World Health Organization

Background documentation for Day 2

This file contains the slides that were shown by the presenters during Day 2 of the meeting as well the background documentation shared with MPAG members ahead of the meeting.

Thursday, 24 March 2022			
	Session 3	**Open**	
12:00 – 12:30	Update on "Rethinking malaria" and preparations for the Africa regional meeting	Dr Akpaka Kalu & Dr Alastair Robb	**For guidance**
12:30 – 13:00	Update on the framework for response to malaria in urban areas	Dr Abdisalan Noor	**For guidance**
13:00 – 13:15	Update on the development of a strategy to respond to antimalarial drug resistance in Africa • Pre read • Presentation	Dr Pascal Ringwald	**For information**

WHO/UCN/GMP/MPAG/2022.04

From the what to the how

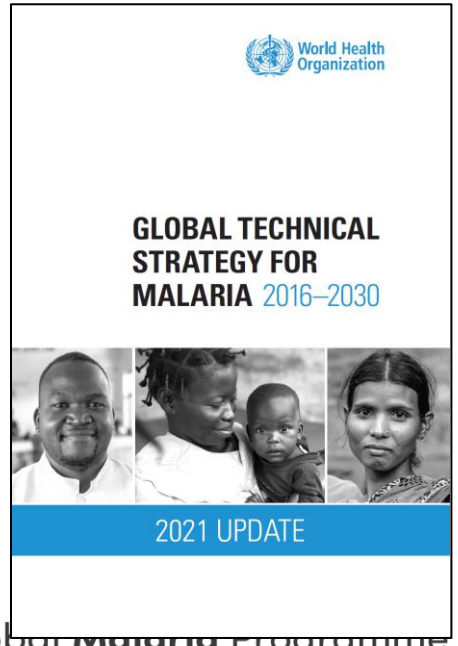
An urgent response to malaria crisis in Africa

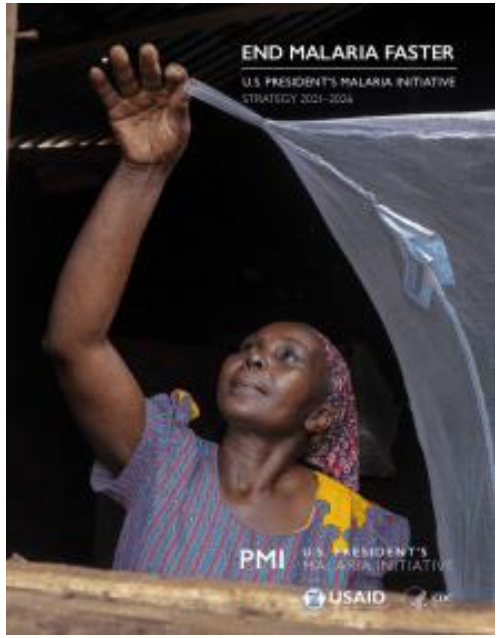
Rethinking malaria in Africa

Global **Malaria** Programme

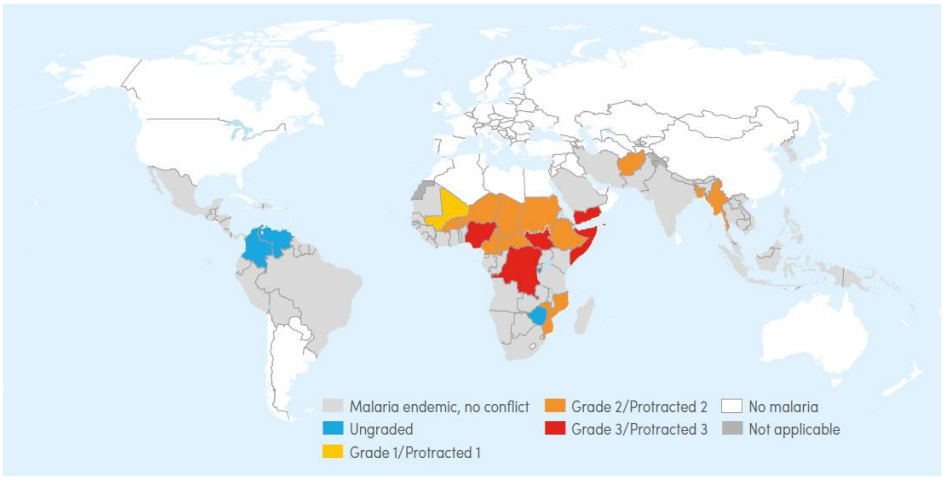
World Health Organization

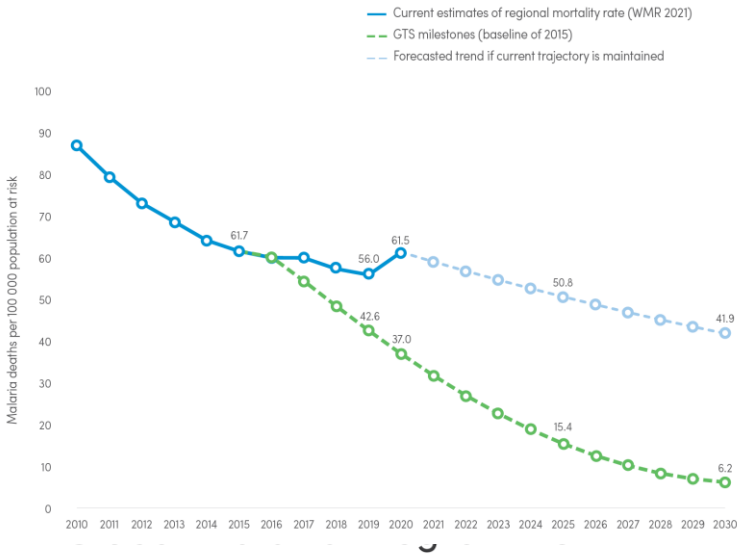
Global context

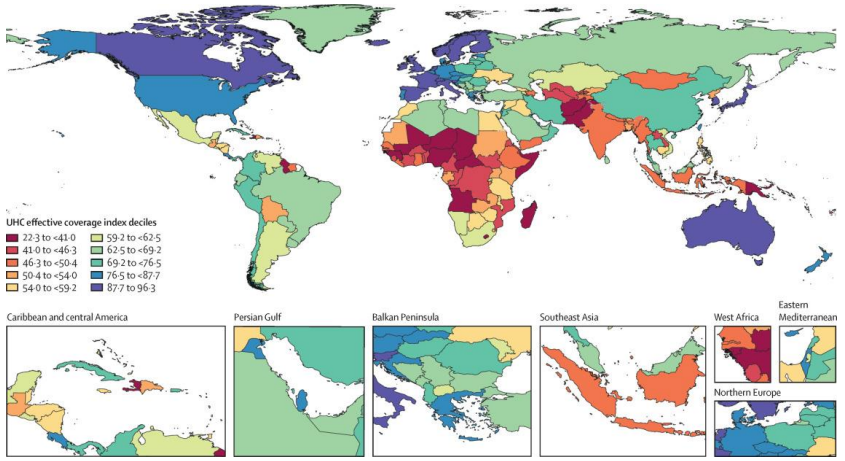




African context







World Health Organization

Rethinking malaria

- Perception *of the problem*

- Malaria needs to be viewed as a **societal problem of development**, not as a medical problem alone

- *Leadership of the problem*

- Malaria eradication needs to be **led by endemic countries** in partnership with multiple stakeholders within each country, including the valuable contribution of national academic and public health institutions

- *Investing in the health workforce*

- Empower through **readiness, training, and education of health workers at all levels**, including paying community health workers

- *Visibility and use of reliable and timely data, knowledge, and information*

- **Malaria data needs to be valued and visible** and used by the public and policy makers

- *Accelerating innovation*

- Globally, we need to give **greater attention to innovation and problem-solving** for malaria elimination and support endemic countries in entrepreneurship, R&D and manufacturing

- Strengthening Health Systems

- Health for all means **solving malaria as a pillar of universal health coverage**

