World Health Organization

Background documentation for Day 1

This file contains the slides that were shown by the presenters during Day 1 of the meeting as well the background documentation shared with MPAG members ahead of the meeting.

Monday, 4 October 2021		
	Session 1	**Open**
12:15 – 13:15	Report from the Director, GMP	Dr Pedro Alonso
13:15 – 14:00	Update on "Rethinking malaria" • Presentation by Dr Akpaka Kalu • Presentation by Dr Rose Leke	Dr Rose Leke & Dr Akpaka Kalu
	Session 2	**Open**
14:15 – 14:45	Update on technical consultation on non-inferiority evaluation of vector control tools • Presentation by Dr Jan Kolaczinski • Draft meting report	Dr Jan Kolaczinski
14:45 – 15:15	Discussion on malaria rebound • Presentation by Dr Caterina Guinovart	Dr David Schellenberg & Dr Caterina Guinovart

WHO/UCN/GMP/MPAG/2021.06

Report from the Global Malaria Programme

Malaria Policy Advisory Group

Geneva, Switzerland

Pedro L. Alonso

Director

3 October 2021

Global **Malaria** Programme

World Health Organization

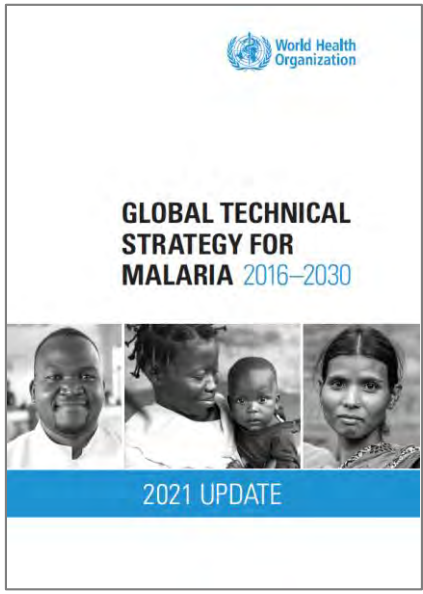
Since April …

- WHA and updated GTS
- Certification of China as malaria free
- Intense work on guidelines development
- Country support
  - STOP malaria
  - MEOC
  - HBHI
  - Emergencies

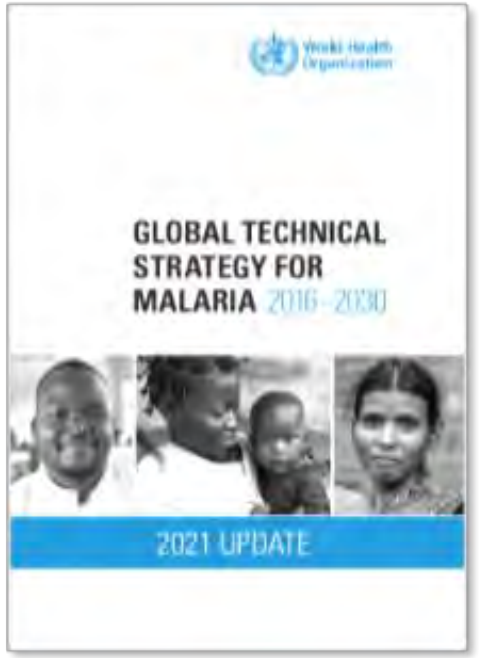
Global Technical Strategy

Principles

- Country ownership and leadership, with involvement and participation of communities, are essential to accelerating progress through a multisectoral approach
- All countries can accelerate efforts towards elimination through combinations of interventions tailored to local contexts
- Improve impact through the use of data to stratify and tailor malaria interventions to the local context
- Equity in access to quality health services, especially for the populations experiencing disadvantage, discrimination and exclusion, is essential.
- Innovation in interventions will enable countries to maximize their progression along the path to elimination.
- A resilient health system underpins the overall success of the malaria response



Global technical strategy for malaria 2016 – 2030 (2021 update)

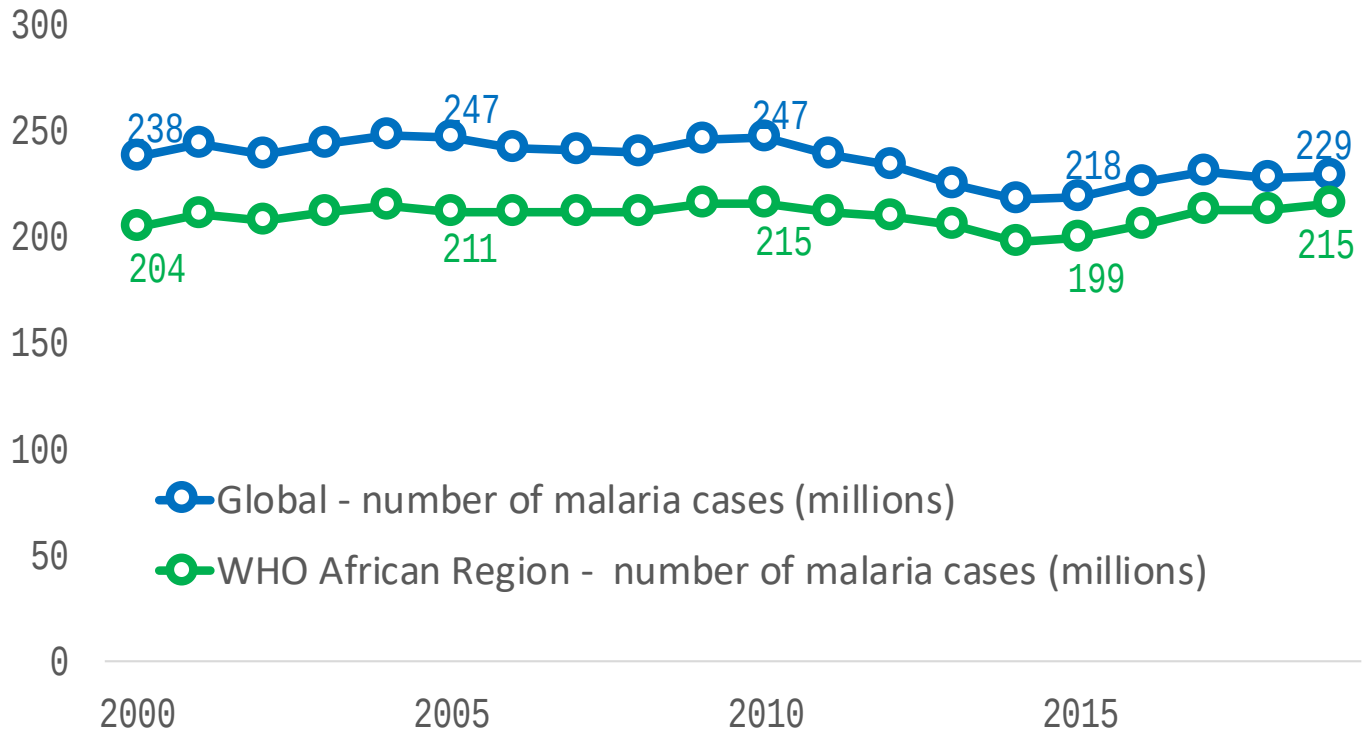


- GTS update was adopted by the World Health Assembly through resolution WHA74.9
- Sponsored by Zambia and USA – and co-sponsored by Botswana, Canada, Chile, China, Colombia, Eswatini, Guyana, Indonesia, Kenya, Monaco, Mozambique, Namibia, Philippines, Peru, Sudan, Switzerland, UK and the EU
- Urges Member States to step up the pace of progress, calls on countries to extend investment in and support of health services, ensuring no one is left behind; sustain and scale up sufficient funding and boost investment in the research and development of new tools

https://apps.who.int/gb/ebwha/pdf_files/WHA74/A74_R9-en.pdf

The global challenge: translating principles and strategies into actions and impact

- The need to re think our global malaria venture: we shall not get a different result if we just go on doing the same thing over and over again
- The need for a new problem solving mind set: driven by data, flexible, acknowledging contextual elements, overcoming silos
- Let data speak – and then embrace innovation



WHO certification of malaria elimination

- June 2021: China was certified malaria-free
- Official requests for certification received from Azerbaijan and Tajikistan. Also expected from Belize and Iran in the near future

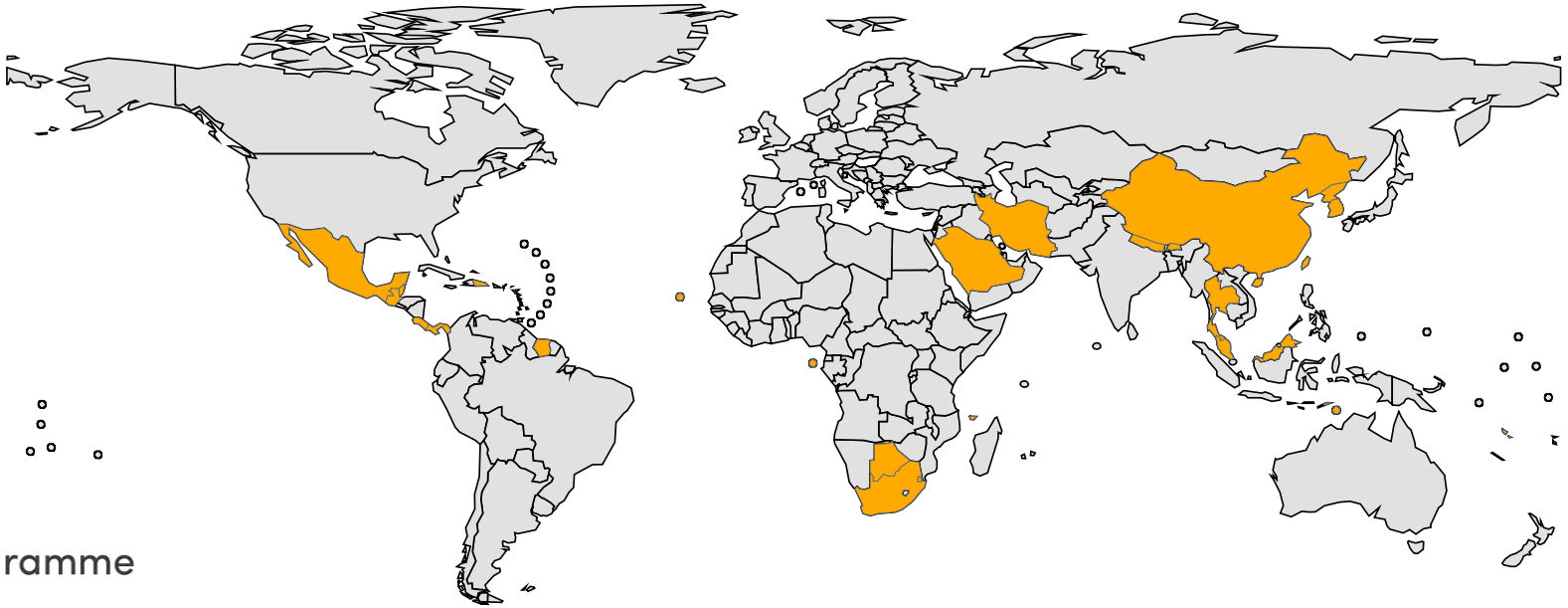
Independent certification mission to China - May 1st – May 28th 2021

Country support

Elimination 2025

E-2025 initiative launched with 25 countries to achieve 2025 milestone

- Eight new countries added: Dominican Republic, Democratic People's Republic of Korea, Guatemala, Honduras, Panama, Sao Tome and Principe, Thailand, Vanuatu
- All countries provided an official acceptance letter and are conducting baseline audits



Malaria Elimination Oversight Committee meeting: 28 June – 1st July

- Virtually participated by eight E2025 countries: Vanuatu, Timor-Leste, Thailand, Mexico, Dominican Republic, Ecuador, Eswatini, Sao Tome and Principe
- Review the progress of malaria elimination, share experiences and lessons
- Analyse results of self-audits by national elimination programs to identify weakness and strength
- Jointly develop solutions to major challenges

Strengthening the capacity of surveillance and response in selected African countries to control Malaria in different settings

UN Peace Agenda 2030 Sub-Fund (UNDESA)

China-Africa networking

2021-2022

Global **Malaria** Programme

World Health Organization

Background

Malaria Journal

BMC

Malar J. 2020; 19: 292.

