilot implementation, requiring a large reprogramming, but this is unlikely. Implementation risks are moderate given the potential complexities of operationalising strategies like MFTs and that partner activities will require close coordination. For scalability, while the intervention is linked to WHO and partner activities, especially the Global Fund and PMI’s activities, there is the risk that despite planned market shaping efforts, prices of ASPY and DHA-PPQ remain too high and limit meaningful scale-up.

6.4. Cost and level of effort

Multi-country pilots are estimated to require US$ 30 million in funding which will allow Unitaid to support pilots in up to five countries. Therefore, a budget of US$ 30 million is proposed in the baseline scenario for 2023. If upside resources are available additional work could include supporting supply-side efforts or pilots of other resistance management strategies like low dose primaquine or triple ACTs (pending further scoping).

7. Proposed resolution - Resolution n°1 (Draft)

Taking note of the analysis provided by the Secretariat set out in document (UNITAID/EB41/2022/6), together with the recommendations of the Policy and Strategy Committee (PSC) presented to EB41 by the Chair of the PSC;

The Executive Board supports the need for Unitaid to focus strategically on “Mitigating antimalarial drug resistance in Africa”, with a view to contributing to the global malaria targets set out in the Global Technical Strategy for Malaria 2016–2030 and the Sustainable Development Goals.

The Executive Board requests the Secretariat to launch appropriate calls for proposals within this Area for Intervention and to present progress on implementation to the PSC.

The Executive Board’s endorsement of this Area for Intervention has no budgetary implications.