Africa thinktank

- The scale of the Africa malaria challenge remains real and underestimated, requiring a **compelling narrative that inspires change**
- It will require **African led and owned** solutions and innovations
- Malaria responses should be **bedded into PHC**, which is rooted in a commitment to social justice and equity
  - It is time to listen to frontline workers and communities, who understand the factors driving their continued experiences of malaria and are well placed to identify appropriate solutions.
  - Defeating malaria requires that its management is integrated into the delivery of quality services
  - Wider determinants of health can be addressed through a coordinated broader multisectoral approach.
- **Reliable and timely data** and information should be generated, analyzed and used by all decision makers starting with where it is collected
- Success will require learning from what is already working, including **HBHI approach**
- Strategic investments are needed to **strengthen Africa's capacities and institutions**

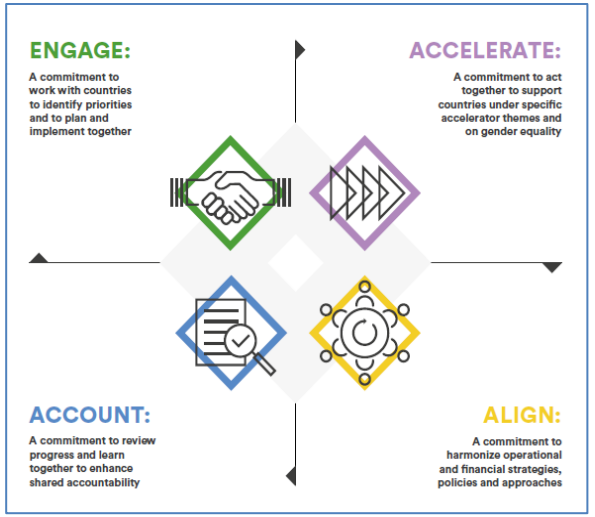
Governance: Who decides?

Country led

- Analysis of regional political context will consider:
  - Whether regional political declarations for malaria have been successful in the past
  - The value of the multiple other political commitments for health and sustainable development
  - The evolving global context over the last 20 years
  - The opportunities to reignite the African political commitment to rid the continent of malaria, through a more inclusive approach based on PHC and strengthened health systems
  - How this political commitment can be best channeled to achieve better malaria outcomes
- Country leadership
  - Strengthening national leadership for health and malaria
  - Data derived NSPs (drawing upon SNT)
  - Building sub national capacity for planning and implementation
  - Community engagement

Partner enabled

- National level dialogue in support of national plan
- Aligning behind a fully costed 3 year business plan and annual operational plan
- Supporting country-level monitoring and evaluation system to inform planning



Strengthening health systems

Malaria response bedded in PHC

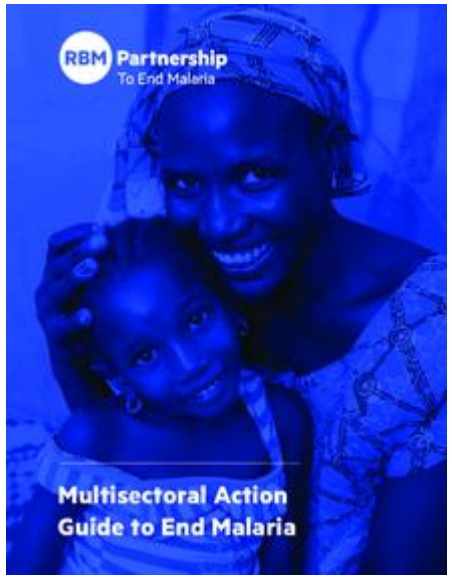
- Defeating malaria requires that its management is integrated into the delivery of quality services
- It is time to listen to frontline workers and communities, who understand the factors driving their continued experiences of malaria and are well placed to identify appropriate solutions.
- Wider determinants of health can be addressed through a coordinated broader multisectoral approach.

Societal problem requiring a societal response

- Malaria needs to be viewed as a societal problem of development, not as a medical problem alone (Rethinking)
- Revised GTS has a deliberate focus on gender, equity and human rights, acknowledging the importance of a whole of society response to addressing social and structural inequities
- Participatory approaches to analyse who is missing out, the barriers they face and disparities to ensure equitable access to quality services
- The most vulnerable cannot address the social and structural inequities themselves and will require different levels playing their respective roles

Multisectoral response

- Good evidence exists on the importance of a multisectoral response to malaria
- This has led to political declarations and commitments
- However, too few countries have successfully managed to secure commitments from other sectors
- There is inadequate knowledge on how to incentivize the different sectors to play their rightful role
- Review where success has been possible and how this was facilitated



Importance of data to define the what, where and how

Operational Unit
(district or equivalent)

WHO recommended interventions with clear targeting **criteria***

(transmission setting, age group, seasonality, efficacy, access etc.)

- LLIN, IRS, LSM,
- IPTp, IPTi, SMC,
- CM (Public HF, iCCM, private)

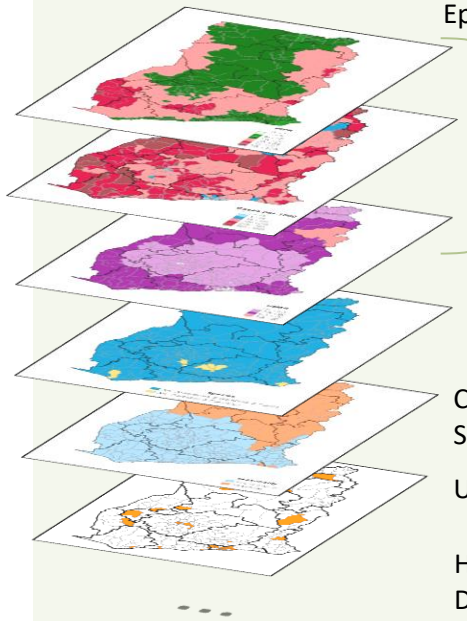
for each intervention, WHO has:

- Recommendation
- Good practice statement
- Country adaptation
- Additional considerations for targeting

Malaria Strategic Plan development

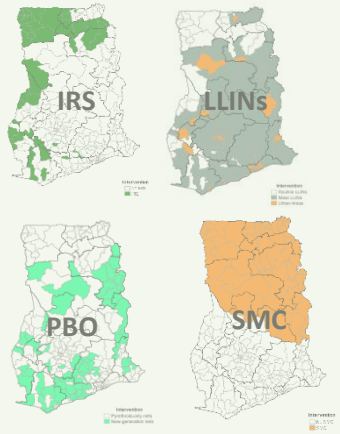
Stratification: Hierarchical ordering of one or multiple layers of information to make decisions

Indicators



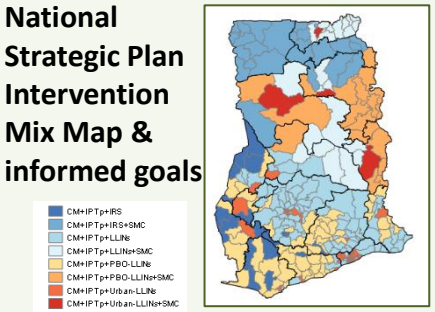
- Epidemiology
  - *Incidence*
  - *Prevalence*
  - *Mortality*
- Entomology
- Climate & Seasonality
- Urbanization
- Health systems
- Drug resistance
- Conflict zones
- Land use
- etc

Intervention targeting: For each intervention, identify the operational unit that meets criteria + operational feasibility

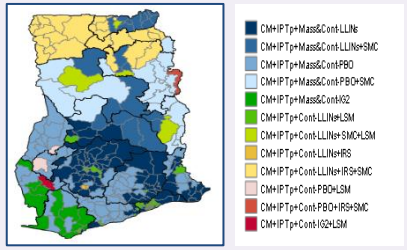


Mathematical models used to evaluate different scenarios and quantify impact of sub-nationally tailored intervention mixes

National Strategic Plan Intervention Mix Map & informed goals



Resource allocation and prioritization



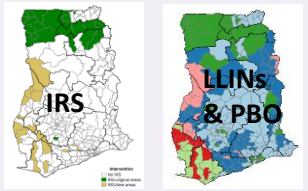
Funded Operational plan

Mathematical models may be used for resource prioritization through cost-effectiveness analysis of different scenarios

Prioritization: Prioritizing intervention to achieve maximum impact within a resource envelope

Implications:

- Less commodities
- Reduced coverage targets,
- Higher efficiency threshold
- Equity



Costing of national strategic plan

How much it costs

$$$

How much there is available

$

World Health Organization

Learning from HBHI approach

- Evaluation by RBM and WHO
- Not of countries or partners but the approach
- Help improve the approach and facilitate expansion

Malaria Stakeholder meeting, Q3 2022

1. GOAL

Policy level consultation with stakeholders to deliberate on the future of the malaria control and elimination enterprise in Africa – based on feedback from multiple streams of analyses intended to advise the dialogue

2. OBJECTIVES

i. To review the findings and conclusions of the "*Interim assessment of HBHI lessons learned*"

ii. To interrogate the findings and recommendations of the *Rethinking Malaria in Africa: Conference of African Thought Leaders* convened by the World Health Organization/Regional Office for Africa (AFRO) and recommendations of "*Rethinking Malaria in the Context of COVID–19 global engagement*" undertaken by Harvard University and its partners, recommendations of RBM meeting on multi-sectoral action against malaria, distil implications and practical steps for action.

iii. To assess the findings of the analysis of the political context in Africa and identify actions needed to further establish political commitment.

iv. To review experiences from the front line, outcome of country case studies on enhancing community participation and identify strategic opportunities for further integrating malaria within PHC in the context of ASTANA declaration on PHC.