PMCID: PMC7429894

Published online 2020 Aug 14. doi: 10.1186/s12936-020-03363-w

PMID: 32799857

Effectiveness of the innovative 1,7-malaria reactive community-based testing and response (1, 7-mRCTR) approach on malaria burden reduction in Southeastern Tanzania

Yeromin P. Mlacha,[2,3,4] Duoquan Wang,[1] Prosper P. Chaki,[2] Tegemeo Gavana,[2] Zhengbin Zhou,[1] Mihayo G. Michael,[2] Rashid Khatib,[2] Godlove Chila,[2] Hajirani M. Msuya,[2] Exavery Chaki,[2] Christina Makungu,[2] Kangming Lin,[5] Ernest Tambo,[6] Susan F. Rumisha,[8] Sigsbert Mkude,[2] Muhidin K. Mahende,[2] Frank Chacky,[7] Penelope Vounatsou,[3,4] Marcel Tanner,[3,4] Honorati Masanja,[2] Maru Aregawi,[9] Ellen Hertzmark,[10] Ning Xiao,[1] Salim Abdulla,[2] and Xiao-Nong Zhou[1]

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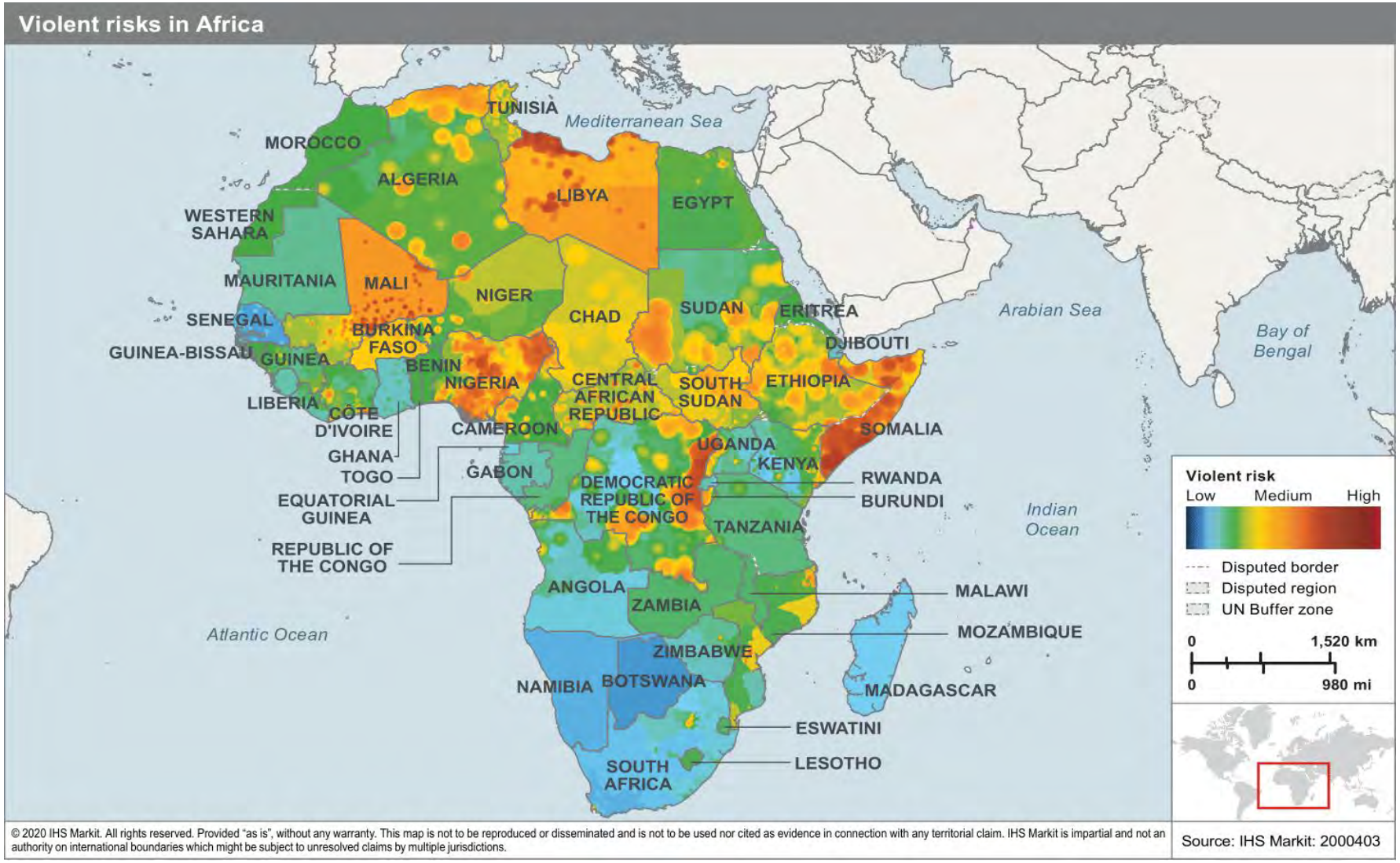
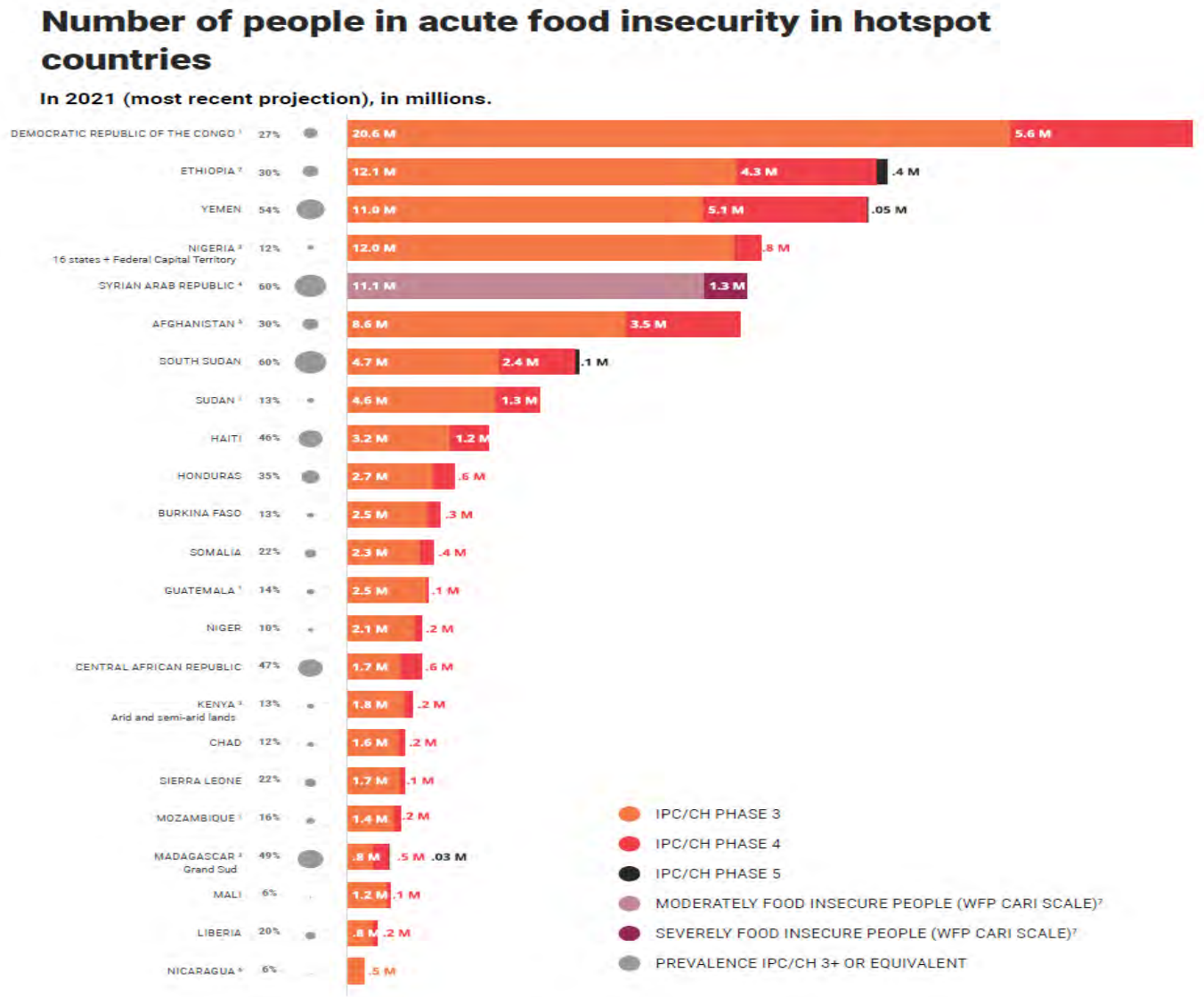
1,7 malaria reactive community-based testing and response (1,7-mRCTR)

- **Interventions:** Weekly testing and response (with ACT), control areas: same as national practices
- **Result**:
  - Malaria parasite prevalence reduced by **81%** in intervention areas
  - The results are promising and being validated through a second phase with DH-PQ in Tanzania (funded by BMGF)
- **Implication:** Useful parasite control, complementary intervention to rapidly reduce malaria burden in high-burden areas (based on macro and micro-stratification)
  - The approach needs to be repeated and validated in other countries and epidemiological settings
- **New Proposal:**
  - GMP wrote a proposal, on this premises, to the UN Agenda 2030 with Chinese fund (for multilateral agencies) in **4 countries** (Burkina Faso, Zambia, Senegal, Tanzania)

Overview over Areas of Armed Conflict in Africa 2021



Food insecurity up to the state of famine has increased by 40% over 2020



Malaria response integrated in overall emergency response

World Health Organization

HUMANITARIAN EMERGENCY
Tigray
June 2021 - Donor Alert

AT A GLANCE

5.2 million people affected by the conflict

3.8 million people in need of essential health care

Close to 2 million internally displaced persons across the region

WHO PRIORITIES

To reduce avoidable morbidity and mortality and promote health among conflict affected populations in the Tigray region by providing accessible essential health services to populations including IPDs, affected host communities

To strengthen surveillance and rapid response mechanism for early detection and immediate response to disease outbreaks and health threats

WHO FUNDING NEED

A Public Health Crisis

Since the conflict in Tigray started at the end of 2020, close to 2 million people have been forced to flee their homes and more than 5 million people are in need of essential emergency aid. More than 350,000 people are now facing catastrophic levels of food insecurity, the highest number of people in famine conditions in the world. Health partners also recorded increasing numbers of children under-five presenting acute malnutrition, representing a direct imminent threat to their lives.

Health is a key component in the response to famine. When there is a severe lack of food, people will starve, but between starvation and death there is nearly always disease. Health risks and threats have increased significantly, and the Tigray Health Cluster estimates that over 3.8 million people are in need of urgent essential health care. The rainy season is expected to start by mid-year in Tigray. The combination of rains, dismal living conditions, severe shortages of

Malaria epidemic prevention and control integrated in the overall emergency response (the example of Tigray where 1 out of two million IDPs at are risk of malaria epidemics):

1. IRS for 750'000 IDPs
2. MDA drugs available for outbreaks of up to among 500'000 IDPs (of 1m at risk)
3. Case management capacity for testing 270'000 fevers with LDH RDTs and treating 70'000 patinets of all ages
4. Technical and fund-raising support by GMP

Difficulties:

Due to civil war the délivery of cash, food, fuel and medical supplies to Mekelle is being seriously interrupted.

Sprayers are soldioring on by foot with little food and fuel and only WHO payment by voucher for future compensation.

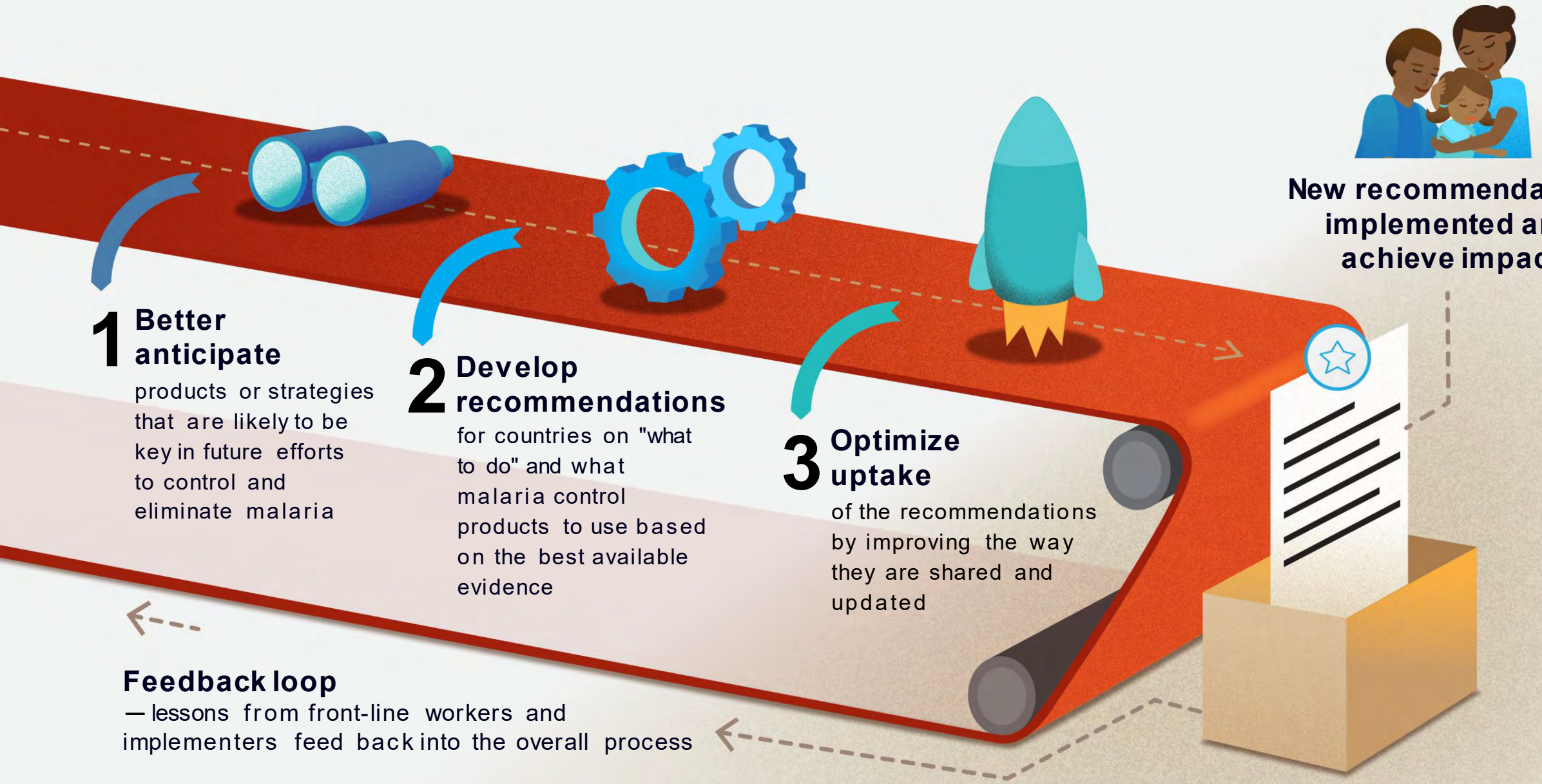
Front of conflict has moved beyond Tigray and malaria problems now also exists in neighbouring regions Amhara and Afar