3. OUTCOME:

Report of stakeholder deliberations on the failing malaria control malaria situation in Africa focused not on "what needs to be done" but on "how tasks can be accomplished in practical terms", building the momentum for a revitalized HBHI approach, an investment and action framework that is applicable to all other diseases

4. PROPOSED STEERING COMMITTEE

Three sponsoring Member State (Sudan, Nigeria and DRC); (ii) African Union Commission (AUC) (iii) African Leaders Malaria Alliance (ALMA); (iv) RBM to end malaria; (iv) UNICEF; (v) UNDP; (vi) ACHEST; (vii) Donor representation. (GFATM, PMI, The World Bank); (viii) regional resource representation from Global rethinking process.; (ix) Civil Society representation through RBM to end malaria (x) Regional development banks

Key message

- Business as usual in not enough
- There needs to be an urgency in the response, with a focus on sustainable and equitable solutions
- ***Declare a malaria crisis in Africa!***
  - Call for WHO and AU to declare a malaria crisis in Africa and appropriate urgent response
  - Call on MPAG to champion and drive the declaration
  - Resourcing of a crisis response to malaria in Africa to fund:
    - Crisis response in 30 priority countries, catchup & sustain drive to 2025 GTS milestones
    - Fast-track development and deployment of new tools – including RTS,S malaria vaccine

Global framework for response to malaria in urban areas

WHO and UN Habitat

These slides present a draft version of the publication. The final product may reflect considerable changes.

Global **Malaria** Programme

World Health Organization

What is the aim of the framework?

- To guide countries, globally, to develop policies, strategies and plans that are system-wide and multi-sectoral to effectively respond to malaria in urban areas. To do so, the framework will rely on existing intervention recommendations from the WHO, best practices from countries as well as inputs from experts and implementation partners.

- To identify important knowledge gaps and define research priorities in the response to malaria in urban areas.

Who is the target audience?

- National and urban government policy makers
- National and subnational malaria programmes
- Funders, development and implementation partners
- Private sector, civil society and advocacy partners
- Researchers
- Communities

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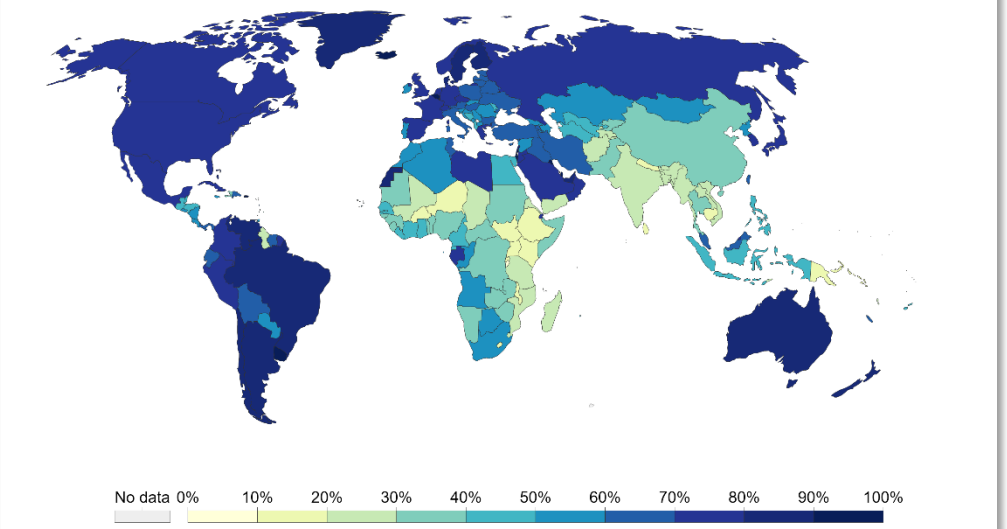
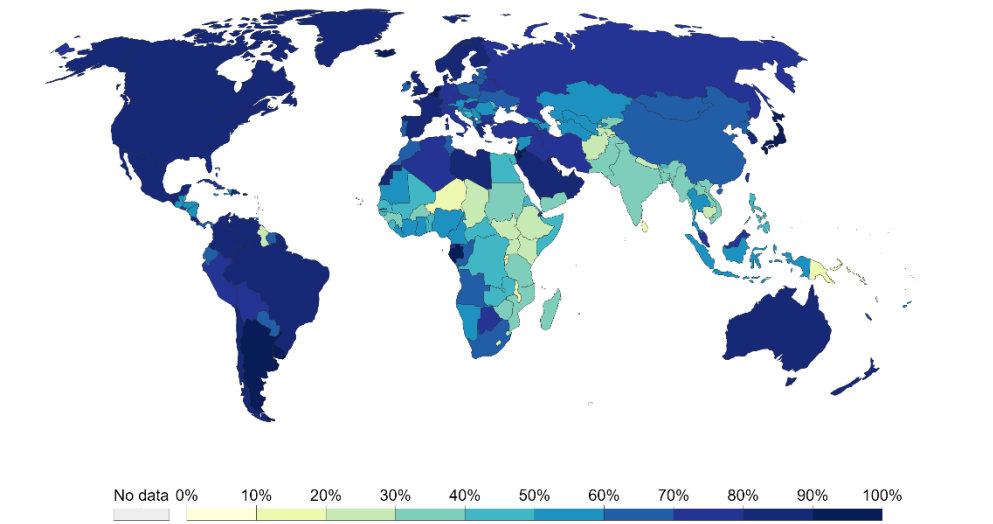


2021



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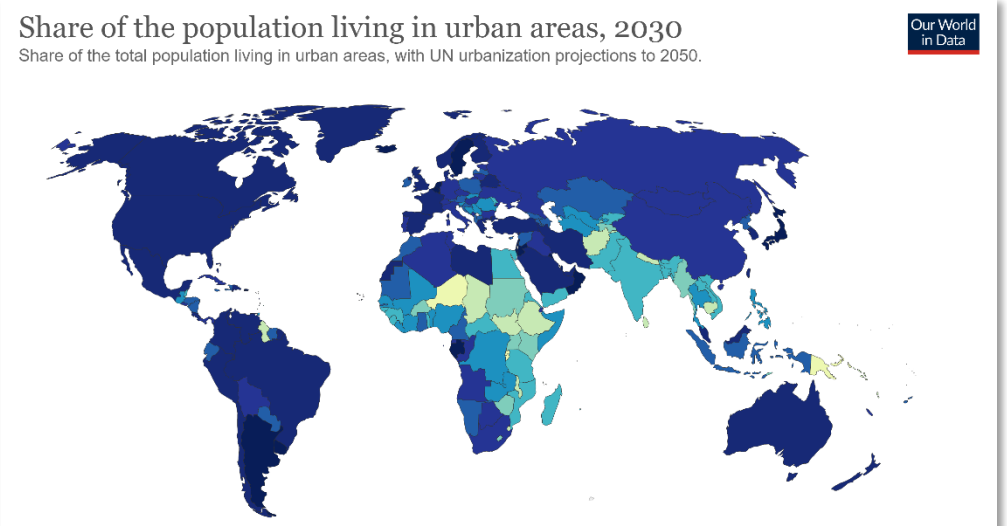

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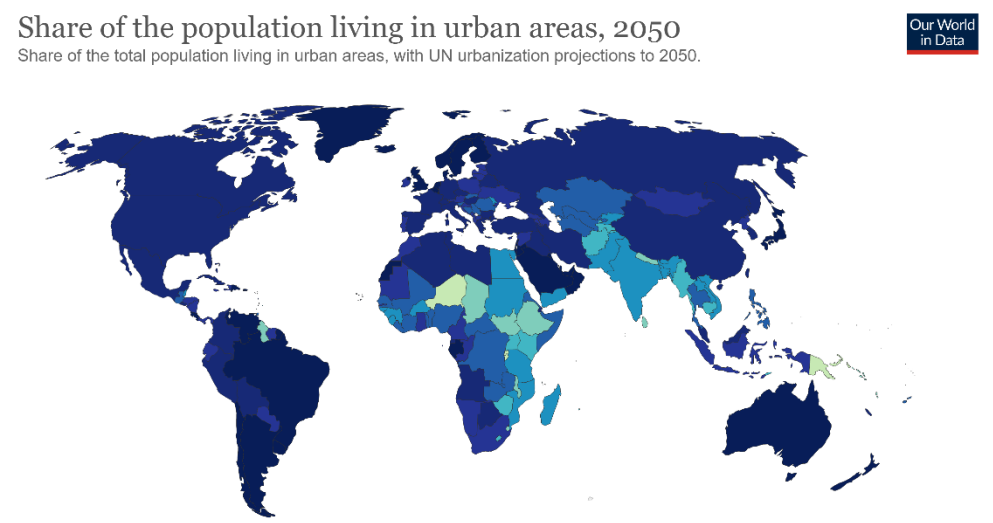


WHO Framework for Response to Malaria in Urban Areas

Consultation launched on 22nd September by

Mayor of Freetown, Hon. Yvonne Aki-Sawyerr

Five thematic groups established:

- Prevention interventions and delivery
- Health care delivery
- Urban governance, policies and planning
- Multisectoral response
- Surveillance, mapping and analysis

Thematic groups discussions were held from October – December 2021

We aim to address those challenges and Transform Freetown through 11 priority sectors using an inclusive approach, underpinned by innovation and data-driven performance management (Hon. Yvonne Aki-Sawyerr)

WHAT

Transform Freetown!

HOW

4 Clusters **11 Priority Sectors**

1. Resilience
- Environmental management
- Urban planning and housing
- Revenue mobilization

2. Human development
- Education
- Skills development
- Job creation (focus: tourism)
- Disabilities

Women & girls

3. Healthy cities
- Health
- Water
- Sanitation

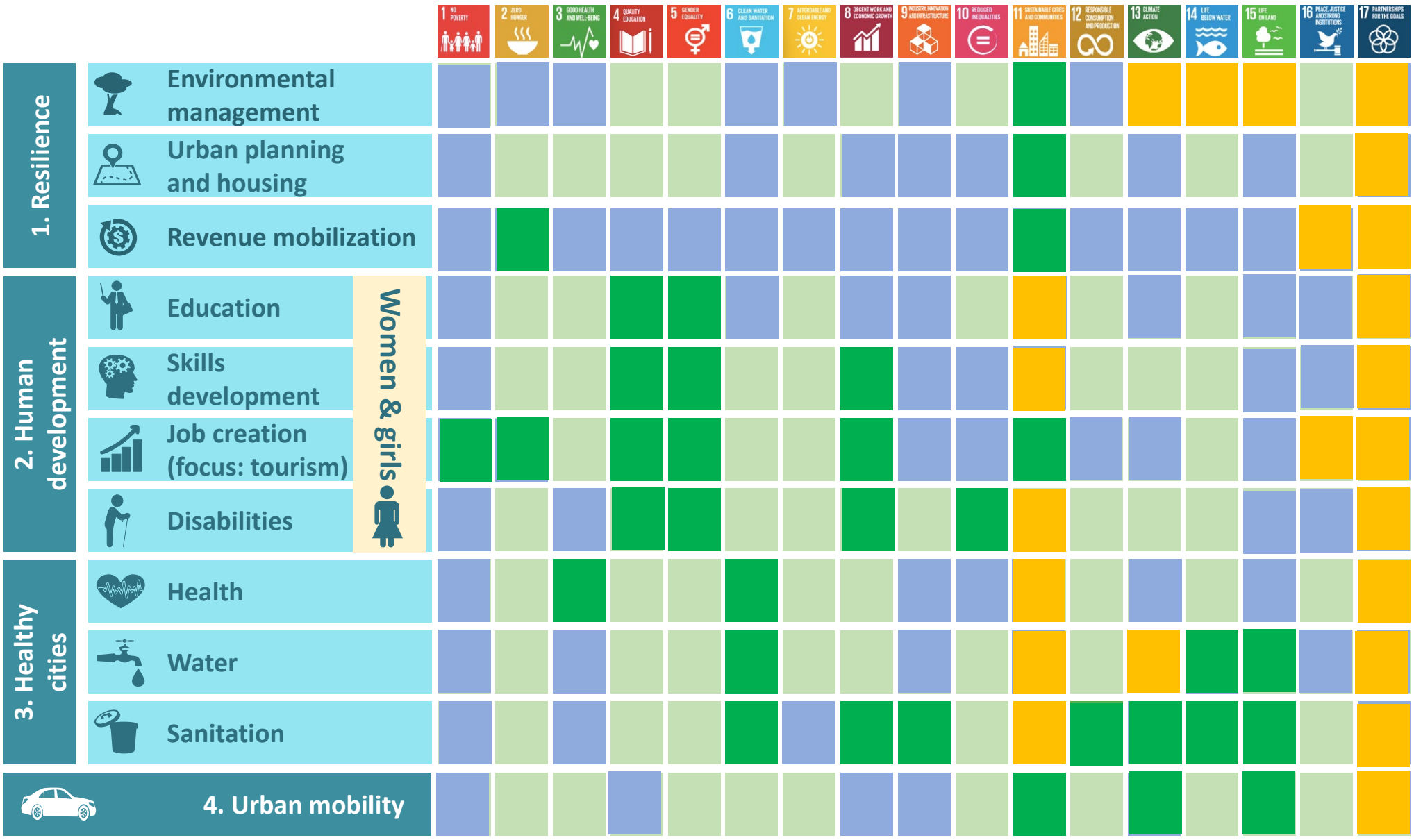
4. Urban mobility

WHO

Multi-stakeholder working groups

- Social players
- Private players
- Public players

The 19 targets within the Transform Freetown priority sectors are directly linked to achievement of the Sustainable Development Goals



Hon. Yvonne Aki-Sawyerr

WHO Framework for Response to Malaria in Urban Areas

	Prevention interventions and delivery	Health care delivery	Urban governance, policies and planning	Multisectoral response (focusing on private and community sectors)	Surveillance, mapping and analysis
Co-chairs	Paola Marchesini Fredros Okumu	Evelyn Ansah Neeraj Dhingra	Alex Ezeh Graham Alabaster	Marcia de Castro Jimmy Opigo	Arantxa Roca-Feltrer Fitsum Tadesse
Secretariat support	Jan Kolaczinski Raman Velayudhan Abdisalan Noor Andrea Alleje Others (TBD)	Andrea Bosman Alastair Robb Abdisalan Noor Andrea Alleje Others (TBD)	Alastair Robb Bayo Fatunmbi Mwalenga Nghipumbwa Abdisalan Noor Andrea Alleje Others (TBD)	Leonard Ortega Roberto Montoya Abdisalan Noor Andrea Alleje Others (TBD)	Abdisalan Noor Beatriz Galatas Jennifer Stevenson Andrea Alleje Others (TBD)
Rapporteurs	Amy Barrette	Nana Aba Williams	Nyawira Gitahi	Jessica Rockwood	Ifeoma Ozodiegwu

Overall co-chairs: Prof Fred Binka and Dr Alex Coutinho

Progress

- Over 120 participants, about 30 consultations, 33 presentations across all thematic groups
- All presentation and meeting reports from each thematic group available online to participants
- *Draft Framework* submitted to MPAG for information.
- Framework targets urban leadership, national programmes, implementation partners. Goes beyond officially approve WHO recommendation and advocates a wholistic approach to the malaria problem
- Framework to be launched by June, jointly with WHO Urban Health and UN Habitat in June 2022
- Pilot studies on microstratification starting in Nigeria with support from BMGF