“High burden high impact” (HBHI) approach

- All 10 HBHI countries completed HBHI country reports on Malaria-COVID-19, including best practices, challenges and lessons learned (2020)
- NMCPs supported at national and sub-national levels through national consultants and operational support for NPOs/IPOs:
  - Ghana, Cameroon, DRC and India
  - Training needs assessment on-going in Uganda, Ghana, Tanzania and 1 state in India
  - WCO India hired 1 consultant (in addition to 1 being supported by GMP)
  - Multi-sectoral response promoted; development of framework in Ghana supported; multi-sectoral meeting in Jharkhand State, India, Q4
- External review of HBHI to be done before end the year; findings and recommendations will be discussed during the regional meeting on re-thinking malaria being planned by AFRO on Q1 2022, and will be used to improve the approach and to promote HBHI in other high burden countries

Our normative work

The 3 steps in the pathway



1 Better anticipate

products or strategies that are likely to be key in future efforts to control and eliminate malaria

2 Develop recommendations

for countries on "what to do" and what malaria control products to use based on the best available evidence

3 Optimize uptake

of the recommendations by improving the way they are shared and updated

New recommendations implemented and achieve impact

Feedback loop

— lessons from front-line workers and implementers feed back into the overall process

1 Better Anticipate

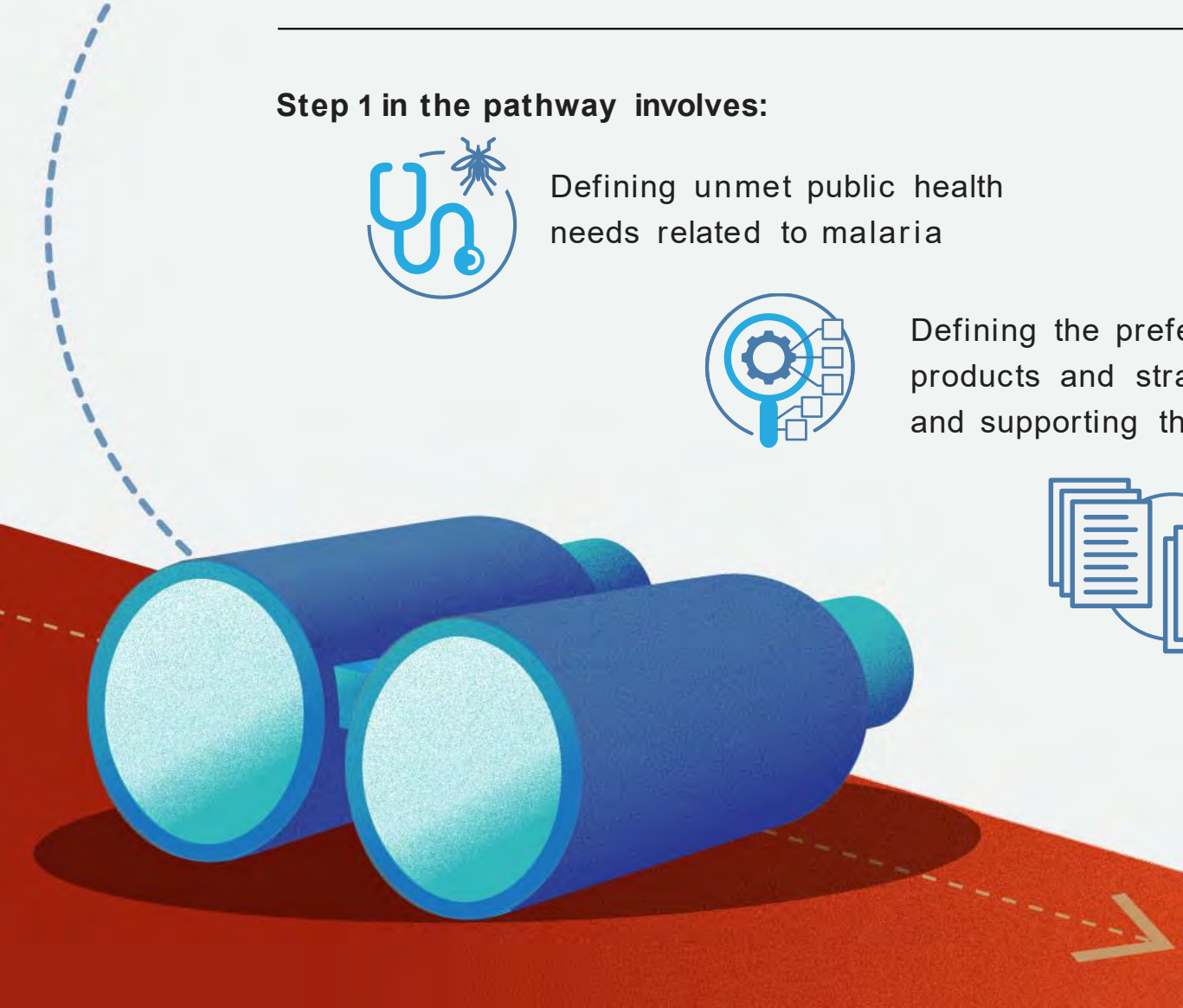
Each year, more than 400 000 people die from malaria worldwide, and there are more than 200 million new cases of the disease. The toll of malaria represents pressing public health needs that are not being met.

Step 1 in the pathway involves:

Defining unmet public health needs related to malaria

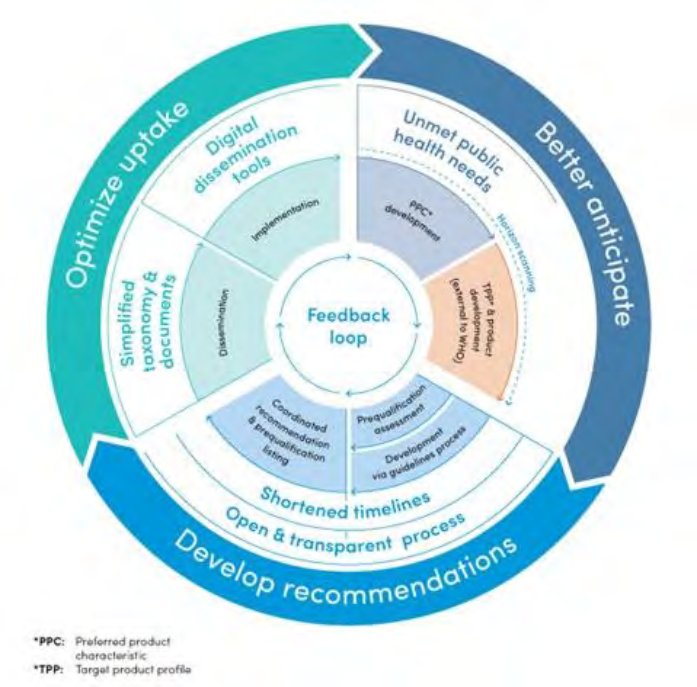
Defining the preferred product characteristics of malaria products and strategies that could address these needs and supporting the R&D effort

Scanning the pipeline of new products and determining whether there is sufficient evidence to support a WHO recommendation



This step provides transparency and predictability and helps shape the R&D space for new products.

Preferred product characteristics (PPCs)



PPCs under development:

- New chemicals for IRS – public consultation complete; document undergoing revision
- Update of existing PPC on endectocides – draft document under development for public consultation
- Tools to control outdoor biting – to be developed
- PPCs for malaria vaccines and for chemoprevention drugs

Monoclonal antibodies for malaria prevention – Nov 3 & 11

Aims and objectives of technical consultation

- Develop malaria mAbs Preferred Product Characteristics (PPCs) via expert Scientific Committee
- Review malaria mAbs pipeline and clinical development pathways
- Inform mAbs guideline development by Norms & Standards for Biological Products
- Align with existing mAbs PPCs for infectious diseases (e.g., RSV, HIV)

Proposed agenda topics

- State of R&D for malaria mAbs for prevention
  - Current and upcoming clinical trials (e.g., CIS43 phase 1, 2)
  - Modelling and example Target Product Profiles (TPPs) (e.g., BMGF)
- Priority use case scenarios (indication, target population, implementation)
- Challenges in clinical development, manufacturing, implementation

2 Develop recommendations

WHO's evidence-informed recommendations on malaria guide national ministries of health as they develop polices and strategic plans to combat the disease; they support decisions around "what to do".

WHO also develops implementation guidance - such as operational and field manuals - to advise countries on "how to" deliver the recommended tools and strategies.

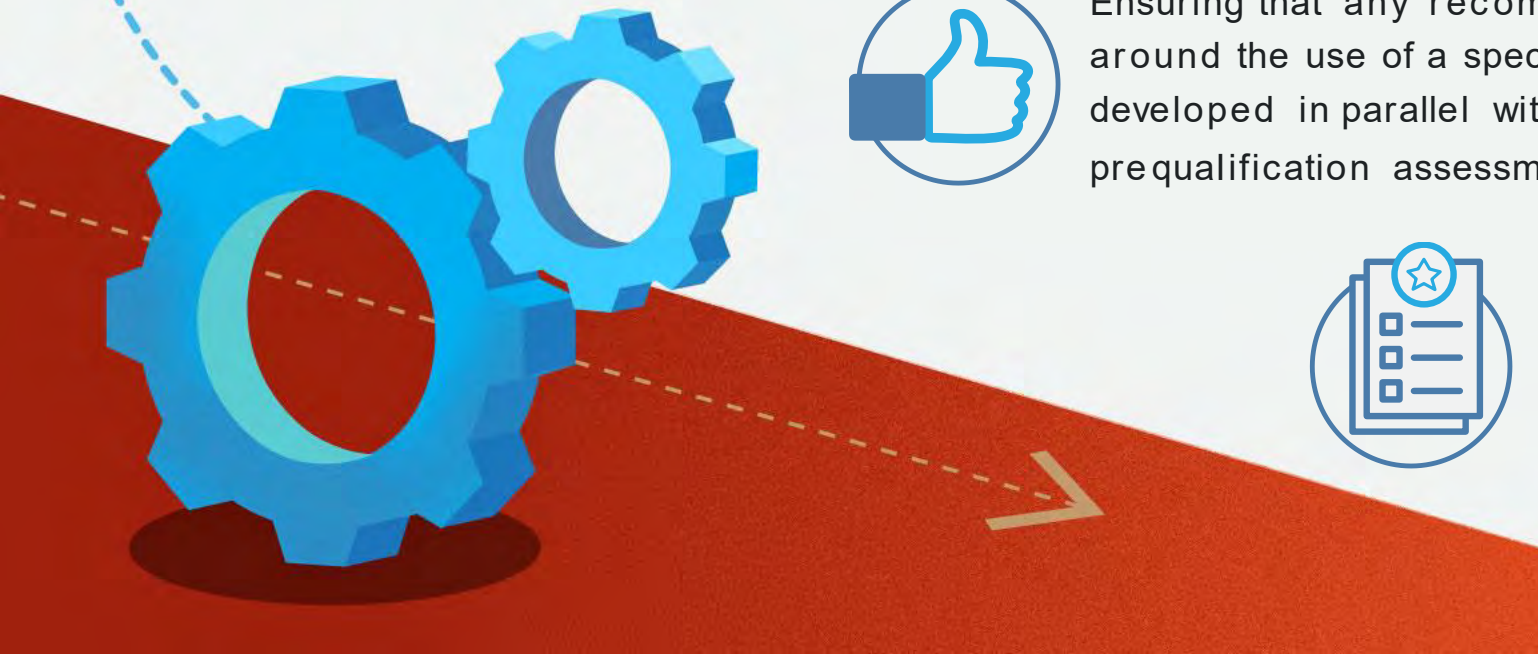
Step 2 in the pathway involves:

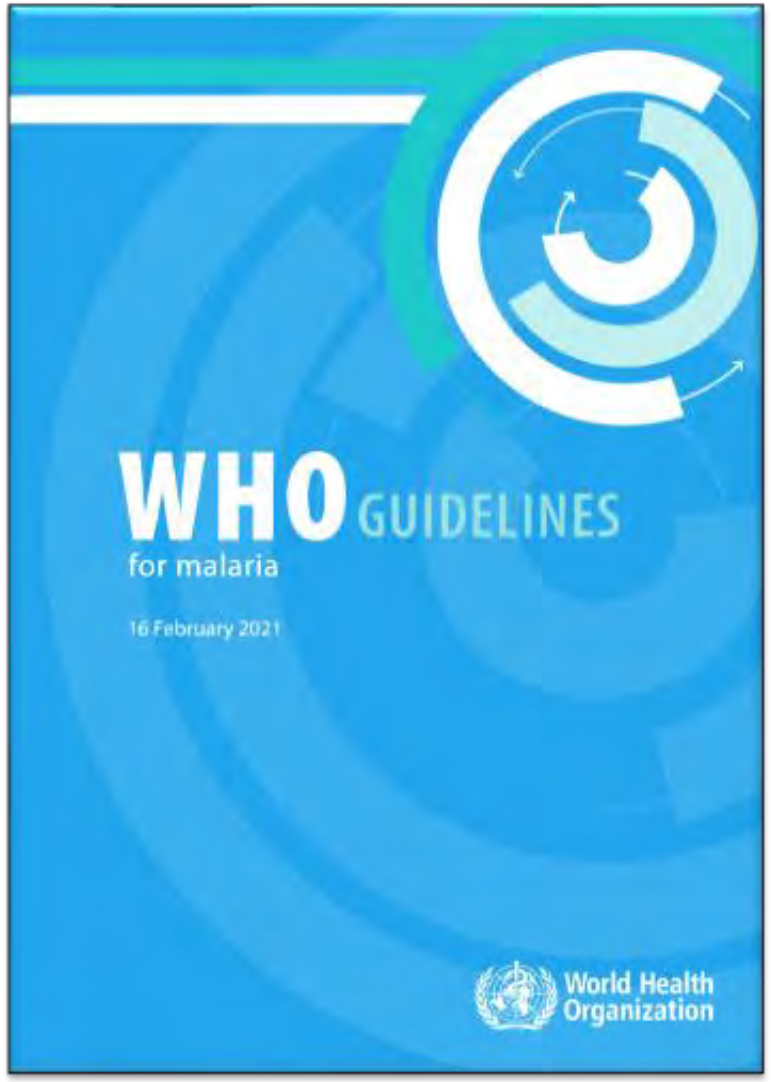
Developing recommendations for new tools and strategies through WHO's transparent, predictable and rigorous guideline development process

Ensuring that any recommendation around the use of a specific product is developed in parallel with its prequalification assessment

The WHO prequalification process ensures that diagnostics, medicines and other disease control products meet global standards of quality, safety and efficacy.

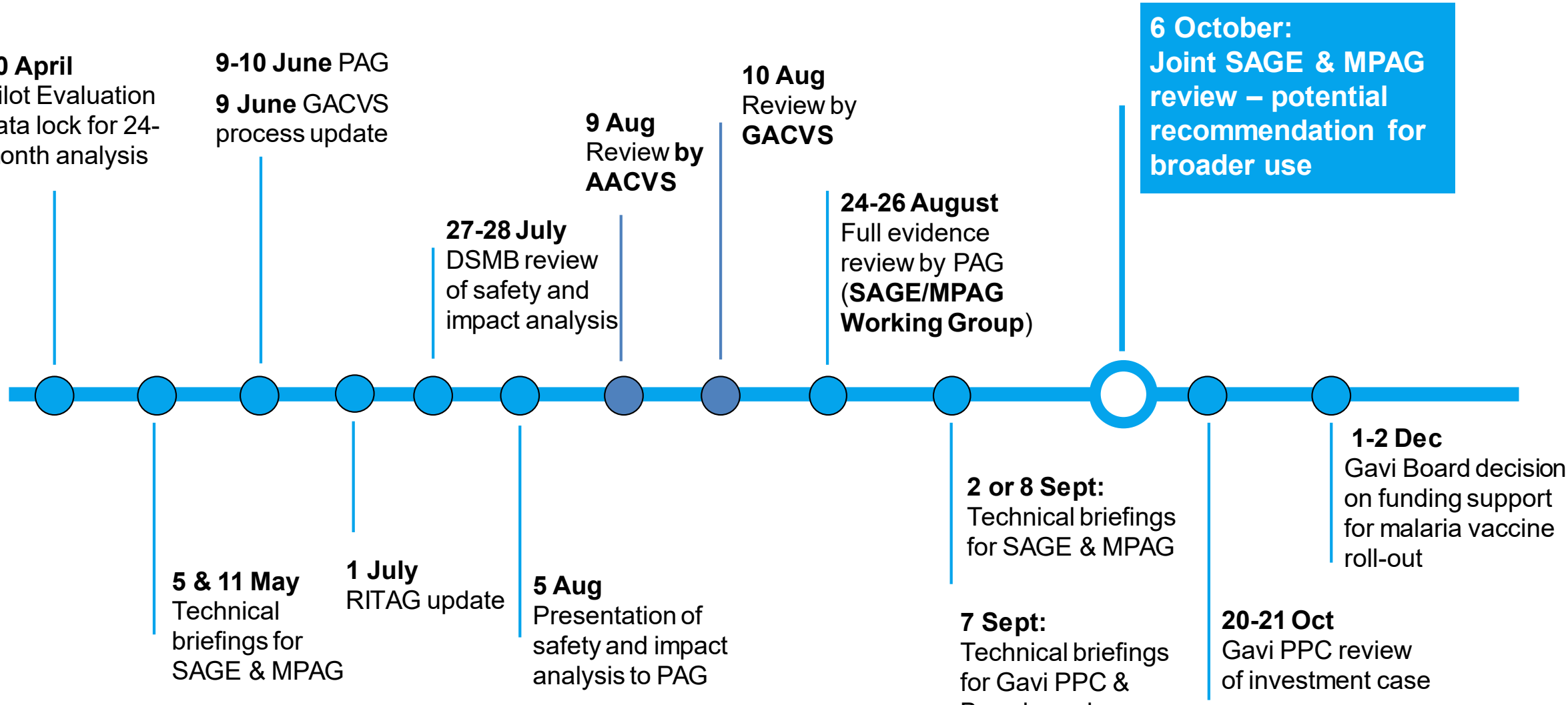
Issuing WHO recommendations and their related prequalification listings at the same time





- WHO Guidelines for Malaria
  - 4 Guidelines Development Groups established – Vector control, Elimination, Chemoprevention, Vaccines & Treatment
  - 1 Planning proposal in development – Diagnosis

RTS,S malaria vaccine: Key anticipated milestones in 2021



3 Optimize uptake

After recommendations are developed, WHO supports their adoption and use in malaria-affected countries.

Step 3 in the pathway involves:

Ensuring the recommendations are easily accessible for all malaria stakeholders

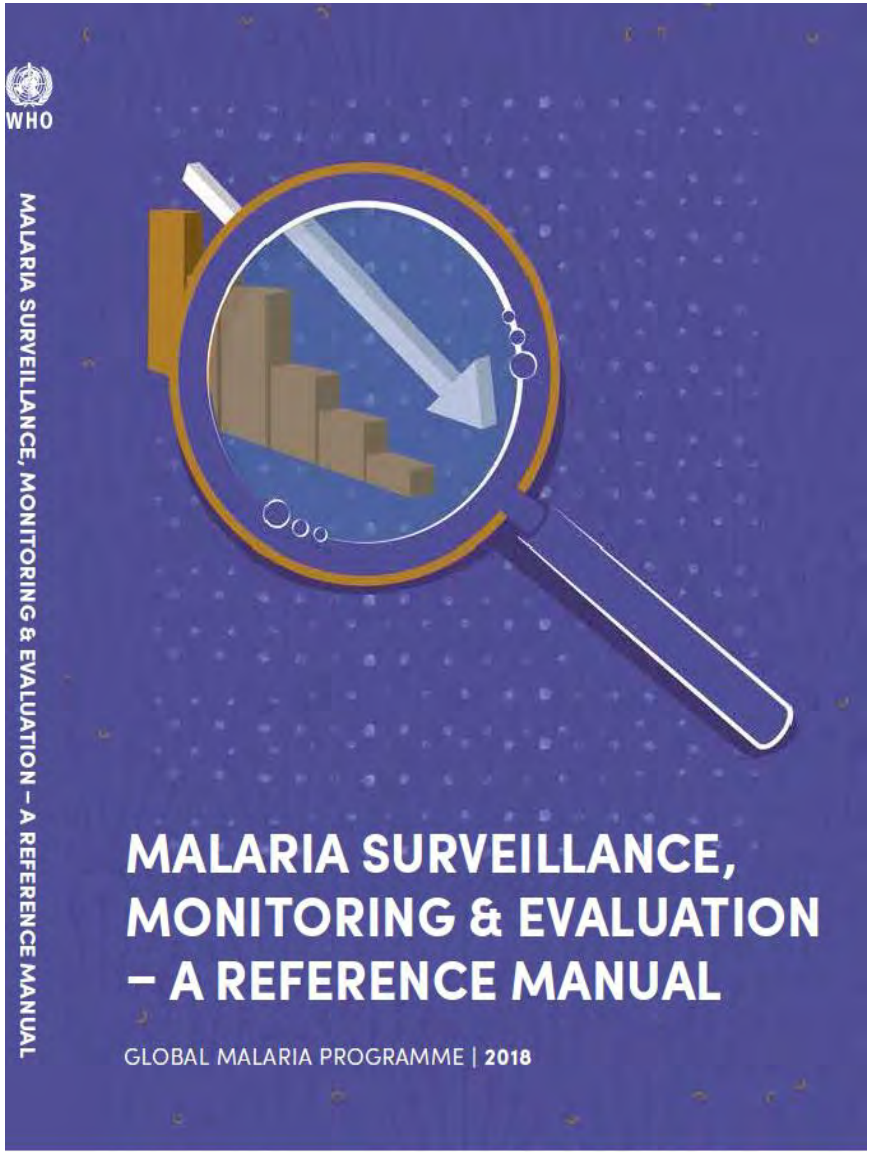
The new *WHO Guidelines for malaria* bring together the Organization's most up-to-date recommendations for malaria in one easy-to-navigate online platform

Supporting the adoption of the recommendations and monitoring their uptake and impact

Identifying the potential need for new or improved recommendations through effective feedback loops

WHO Malaria toolkit app

Updating the SME Reference manual



Launched in March 2018; 2nd edition anticipated in March 2022

Consolidated systems, epidemiological, entomological, drug and insecticide efficacy and epidemics surveillance into one document, with an additional section on M&E

Proposed updates include:

1. Revision of entomological; elimination; epidemics and M&E sections
2. Addition of a new section on data to action
3. Expansion of annexes to reflect new tools, including digital tools developed since 2018

World malaria report 2021 – anticipated launch 2 December 2021

World Malaria Report 2021

- Similar structure to the 2020 report without the detailed review chapters
- Expansion of the malaria in pregnancy sections to include potential impact of optimizing IPTp and the missed opportunities
- A new section on the epidemiology and trends of severe malaria, focusing on SSA
- An updated section on the malaria response during the COVID-19 pandemic with likely impact on burden of disease given the reported disruptions in health services

Technical consultation on the burden of and response to malaria in urban areas

To develop a *WHO Global Framework for the Response to Malaria in Urban Areas* to address the increasing urban population growth and evolving malaria transmission dynamics in malaria-endemic countries

- Review to be completed in December

Launched by the Mayor of Freetown, Hon Yvonne Aki-Sawyerr

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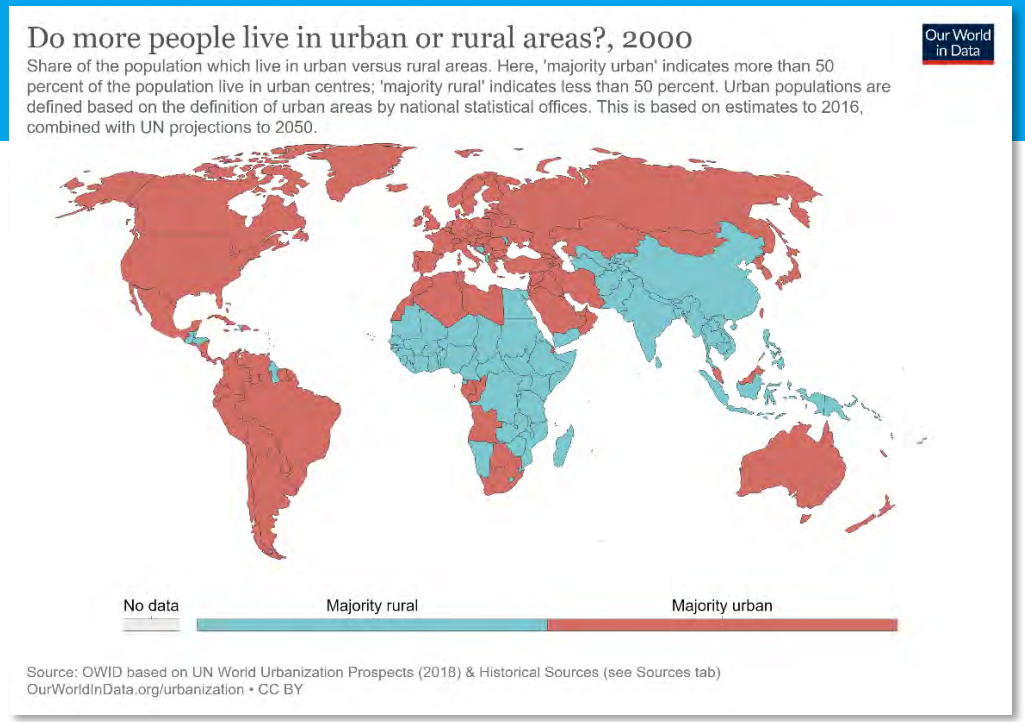
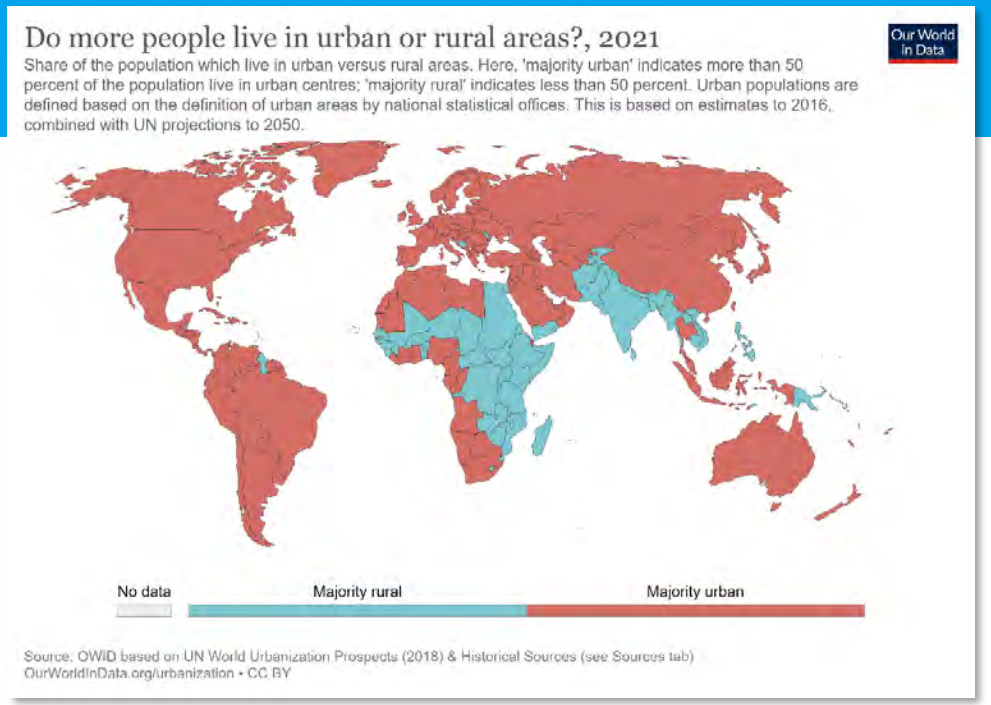