Structure

Section	Purpose	Main content
The Framework at a glance	A quick read for: urban leaders, • policy makers, national programmes • partners • general public	• Who is this document for? • • Why focus on malaria in urban areas? • • Why control malaria and other mosquito-transmitted diseases in towns and cities? • How do you control malaria and other mosquito-transmitted diseases in towns and cities? • What is the role of city leaders? • What are the economic benefits? • Securing resources for urban malaria control • Aim of the framework • What's new about this approach • Actions required

Structure

Section	Purpose	Main content

Introduction	Defining the foundation technical issues	• Defining urban areas
		• Urban growth
		• The urban malaria problem
		  ○ Ecology of urban malaria
		  ○ Epidemiology of urban malaria
		  ○ The need for a response to malaria in urban areas

Structure

Section	Purpose	Main content
A vision for response to malaria in urban settings	Identifying the governance, technical, systemic and multisectoral enablers	• Alignment with the development goals • Integration with sustainable city growth and One Health • Urban leadership and governance • Delivering quality services • Identifying, engaging and mobilizing the multisector response • Community engagement and support • Adapting surveillance monitoring and evaluation systems for malaria to urban contexts • Mobilizing resources for urban malaria control

Structure

Section	Purpose	Main content
Planning, implementing, and monitoring the response to malaria in urban areas	Designing a locally tailored response	• Developing the urban malaria response plan • Actions in the malaria response *Action 1*. Prevent malaria in urban areas through targeted response *Action 2* Provide access to prompt diagnosis and effective treatment of malaria *Action 3* Enhance surveillance and the use of data for decision making (microstratification and subnational tailoring, M&E)

Structure

Section	Purpose	Main content
Innovation, research, and development	Identify important gaps in knowledge, tools and approaches & define priority R&D questions	Priority RnD areas

Malaria Policy Advisory Group Meeting
23—24 March 2022, Geneva, Switzerland
Background document for Session 3

Update on the development of a strategy to respond to antimalarial drug resistance in Africa

Pascal Ringwald and Charlotte Rasmussen, WHO Global Malaria Programme

Context

Artemisinin-based combination therapies (ACTs) were originally introduced more than 20 years ago to prevent the emergence of drug resistance that was already impacting decade-old monotherapies such as chloroquine. While there are currently 6 recommended ACTs in the *WHO Guidelines for malaria*, artemether-lumefantrine (AL) represents most treatment courses, with over 85% of antimalarial courses procured by the Global Fund being AL. Several factors explain this pre-eminence:

1. AL was the first ACT to be developed
2. AL is the cheapest along with artesunate-amodiaquine (ASAQ), with US$ 0.57 per course versus US$ 2-3 for other ACTs, according to Global Fund reference prices
3. AL is the most accessible with a dozen of suppliers having significant production capacity, including the originator and several generic makers
4. The *WHO Guidelines for malaria* are not explicit on the need to "rotate" ACTs and to have multiple first line ACTs, unlike HIV Treatment Guidelines which clearly delineate first, second- and third- line treatments with updates every 5 years of the antiretrovirals recommended for the first line

While ASAQ is widely used in francophone Africa, the remaining ACTs are rarely used, except perhaps in the Greater Mekong Subregion (GMS), where artemisinin partial resistance appeared 15 years ago.

With the heavy use of AL, especially in African countries where the malaria burden is the heaviest, artemisinin partial resistance is surfacing as confirmed by a 2021 study in Uganda, Rwanda and other Eastern African countries. This is due to new mutations that have emerged in multiples foci and not from resistant parasites imported from the GMS, which had been a hypothesis raised by malaria experts. That growing phenomenon is only reinforced with the mis-use or overuse of artemisinin-based therapies, such as:

1. The overuse of injectable artesunate by clinics in some countries for commercial reasons
2. The absence of referral following rectal artesunate pre-referral treatment (meaning that all the parasites might not be killed)
3. The use of non-effective artemisia tea which still contains enough artemisinin to contribute to the emergence of resistance

While artemisinin treatments are still effective for now, studies suggest that they take longer to kill *P. falciparum* parasites. Early evidence is also suggesting that failures of partner drugs, notably lumefantrine, the partner drug in AL as put forward by the US CDC (to be confirmed, might be due to an analysis issue) and piperaquine, the partner drug in DHA-piperaquine is emerging.

Emerging resistance, both to artemisinin and partner drugs poses a major threat to the fight against malaria, in countries that are far from being on the path of malaria elimination. Additional ACTs – beyond AL and ASAQ – often face market failures, which means that rapid scale up would be

challenging with prices 3 to 4 times that of AL and a limited number of quality-assured suppliers. In parallel, new tools are unlikely to help solve this problem soon with a weak pipeline of non-artemisinin combination therapies with ganaplacide-lumefantrine in patient exploratory phase (Phase IIb) as the most advanced non-artemisinin combination therapy. This new drug would help in the fight against artemisinin partial resistance but might be made inefficient if lumefantrine resistance were confirmed, and millions of dollars of investments could go to waste. More broadly, given that the antimalarial market is mature and with low margins, malaria is not a priority disease for innovation by pharma companies.

There is therefore a need to define a new drug resistance strategy to both better use existing tools to prevent the emergence of resistance and to develop new tools and strategies to tackle resistance once it has emerged. Learnings from the *Global plan for artemisinin resistance containment* (GPARC) and the GMS elimination strategy should be leveraged for this effort. The strategies that were successfully deployed in the GMS, for instance rapidly scaling up ACTs, promoting the use of single dose primaquine, are however unlikelyto be sufficient in non-elimination settings. This strategy will have to be comprehensive and cover areas beyond the immediate scope of drug resistance, for example by addressing counterfeit drugs, clarifying treatment guidelines, and using other tools such as vector control products, among other potential solutions.

Approach

The approach is articulated around three macro phases: a first phase aiming to build technical consensus on aconsolidated fact base, a second phase aiming to develop the new drug resistance strategy, and a third phase aiming to develop an implementation roadmap.

Phase 1a: Baselining (~2 weeks)

Objective: Collect all relevant information for the good delivery of the project, set up project governance andsupport a scoping meeting with Technical Committee to align on a problem statement

We introduce two workstreams, a technical workstream, and a stakeholder engagement workstream. The technical workstream will focus on generating scientific consensus on the problem statement, state of play,and key interventions that could be used to address drug resistance. The stakeholder engagement workstream will focus on defining project governance, defining which stakeholders to engage and when, raising awareness on the drug resistance issue, and then ensuring buy-in and commitment around the new strategy.

Key activities – Technical workstream:

- Collect existing materials (previous strategies, supporting data, papers)
- Revise and detail workplan based on initial engagement; decide how best to approach the development of a new strategy
- Schedule interviews and write interview guides
- Support scoping meeting with Technical Committee (experts) to discuss scoping questions and alignon a problem statement
    - Threat and potential impact of artemisinin partial resistance
    - Threat and potential impact of partner drug resistance (notably lumefantrine)
    - Threat of resistance against multiple partner drugs (e.g., lumefantrine and piperaquine treatment failures appearing in the same area)

Key activities – Stakeholder engagement workstream:

- Map out key stakeholders to include in engagement plan (e.g., technical partners, civil society, communities, private sector)
    - Incoming hypothesis: 40+ countries in AFRO, 4-5 in EMRO
- Refine project governance (e.g., key meetings, Core Team, SteerCo, whole group session…) and determine how best to engage with stakeholders
- Build engagement plan to syndicate new strategy
    - Technical stakeholders for technical input into draft strategy
    - Other stakeholders who will contribute to increasing awareness on the drug resistance topic,raise funds and ensure political and financial commitment at global and ministerial levels

Main deliverables
• Compilation of existing work
• Interview list
• Revised workplan, approach and project governance
• Engagement plan
• Agreed problem statement

Phase 1b: Articulated technical fact base development (~7 weeks)

Objective: Build comprehensive fact base on drug resistance and build scientific consensus on effectivenessand prioritization of interventions

Key activities – Technical workstream:

- Build comprehensive fact base of drug resistance issue through targeted expert interviews andliterature search
    - Existing cases and timeline of drug resistance
    - Prevalence to date
    - Case studies (GMS, Eastern Africa)
    - Resistance archetypes
    - Drivers of drug resistance and root causes
    - Possible scenarios and patterns of emergence
    - Strengths and weaknesses or currently available capacity that can be used to curb resistance
        - Interventions that prevent the emergence of resistance
        - Interventions that contain and address resistance once it has emerged
    - Past and planned investments to curb resistance (including surveillance capacity mapping, e.g., mapping of molecular resistance tracking capacity and sampling platforms)