2021



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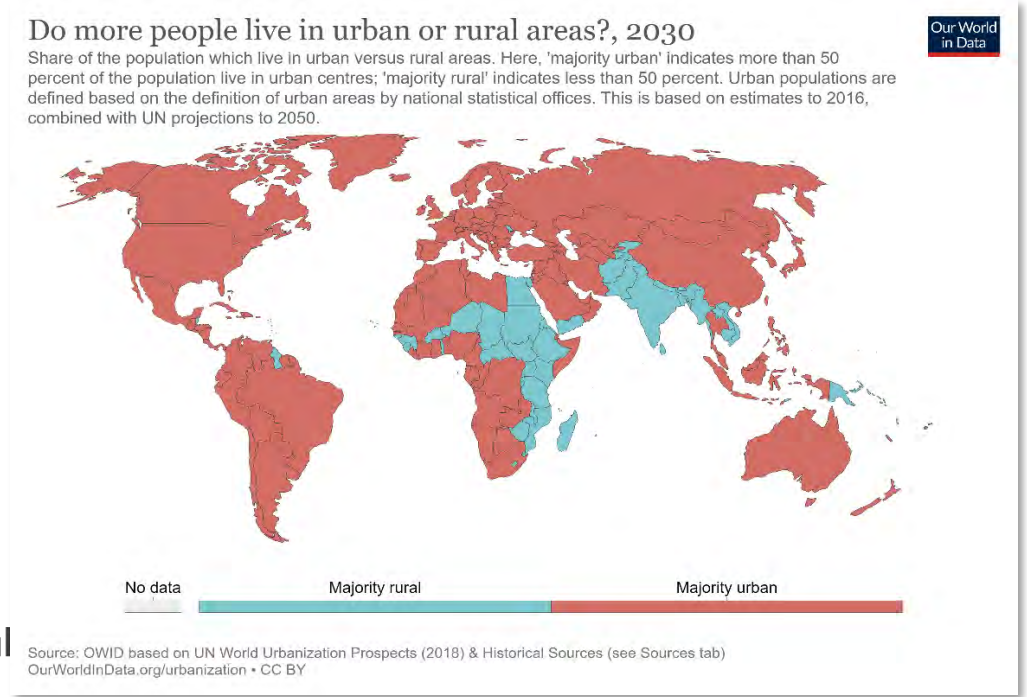

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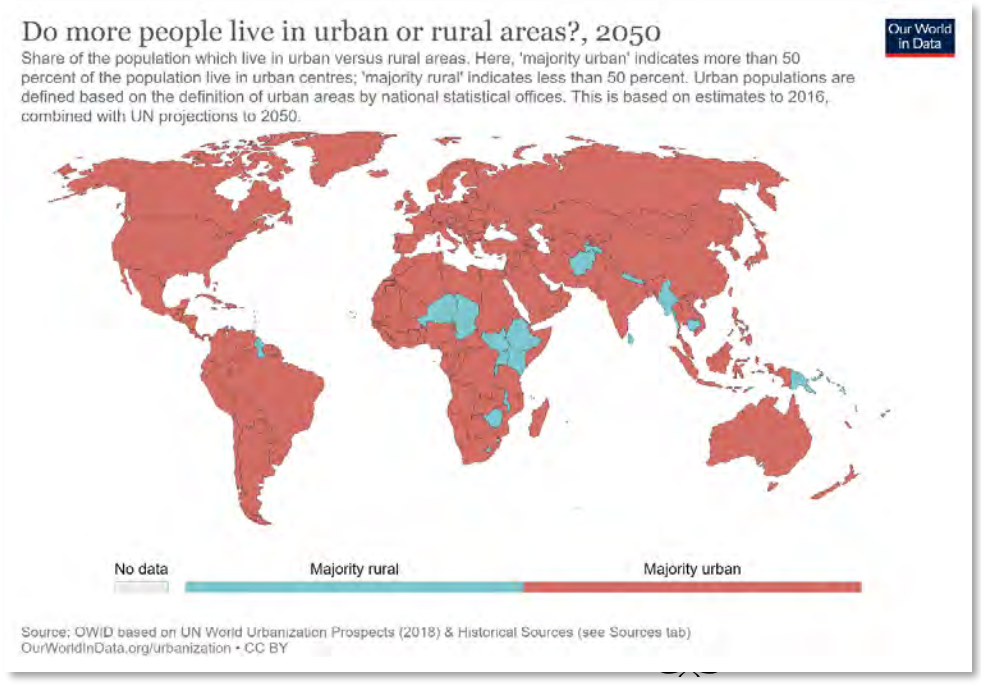

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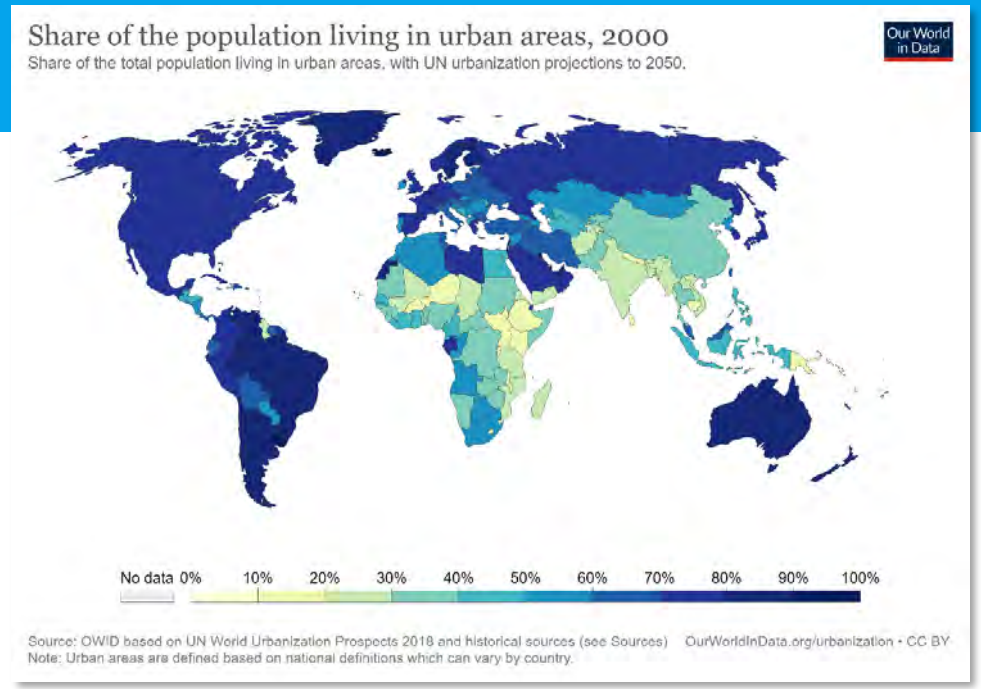
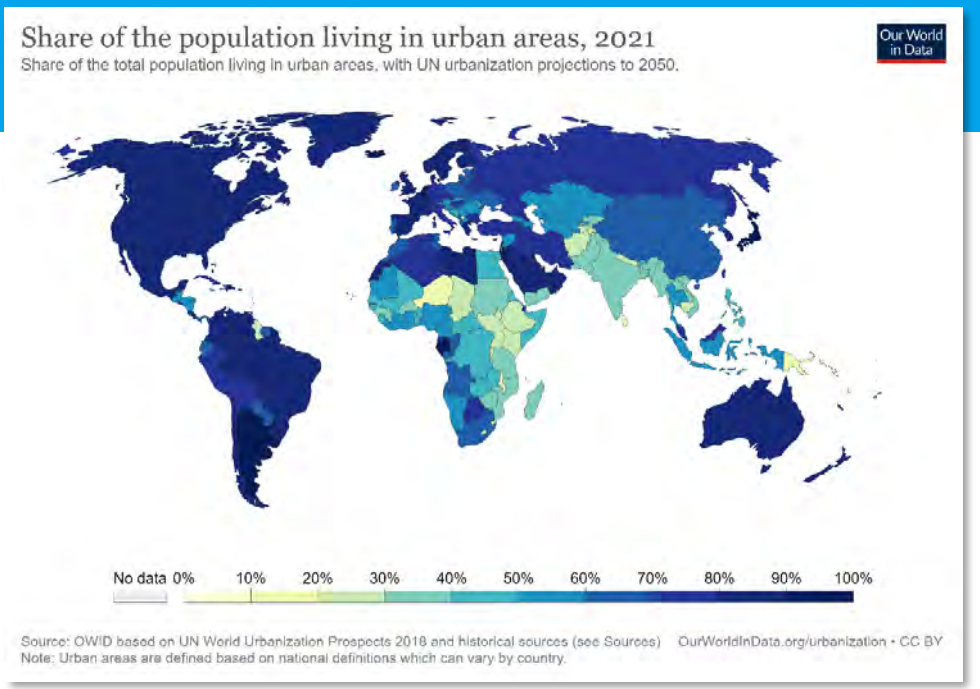


2021



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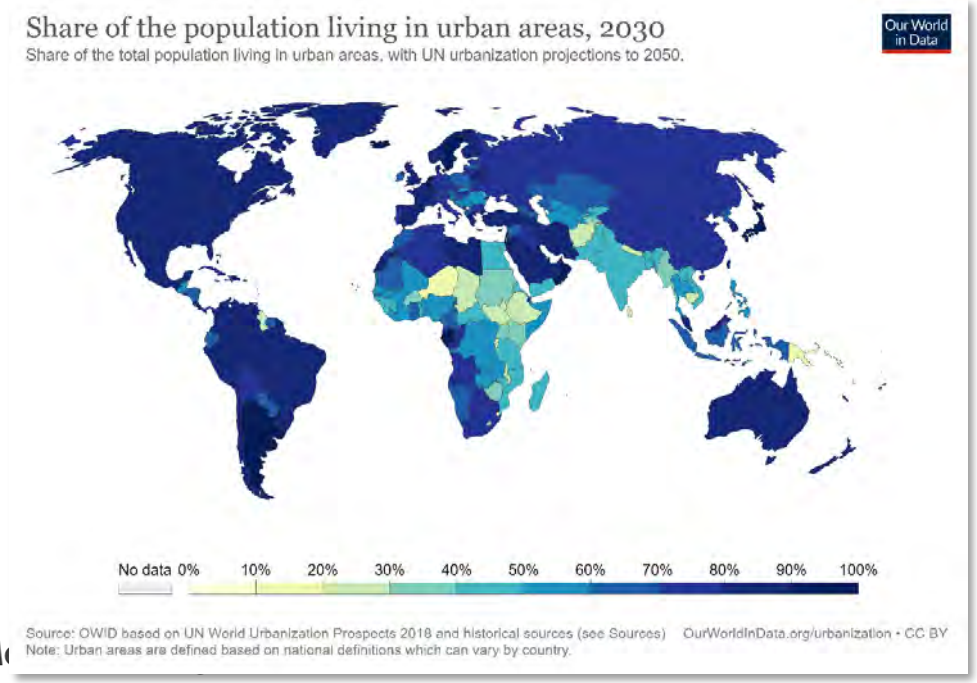