- Generate consensus on interventions to prioritize
    - Determine effectiveness of interventions based on historical case studies (e.g., GMS) andmodelling work (incl. surveillance as an intervention)
    - Determine desired health outcomes (theory of change)
    - Assess trade-offs for interventions and evaluate their impact & feasibility
    - Prioritize interventions based on trade-offs and desired health outcomes and match interventions with relevant resistance archetypes
    - Determine capabilities needed to support interventions

Key activities – Stakeholder engagement workstream:

- Map out ongoing advocacy efforts around drug resistance
- Iterate on engagement plan

Main deliverables
• Comprehensive fact base with o Heatmap of drug resistance o Resistance archetypes o Drivers of resistance (including gaps in activities) and root causes • Prioritized interventions o Toolbox of interventions o Health outcomes and theory of change o Consensus on priority interventions for each resistance archetype o Capabilities available and needed (incl. surveillance capacity)

Phase 2: Strategy development (~10 weeks)

It is important to note that Phase 2 will only be launched once technical consensus has been reached among the scientific community on the malaria drug resistance issue. An estimate of 7 weeks to build a robust fact base and reach technical consensus has been made. A go / no go decision at the end of Phase 1b will be made based on whether consensus has been reached. Phase 1b may have to be extended by a few weeks if additional alignment between key stakeholders is required.

Objective: Write draft drug resistance strategy, support public consultation phase, address comments, and finalize strategy. This phase will focus on co-creating a strategy with key stakeholders and generating buy-in and commitment, through a mix of input collection and socialization activities. The list of specific activities andcountries / stakeholders to involve in this process will be refined during Phase 1b but will likely involve a mix of online consultation, regional / multi-country workshops and roadshows.

Key activities – Technical workstream:

- Write up draft strategy based on options prioritized in previous phase
- Validate first draft of strategy with Steering Committee
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- Capture all comments and questions
- Make relevant changes

- Finalize strategy

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- Socialize new strategy with key stakeholders identified in engagement plan
- Conduct multi-country / regional workshops to present strategy and gather feedback

Main deliverables
• Finalized drug resistance strategy • Compendium of comments received during public consultation (and how they were addressed)

Phase 3: Implementation roadmap (~10 weeks)

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  - Roles & responsibilities
  - Results framework
  - Costing & financing
- Set up multi-stakeholder working groups to iterate on first draft of implementation plan components
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Key activities – Stakeholder engagement workstream:

- Broaden Steering Committee to include other funders and local implementers
- Onboard new members
- Socialize implementation plan with all stakeholders
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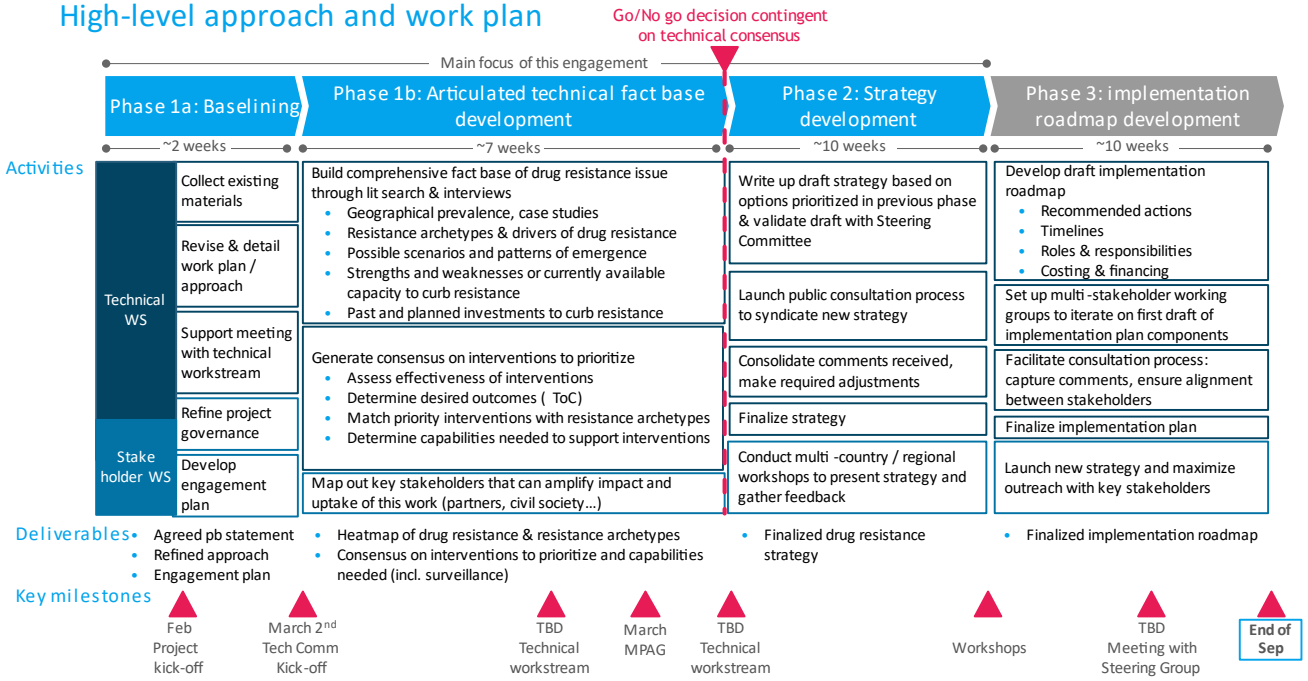
Main deliverables
• Finalized implementation roadmap with clear timelines and accountable stakeholders

High-level approach and work plan



Malaria Policy Advisory Group Meeting
23—24 March 2022, Geneva, Switzerland
Background document for Session 3

Update on the development of a strategy to respond to antimalarial drug resistance in Africa

Pascal Ringwald and Charlotte Rasmussen, WHO Global Malaria Programme

Context

Artemisinin-based combination therapies (ACTs) were originally introduced more than 20 years ago to prevent the emergence of drug resistance that was already impacting decade-old monotherapies such as chloroquine. While there are currently 6 recommended ACTs in the *WHO Guidelines for malaria*, artemether-lumefantrine (AL) represents most treatment courses, with over 85% of antimalarial courses procured by the Global Fund being AL. Several factors explain this pre-eminence:

1. AL was the first ACT to be developed
2. AL is the cheapest along with artesunate-amodiaquine (ASAQ), with US$ 0.57 per course versus US$ 2-3 for other ACTs, according to Global Fund reference prices
3. AL is the most accessible with a dozen of suppliers having significant production capacity, including the originator and several generic makers
4. The *WHO Guidelines for malaria* are not explicit on the need to "rotate" ACTs and to have multiple first line ACTs, unlike HIV Treatment Guidelines which clearly delineate first, second- and third- line treatments with updates every 5 years of the antiretrovirals recommended for the first line

While ASAQ is widely used in francophone Africa, the remaining ACTs are rarely used, except perhaps in the Greater Mekong Subregion (GMS), where artemisinin partial resistance appeared 15 years ago.

With the heavy use of AL, especially in African countries where the malaria burden is the heaviest, artemisinin partial resistance is surfacing as confirmed by a 2021 study in Uganda, Rwanda and other Eastern African countries. This is due to new mutations that have emerged in multiples foci and not from resistant parasites imported from the GMS, which had been a hypothesis raised by malaria experts. That growing phenomenon is only reinforced with the mis-use or overuse of artemisinin-based therapies, such as:

1. The overuse of injectable artesunate by clinics in some countries for commercial reasons
2. The absence of referral following rectal artesunate pre-referral treatment (meaning that all the parasites might not be killed)
3. The use of non-effective artemisia tea which still contains enough artemisinin to contribute to the emergence of resistance

While artemisinin treatments are still effective for now, studies suggest that they take longer to kill *P. falciparum* parasites. Early evidence is also suggesting that failures of partner drugs, notably lumefantrine, the partner drug in AL as put forward by the US CDC (to be confirmed, might be due to an analysis issue) and piperaquine, the partner drug in DHA-piperaquine is emerging.

Emerging resistance, both to artemisinin and partner drugs poses a major threat to the fight against malaria, in countries that are far from being on the path of malaria elimination. Additional ACTs – beyond AL and ASAQ – often face market failures, which means that rapid scale up would be

challenging with prices 3 to 4 times that of AL and a limited number of quality-assured suppliers. In parallel, new tools are unlikely to help solve this problem soon with a weak pipeline of non-artemisinin combination therapies with ganaplacide-lumefantrine in patient exploratory phase (Phase IIb) as the most advanced non-artemisinin combination therapy. This new drug would help in the fight against artemisinin partial resistance but might be made inefficient if lumefantrine resistance were confirmed, and millions of dollars of investments could go to waste. More broadly, given that the antimalarial market is mature and with low margins, malaria is not a priority disease for innovation by pharma companies.

There is therefore a need to define a new drug resistance strategy to both better use existing tools to prevent the emergence of resistance and to develop new tools and strategies to tackle resistance once it has emerged. Learnings from the *Global plan for artemisinin resistance containment* (GPARC) and the GMS elimination strategy should be leveraged for this effort. The strategies that were successfully deployed in the GMS, for instance rapidly scaling up ACTs, promoting the use of single dose primaquine, are however unlikelyto be sufficient in non-elimination settings. This strategy will have to be comprehensive and cover areas beyond the immediate scope of drug resistance, for example by addressing counterfeit drugs, clarifying treatment guidelines, and using other tools such as vector control products, among other potential solutions.

Approach

The approach is articulated around three macro phases: a first phase aiming to build technical consensus on aconsolidated fact base, a second phase aiming to develop the new drug resistance strategy, and a third phase aiming to develop an implementation roadmap.

Phase 1a: Baselining (~2 weeks)

Objective: Collect all relevant information for the good delivery of the project, set up project governance andsupport a scoping meeting with Technical Committee to align on a problem statement

We introduce two workstreams, a technical workstream, and a stakeholder engagement workstream. The technical workstream will focus on generating scientific consensus on the problem statement, state of play,and key interventions that could be used to address drug resistance. The stakeholder engagement workstream will focus on defining project governance, defining which stakeholders to engage and when, raising awareness on the drug resistance issue, and then ensuring buy-in and commitment around the new strategy.

Key activities – Technical workstream:

- Collect existing materials (previous strategies, supporting data, papers)
- Revise and detail workplan based on initial engagement; decide how best to approach the development of a new strategy
- Schedule interviews and write interview guides
- Support scoping meeting with Technical Committee (experts) to discuss scoping questions and alignon a problem statement
    - Threat and potential impact of artemisinin partial resistance
    - Threat and potential impact of partner drug resistance (notably lumefantrine)
    - Threat of resistance against multiple partner drugs (e.g., lumefantrine and piperaquine treatment failures appearing in the same area)

Key activities – Stakeholder engagement workstream:

- Map out key stakeholders to include in engagement plan (e.g., technical partners, civil society, communities, private sector)
    - Incoming hypothesis: 40+ countries in AFRO, 4-5 in EMRO
- Refine project governance (e.g., key meetings, Core Team, SteerCo, whole group session…) and determine how best to engage with stakeholders
- Build engagement plan to syndicate new strategy
    - Technical stakeholders for technical input into draft strategy
    - Other stakeholders who will contribute to increasing awareness on the drug resistance topic,raise funds and ensure political and financial commitment at global and ministerial levels

Main deliverables
• Compilation of existing work
• Interview list
• Revised workplan, approach and project governance
• Engagement plan
• Agreed problem statement

Phase 1b: Articulated technical fact base development (~7 weeks)

Objective: Build comprehensive fact base on drug resistance and build scientific consensus on effectivenessand prioritization of interventions

Key activities – Technical workstream:

- Build comprehensive fact base of drug resistance issue through targeted expert interviews andliterature search
    - Existing cases and timeline of drug resistance
    - Prevalence to date
    - Case studies (GMS, Eastern Africa)
    - Resistance archetypes
    - Drivers of drug resistance and root causes
    - Possible scenarios and patterns of emergence
    - Strengths and weaknesses or currently available capacity that can be used to curb resistance
        - Interventions that prevent the emergence of resistance
        - Interventions that contain and address resistance once it has emerged
    - Past and planned investments to curb resistance (including surveillance capacity mapping, e.g., mapping of molecular resistance tracking capacity and sampling platforms)

- Generate consensus on interventions to prioritize
    - Determine effectiveness of interventions based on historical case studies (e.g., GMS) andmodelling work (incl. surveillance as an intervention)
    - Determine desired health outcomes (theory of change)
    - Assess trade-offs for interventions and evaluate their impact & feasibility
    - Prioritize interventions based on trade-offs and desired health outcomes and match interventions with relevant resistance archetypes
    - Determine capabilities needed to support interventions

Key activities – Stakeholder engagement workstream:

- Map out ongoing advocacy efforts around drug resistance
- Iterate on engagement plan

Main deliverables
• Comprehensive fact base with o Heatmap of drug resistance o Resistance archetypes o Drivers of resistance (including gaps in activities) and root causes • Prioritized interventions o Toolbox of interventions o Health outcomes and theory of change o Consensus on priority interventions for each resistance archetype o Capabilities available and needed (incl. surveillance capacity)

Phase 2: Strategy development (~10 weeks)

It is important to note that Phase 2 will only be launched once technical consensus has been reached among the scientific community on the malaria drug resistance issue. An estimate of 7 weeks to build a robust fact base and reach technical consensus has been made. A go / no go decision at the end of Phase 1b will be made based on whether consensus has been reached. Phase 1b may have to be extended by a few weeks if additional alignment between key stakeholders is required.

Objective: Write draft drug resistance strategy, support public consultation phase, address comments, and finalize strategy. This phase will focus on co-creating a strategy with key stakeholders and generating buy-in and commitment, through a mix of input collection and socialization activities. The list of specific activities andcountries / stakeholders to involve in this process will be refined during Phase 1b but will likely involve a mix of online consultation, regional / multi-country workshops and roadshows.

Key activities – Technical workstream:

- Write up draft strategy based on options prioritized in previous phase
- Validate first draft of strategy with Steering Committee
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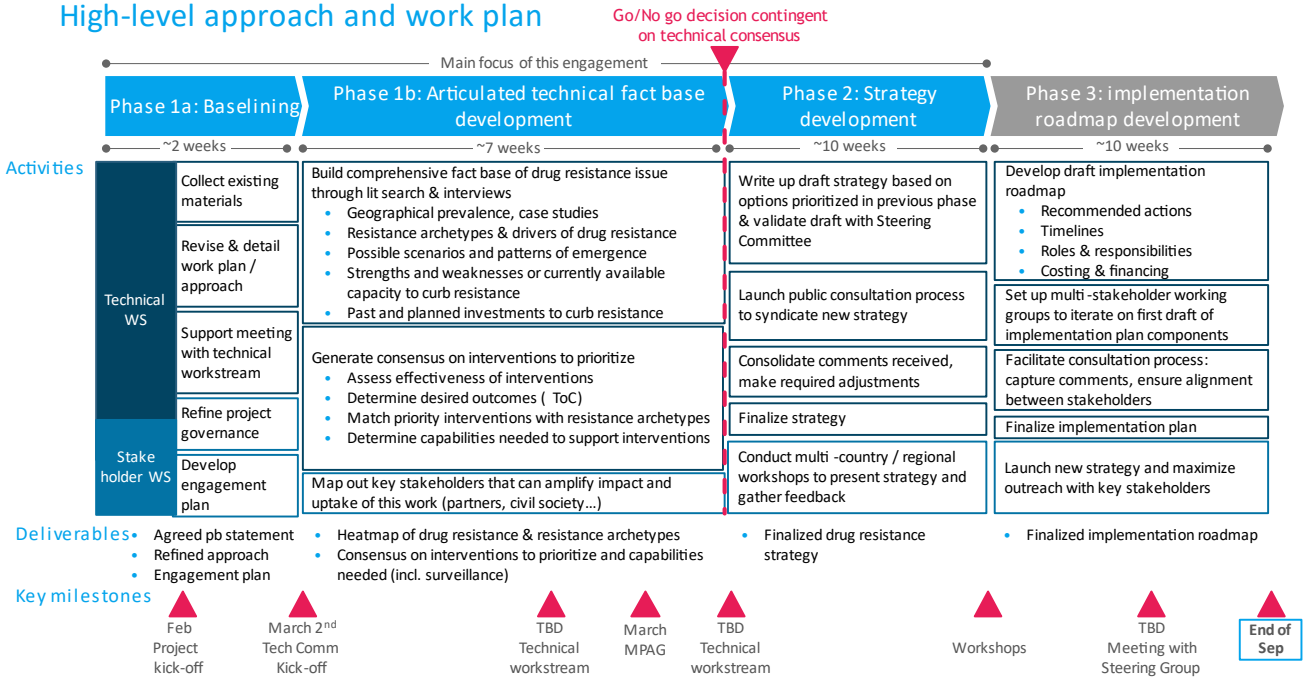
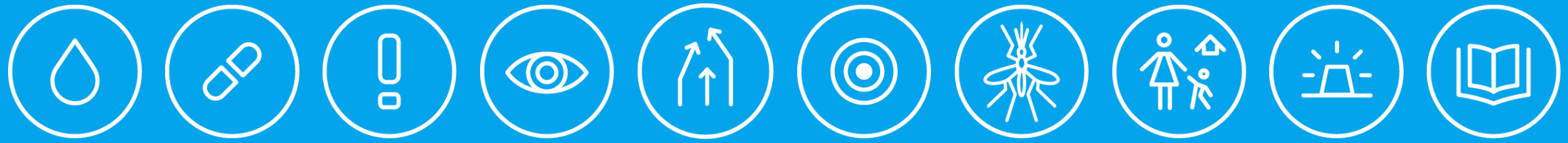