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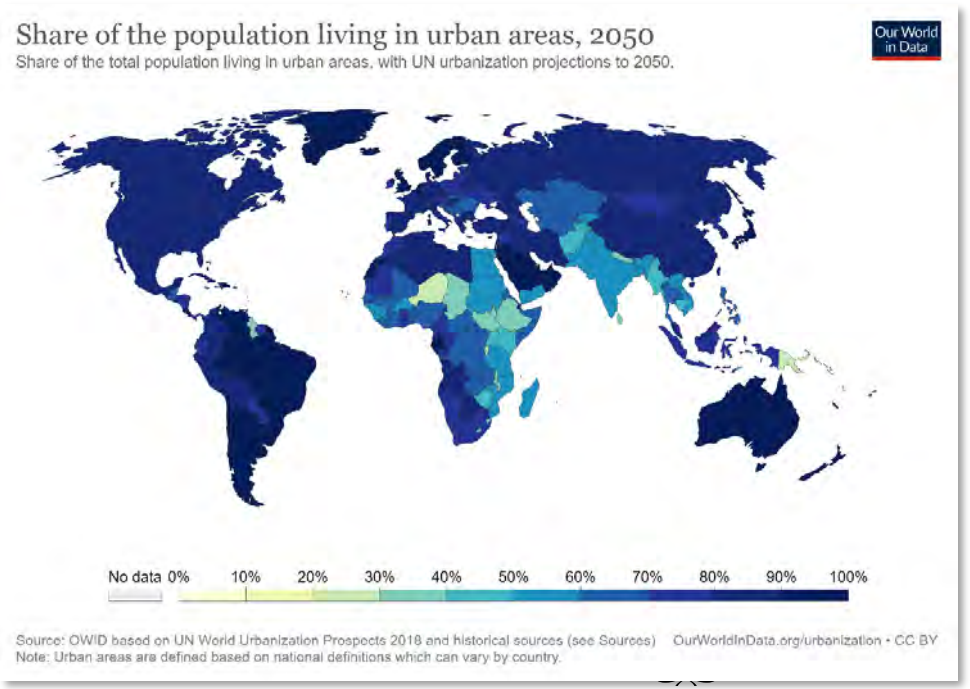
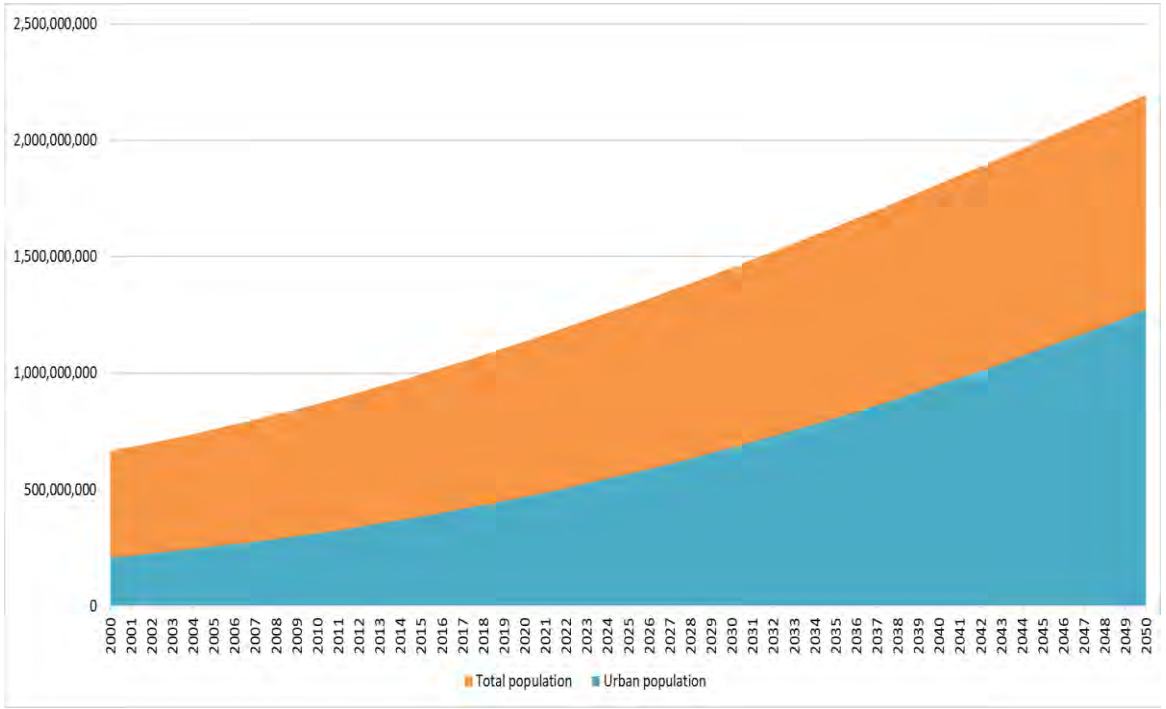


Global M

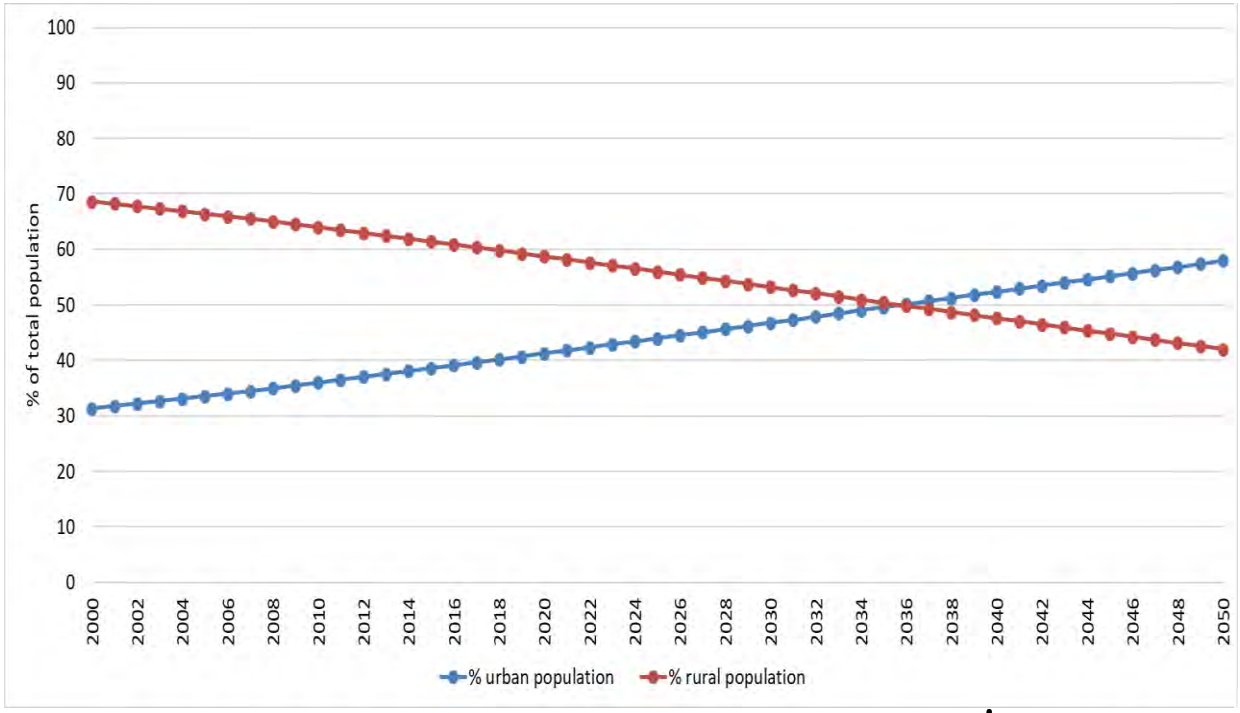
Population count, SSA



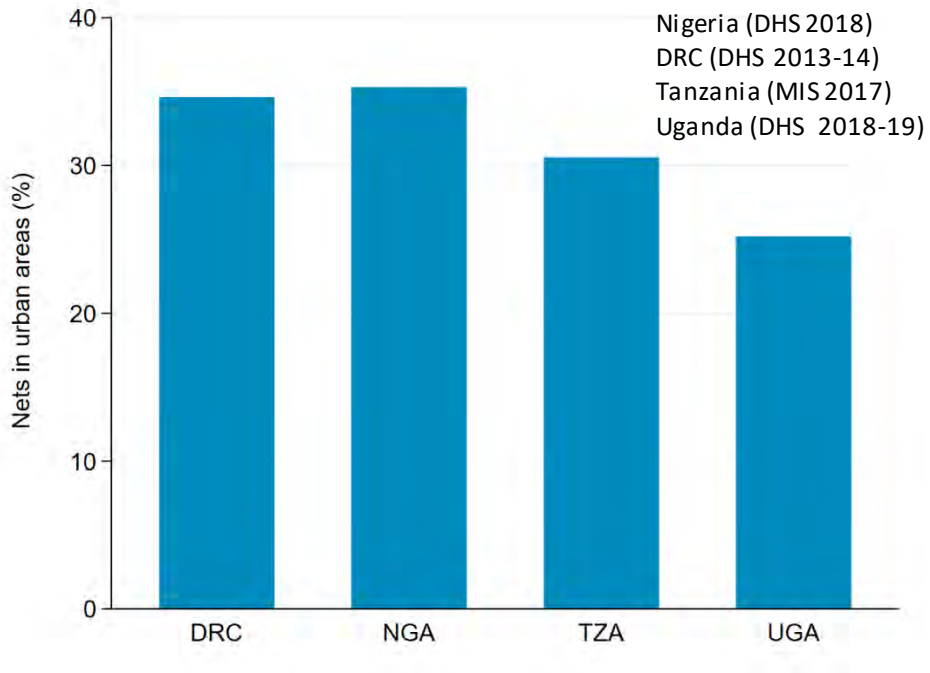
In the 10 highest burden countries in SSA, 43% of population already in urban areas in 2020

Rapid Urban Population Growth in malaria endemic countries

% urban, rural, SSA



Country	Definition	Year	% of population	% of malaria cases (mainly public sector)
Cameroon	Yaounde and Doula	2019	25.1	22
Ghana	Provincial capitals, National capital	2018	28.3	13
Nigeria	Those with ≥ 1 million people	2020	15.9	11.1



RURAL	URBAN
Transmission mainly due to natural ecology	Transmission influenced considerably by environmental modifications and prevalence/incidence influenced by human population movement
Transmission is generalized	Transmission is focal, often higher in peri-urban areas and urban slums with very few areas accounting for most of local infections
Most older children and adults have immunity	Overall population immunity is low
Most infections locally acquired	Large proportion of infections linked to travel to and from higher transmission rural areas
The public health sector is the main source of care for fevers	The private health sector is a major source of care for fevers
High acceptability of IRS and ITNs and use of ITNs	Moderate/low acceptability of IRS and ITNs and use of ITNs
Most housing types allow for high levels of indoor biting	Most housing types reduce indoor biting

Guiding questions

1. How do we define urbanization with respect to the malaria response?
2. What drives malaria transmission and disease patterns in urban areas?
3. What information do we need to appropriately tailor malaria interventions in urban settings?
4. What are the current approaches for malaria prevention and treatment in urban settings and which ones have a WHO policy recommendation, which ones don't and which of these are adaptable as best practice?
5. What are the challenges and what opportunities do urban planning, health policies and health systems provide in the malaria response?
6. How do we ensure urban governance and leadership in malaria endemic countries prioritize malaria as part of the broader New Urban Agenda, urban development and health systems?
7. What is the role of various sectors (especially private, NGOs, civil society and community) in the response to malaria in urban areas and do we optimize it?
8. How do we integrate malaria better into surveillance and control of other vector borne diseases?
9. What opportunities do urban planning, health policies and health systems provide in the malaria response?
10. What are the knowledge gaps and the key operational research priorities?

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.

What is NOT the aim of the framework?

- To be prescriptive and unnecessarily detailed in its guidance as the urban context is highly variable within and between countries.
- To contravene existing WHO recommendations on malaria interventions while recognizing the need for adaptation to country contexts.

Who is the target audience?

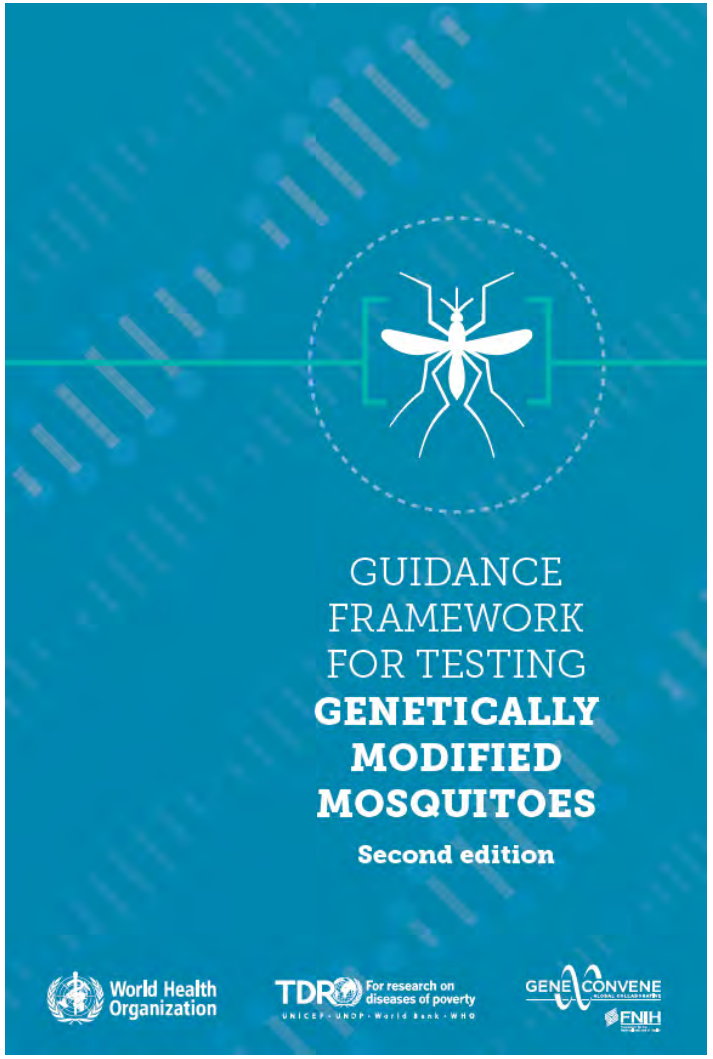
- National and urban government policy makers
- National and subnational malaria programmes
- Funders, development and implementation partners

Structure and participation (n=135)

	Prevention interventions and delivery (33)	Health care delivery (33)	Urban governance, policies and planning (18)	Multisectoral response (focusing on private and community sectors) (15)	Surveillance, mapping and analysis (36)
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	Laurent Carrington	Nana Aba Williams	Nyawira Gitahi	Jessica Rockwood	Ifeoma Ozodiegwu

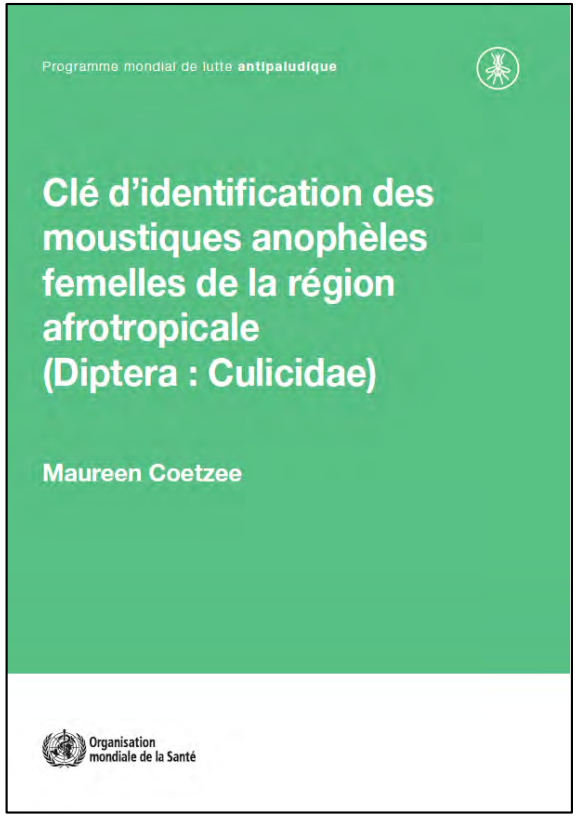
Overall co-chairs: Prof Fred Binka and Dr Alex Coutinho

Guidance Framework for testing Genetically Modified Mosquitoes 2nd ed.