Strategy to respond to antimalarial drug resistance in Africa

MPAG



23 - 24 March 2022

Global **Malaria** Programme

World Health Organization

Why we need a strategy for antimalarial drug resistance in Africa exercise

Context

- **Artemisinin-based combination therapies** (ACTs) as main medicine to fight malaria.
- WHO recommends 6 ACTs, yet there is **heavy reliance on artemether-lumefantrine** (85% of courses procured by GF).
- ACT treatment failures due to artemisinin partial resistance and partner drug resistance appeared in **GMS.**
- High number of cases (>90% of global malaria cases) and reliance on few treatments put Africa particularly at risk **if resistance emerges and spreads.**

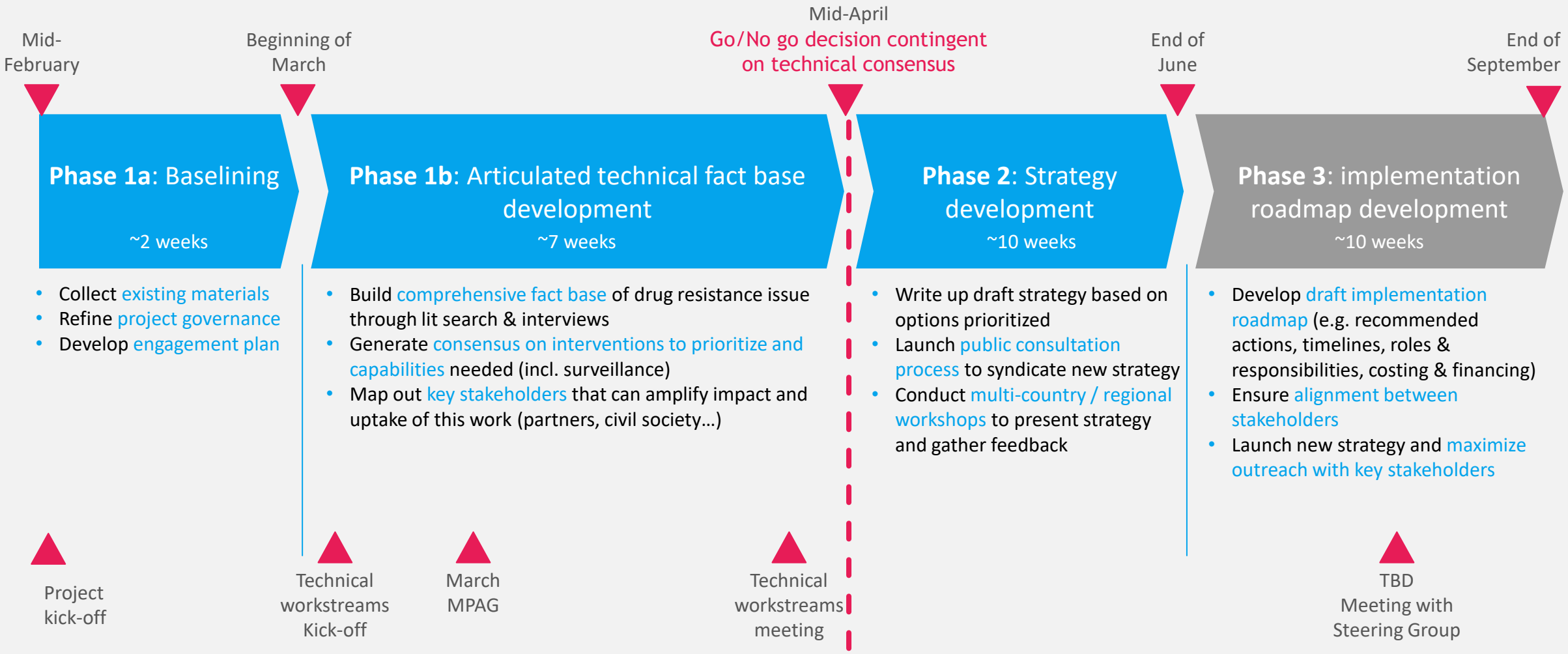
Problem statement

- **Artemisinin partial resistance** confirmed in Uganda, Rwanda and Horn of Africa.
- Artemisinin partial resistance is translated as **delayed parasite clearance**.
- Artemisinin partial resistance **puts pressure on partner drug** and might trigger de novo emergence of resistance or selection of existing partner drug resistance.

Way forward

- **Need to define a strategy to respond to antimalarial drug resistance in Africa, and**
  1. **Prevent the emergence of resistance**
  2. **Tackle resistance once it has emerged**
- **Strategy will likely rely on a better use of existing tools & development of new tools & strategies, with actions at global, regional and local level**

A two-phase approach to develop global strategy



A project managed by a diversified Leadership team and a project team responsible for the daily management

World Health Organization

Non-WHO

Roles & responsibilities

Leadership Team

- Pedro Alonso
- Erin Shutes
- Kalu Akpaka (AFRO)
- Benido Impouma (AFRO)
- Ghasem Zamani (EMRO)

- Dyann Wirth (MPAG Chair, Harvard)
- Bruno Moonen (BMGF)

- Review & discuss findings
- Manage major risks, interdependencies and roadblocks
- Validate recommendations

Project Team

- Pascal Ringwald
- Charlotte Rasmussen

Support from BCG team

- Monitor progress against work plan
- Focus on meeting deliverables
- Facilitate technical discussions and prepare briefings
- Consolidate findings & technical consensus

A proposed constituencies for multi-disciplinary consultation of 6 technical workstreams

Drug resistance
Lead: P. Ringwald

Establish scientific consensus on the current status of artemisinin partial resistance and partner drug resistance in Africa, and on their **threat and potential impact**

Surveillance & Modeling
Lead: A. Noor

Accurately **identify gaps in surveillance & modeling needs** that hamper capacity to address artemisinin partial resistance and/or partner drug resistance

Market shaping
Lead: A. Robb

Understand market challenges in case of drug resistance and **assess potential interventions** & options ensuring a healthy market for antimalarials

Quality of care, policy & private sector
Lead: A. Bosman

Identify drivers of resistance linked to **choice and availability of products at country-level, quality of care, policy & private sector and derive interventions** to mitigate risk of spread of drug resistance

Vector control
Lead: J. Kolaczinski

Identify vector control drivers of drug resistance and **derive interventions** to mitigate risk of drug resistance emergence and/or spread

Communication

Relevant in Phase 2

Key messages from Technical workstream | Situation still under control, but measures should be implemented to avoid ACT treatment failure

- Artemisinin partial resistance confirmed in Rwanda, Uganda, Horn of Africa
- Lack of geographical coverage of data

- Fitness cost and parasite genetic background expected to play a key role in its ability to spread
- Spread potential likely to differ from GMS

- For partner drugs, scattered reports of treatment failure but no resistance confirmed (*in vitro,* molecular markers or blood levels)

- Potential risk of issue underestimation by local stakeholders (≠ GMS)
- Communication and advocacy will play a key role