- Revised version of joint WHO, TDR, FNIH document originally published in 2014
- Updated in response to technical progress and lessons learned
- Provides essential standards to inform future research and development on genetically modified mosquitoes (GMMs)
- Describes best practices for safety and efficacy testing, ethical and engagement obligations and regulatory oversight for different types of GMMs at each phase of the testing pathway for different GMM types
- Will contribute to comparability of results and credibility of conclusions to facilitate country decision-making

Vector control updates

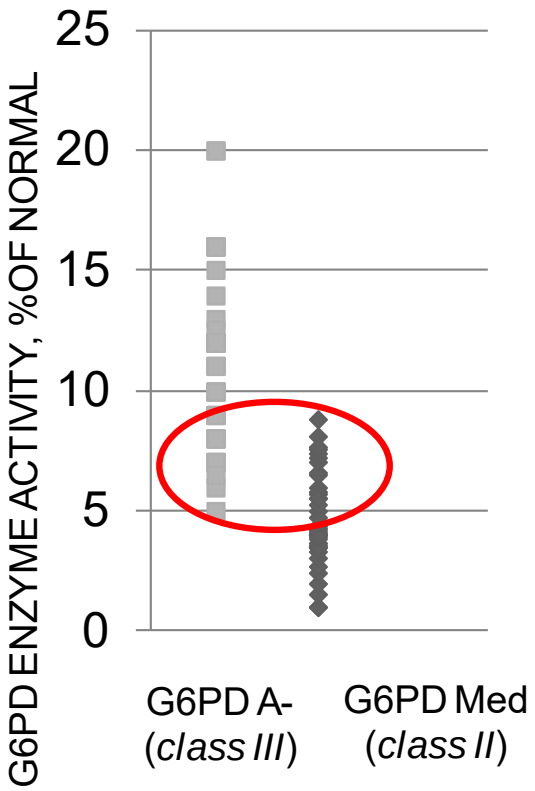


Consultation on economics & insecticide resistance (14-16 Sept 2021)

- To define and implement a process to explicitly apply economic principles to insecticide resistance management of malaria vectors

- Translation of Identification key for *Anopheles* in Africa (Coetzee 2021) to support surveillance activities for the invasive vector *Anopheles stephensi*
  - French translation published Sept 2021 (https://www.who.int/fr/publications-detail/WHO-UCN-GMP-2021.04)
  - Arabic translation ongoing

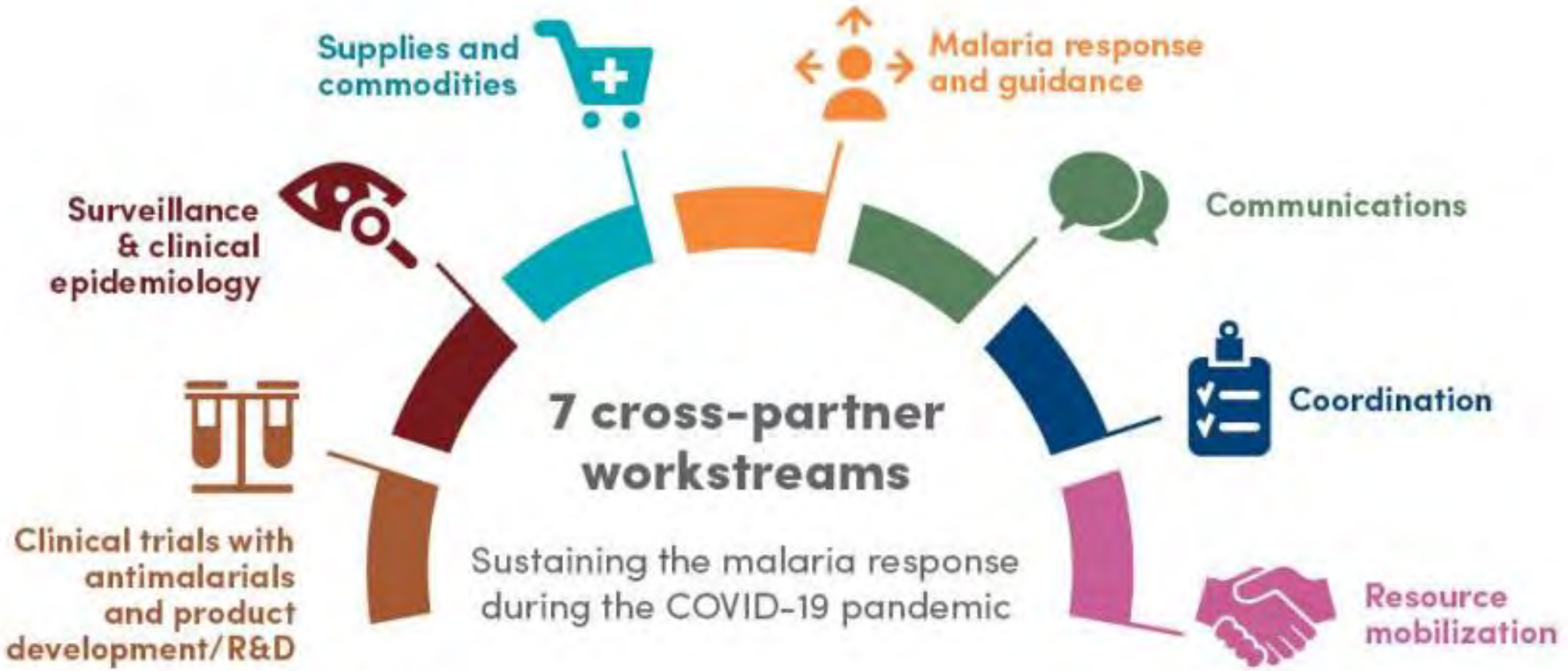
Updating WHO classification on G6PD



Courtesy of Prof. Lucio Luzzato

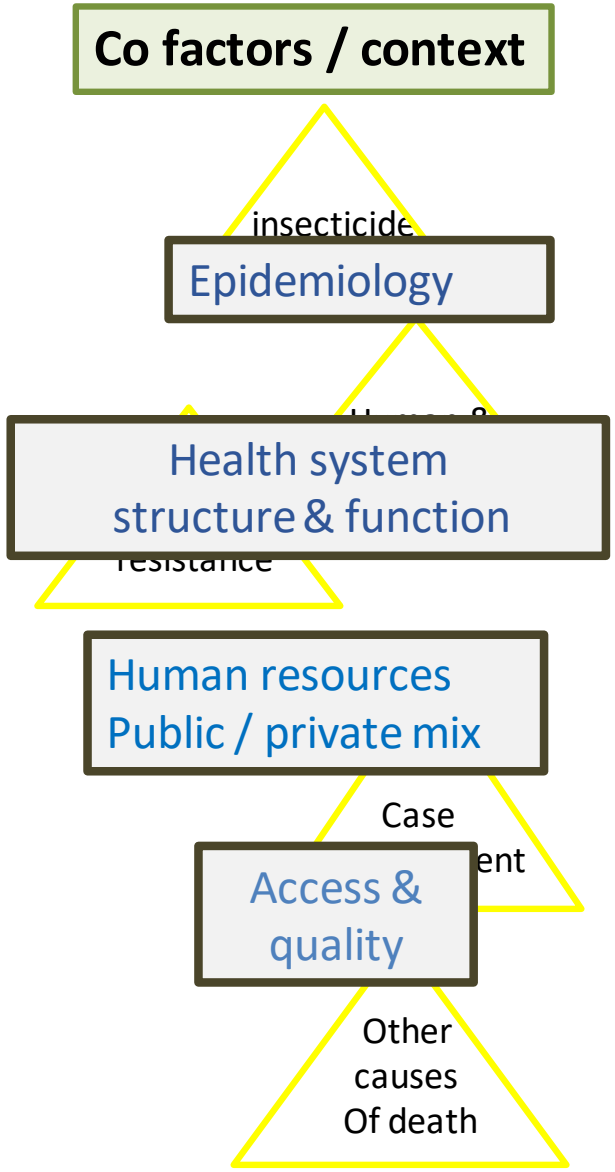
- Interest on G6PD variants and hemolytic risks for safe administration of tafenoquine and primaquine.
- WHO classification of G6PD variants is outdated (1985).
- WHO Genomics Initiative proposed WHO/GMP convenes technical consultation to revise the G6PD classification - endorsed by MPAG in Oct 2019.
- Literature review to inform the consultation near completion:
  I. Define the distribution of G6PD activity in males of the main variants of public health interest (classes II, III and III/II).
  II. Analyze overlap of G6PD activity between different variants.
  III. Review distribution of G6PD activity in males with deficiency in relation to detection thresholds for point-of-care G6PD tests.

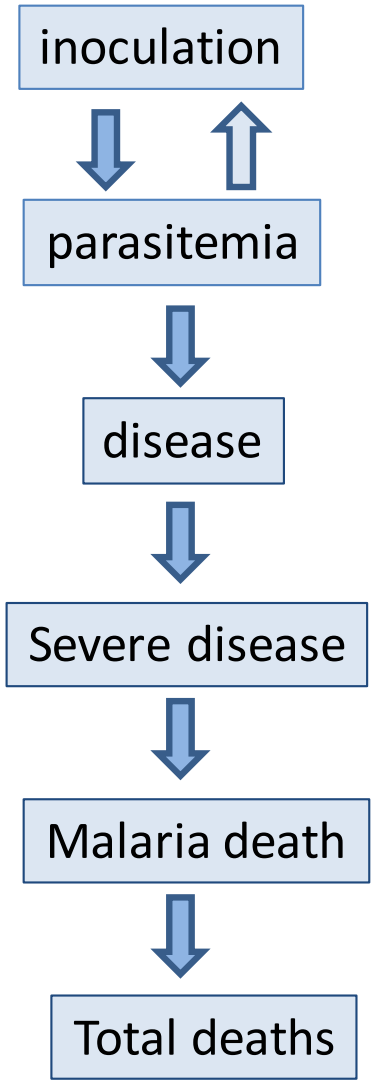
Malaria & COVID-19 cross-partner workstreams

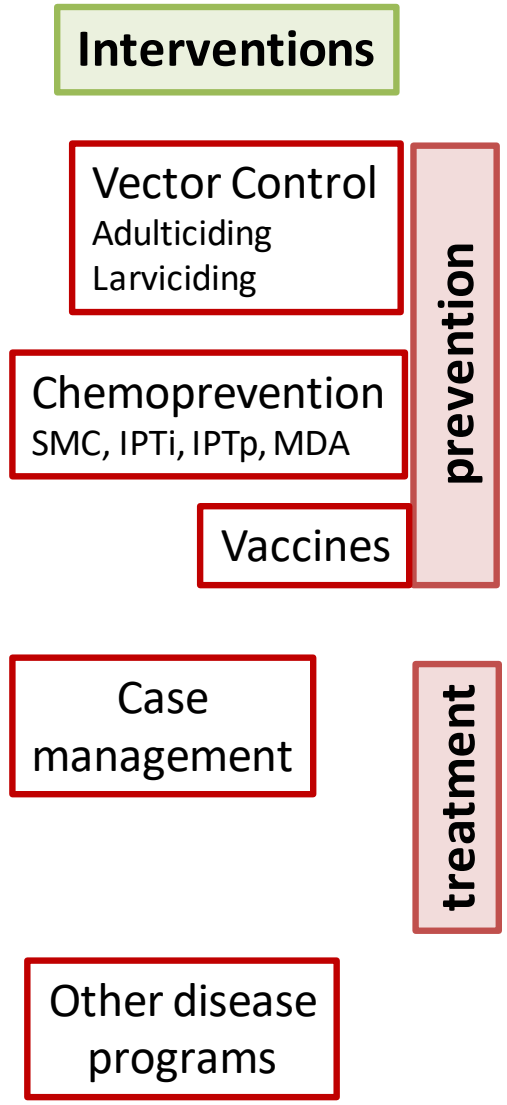


Problem solving

From mosquito bites to death. Not one size fits all







New operational manual on sub-national tailoring of malaria interventions

Sub-national tailoring of malaria interventions: an operational manual

- Builds on the HBHI experience but extends to all malaria endemic contexts
- Consolidates approaches on data for decision making to support national malaria strategic plans
- Expands on approaches for stratification, criteria for intervention targeting sub-nationally and identifying optimal mixes of interventions
- Introduces the role of modeling (transmission dynamic modeling, cost-effectiveness analysis etc.) to inform decisions on intervention mixes and prioritization sub-nationally
- Anticipated March 2022

Malaria: a problem to be solved and a time to be bold

Nat Med **27,** 1506–1509 (2021)

PULLING IT TOGETHER IN AFRICA:

From "Rethinking Malaria" to "New Agenda for Malaria in Africa"

Rethinking Malaria – The call for a clear and action-oriented endpoint

- **RECURRENT QUESTION ON "RETHINKING MALARIA":**
  - What is the end point of the "Rethinking Malaria processes"? Or is it just another set of academic papers to make another set of professors?
- **RESPONSES:**
  - "The Rethinking Malaria Initiatives" are timely interventions for course correction in a journey we know is heading in the wrong direction.
  - "The Rethinking Malaria Initiatives" will end in a Regional Stakeholders Meeting to review progress and lessons from the implementation of HBHI, consider findings and recommendations from Rethinking Malaria and related processes and chart the ways forward.
  - Authors of the Harvard paper, "Rethinking Malaria Governance" concur on the need for "Rethinking Malaria" to result in change:

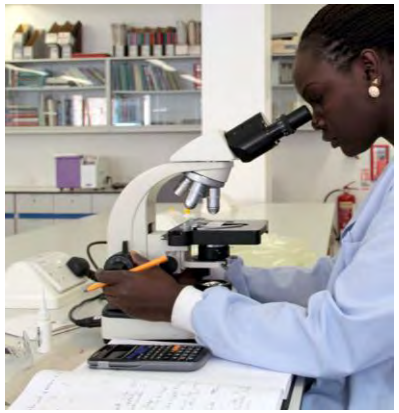
"We offer these proposed five changes in malaria governance for discussion by an expanded "malaria community." Building consensus around these five changes and implementing them will not be easy. The changes involve significant changes in power and in how malaria control happens. But we believe that a global debate on these five changes is critical to Rethinking Malaria and to putting malaria back on track toward elimination."

Interrogate, Harmonize & Align relevant findings and recommendations towards country-level action

1. Africa Thinktank on Rethinking Malaria – 10/11 June 2021
2. Harvard Rethinking Malaria papers – 1 Sep; virtual academic meeting 28/29 Sep;
3. WHO consultation on urban malaria – 22 September 2021
4. Independent review of HBHI implementation – Ongoing
5. Independent review of year 2000 Abuja declaration on roll back malaria – Ongoing
6. Case studies on community engagement - Ongoing
7. Emerging/new malaria tools and technologies – RTS,S; mRNA malaria vaccine; R24 malaria vaccine; etc.
8. Scan of health innovations environment useful to malaria enterprise – Ongoing
9. Consultations on multisectoral response to malaria – Ongoing, by RBM

Emerging lessons for African countries

- Consider malaria as societal problem of development, not as a medical issue alone; a socio-economic and development challenge needing a broadening of definitions, framework arrangements and partnerships
- Endemic countries must lead the malaria response in partnership with in-country stakeholders
- Empower health workers at all levels through readiness and training, including paying community health workers and enhancing supervision
- Make malaria data valued and visible and used by the public and policy-makers, as has happened with COVID-19 for decision-making
- Pay greater attention to innovation and problem-solving for malaria elimination and support endemic countries in entrepreneurship, research and development, and manufacturing
- Include malaria as part of attaining Universal Health Coverage – and delivering "Health for all"
- Enhance domestic resource mobilization for malaria control by better articulating the cost benefit argument and leveraging resources from related sectors (mining , agriculture, urban development, etc.)
- Enhance domestic research capacities and commodity value chains
- Invest in science knowledge and data to find new tools and innovation
- Recognize the importance and opportunity for African leadership, from the highest political level to those communities most affected



Strategic focus on “Investing for sustainable impact on malaria burden” – country actions

- Adopt a “comprehensive, whole of society investment approach” by paying equal and concurrent investment attention to a triple response to malaria:
  - Sustain and expand implementation of the **“Technical Response”** for country programmes to adopt appropriate intervention mixes and commodities for malaria prevention and treatment;
  - Prioritize **“Health Systems Response”:** invest in strengthening primary health care platforms and the delivery of people-centered health service to optimize service delivery; and enhance country capacities for disease mapping, stratification & tailoring of disease specific interventions, and the integration of malaria into sector planning & delivery; and
  - Mainstream **“Multi-sectoral Response”** focused on mobilizing participation of private and non-health sector organizations to reinvigorate community participation, address determinants of health and saturate prioritized high burden and left behind communities with tailored interventions,
- Accelerate malaria burden reduction through investment efficiency to achieve more with available resources

Pulling it together –

TOWARDS A NEW AGENDA FOR MALARIA IN AFRICA

1. ***Develop "Rethinking Malaria framework of actions"*** – a matrix aligning the 6 HBHI pillars with proposed strategic actions emerging from Rethinking malaria, and the other strategic analyses and landscape scanning activities
   - Will inform a course correction towards the 2030 GTS targets; regional malaria stakeholders will review, interrogate and adapt towards a New Agenda for Malaria in Africa – work ongoing
2. ***Regional Malaria Stakeholders Meeting, Q1 2022*** to review progress and lessons from the implementation of HBHI, consider findings and recommendations from Rethinking Malaria and chart the ways forward – adoption of A New Agenda for Malaria in Africa
   - Malaria endemic country participants: Nine representatives from each of the 47 malaria-endemic countries in Africa, representing priority non-health sector ministries, private sector and civil society coalitions on malaria and the health sector ministry
   - Regional and global partner participants: representing malaria, health systems, determinants of health, etc.
3. ***Expand of HBHI implementation*** to all 39 moderate to high transmission malaria-endemic countries of Africa – Planned; implement the Rethinking Malaria Framework of Action
4. ***Enhance AFRO capacity to drive change*** – ongoing strengthening of capacities in the WHO Africa Region for use of analytics to drive stratification mapping, identification and prioritization of left behind communities to target with tailored interventions

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Rethinking Malaria in the Context of COVID–19

Rose Gana Fomban Leke
Chair, Rethinking Malaria in the Context of COVID–19
Emeritus Professor of Immunology and Parasitology
University of Yaoundé I

Malaria Policy Advisory Group

4 October 2021

"Rethinking Malaria in the Context of COVID–19"

STEERING COMMITTEE:
Rose Leke, Michael Reich, Dyann Wirth, Pedro Alonso, Alastair Robb, and Carmen Mejia

WORKING GROUP CO-CHAIRS:
Malaria Governance - Michael R. Reich and Speciosa Wandira Kazibwe
Integrated Service Delivery for Malaria - Evelyn Ansah and Corrina Moucheraud
Training and Capacity Building for Malaria - Núria Casamitjana, Marcia Castro, Friday Okonofua, and Marcel Tanner

EXTERNAL ADVISORY COMMITTEE:
An external Advisory Committee composed of experts and thought leaders from diverse sectors and disciplines is responsible for providing feedback on the "Rethinking Malaria" work products and processes. In addition to offering insights on broad areas of global health across workstreams, Advisors meet with specific Working Groups to share ideas, review findings, and discuss manuscript content and recommendations.

*For more information, including biographies, manuscripts, etc.
https://www.defeatingmalaria.harvard.edu/rethinking-malaria/

Global Webinars Furthering the Dialogue on Malaria/COVID–19

September 3–4, 2020: public webinar series titled, "Responding to the Double Challenge of Malaria and COVID-19," convened by the WHO's Global Malaria Programme

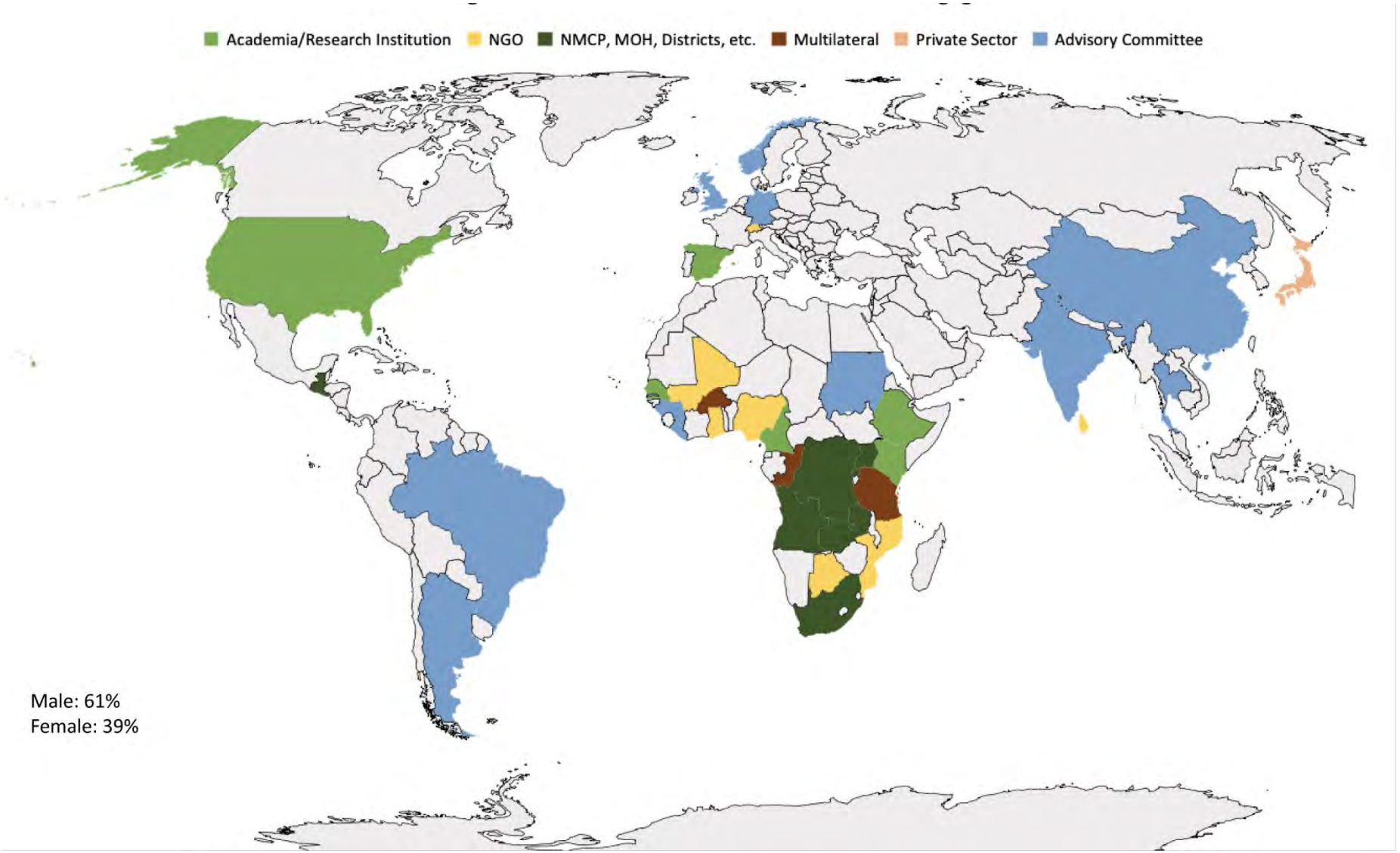
January 28, 2021: a virtual forum titled, "Updating WHO's Global Strategy for Malaria," convened by the WHO's Global Malaria Programme

March and July 2021: numerous Working Group-specific and one-on-one meetings with External Advisory Committee members, convened by Harvard University

June 10, 2021: a regional conference titled, "Rethinking Malaria in Africa Conference," focused on responding to the 5-year stagnation in malaria burden reduction in Africa, convened by the WHO and facilitated by the African Center for Global Health and Social Transformation (ACHEST)

Various webinars sponsored by malaria/global health organizations, including: Africa CDC, Catholic Relief Services, Friends of the Global Fight, GBC Health, JC Flowers Foundation, RBM Partnership to End Malaria, MESA, PATH, The Global Fund, US President's Malaria Initiative, WHO, and more

"Rethinking Malaria in the Context of COVID–19" Global Engagement



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Rethinking Malaria in the Context to COVID-19

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WG1-1. Rethinking Governance of Malaria_Reich_Wandira-Kazibwe.pdf (175.9Kb)
WG1-2. Malaria in the Governance of District Health Systems_Coleman.pdf (169.3Kb)
WG1-3. Rethinking Malaria_Governance Lessons_Ohiri et al.pdf (344.4Kb)
WG1-4. Financing Malaria Rannan-Eliya.pdf (151.1Kb)
WG1-5. Decolonizing Malaria Governance Bump Aniebo.pdf (152.4Kb)
WG1-6. Rethinking Communications for Governance of Malaria Programs_Opigo_Guyer.pdf (1.304Mb)
WG2-1. Rethinking Integrated Service Delivery for Malaria_Ansah&Moucheraud.pdf (3.519Mb)
WG3-1. Rethinking Malaria Control and Elimination in Africa_Okumu et al.pdf (754.6Kb)
WG3-2. Rethinking Human Resources and Capacity Building Needs_Mwenesi et al.pdf (298.9Kb)
Rethinking Malaria_WG#1 Final Manuscripts_14Sept2021_wAbstracts.pdf (1.959Mb)

Citation
"Rethinking Malaria in the Context to COVID-19." Harvard University's Defeating Malaria: From the Genes to the Globe Initiative. Discussion Papers, 2021.

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Harvard's Defeating Malaria Initiative website:
https://www.defeatingmalaria.harvard.edu/rethinking-malaria/

Digital Access to Scholarship at Harvard (DASH) website:
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Rethinking Malaria website:
https://rethinkingmalaria.org/

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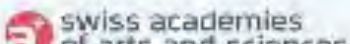
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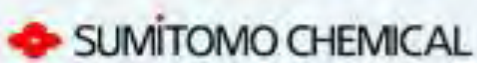
SUMITOMO CHEMICAL

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REGISTER TODAY!

Rethinking Malaria in the Context of COVID-19

~ A Global Webinar ~

September 1, 2021

8:00am–11:00am EDT

6am–9am CST

12pm–3pm GMT | 1pm–4pm WAT

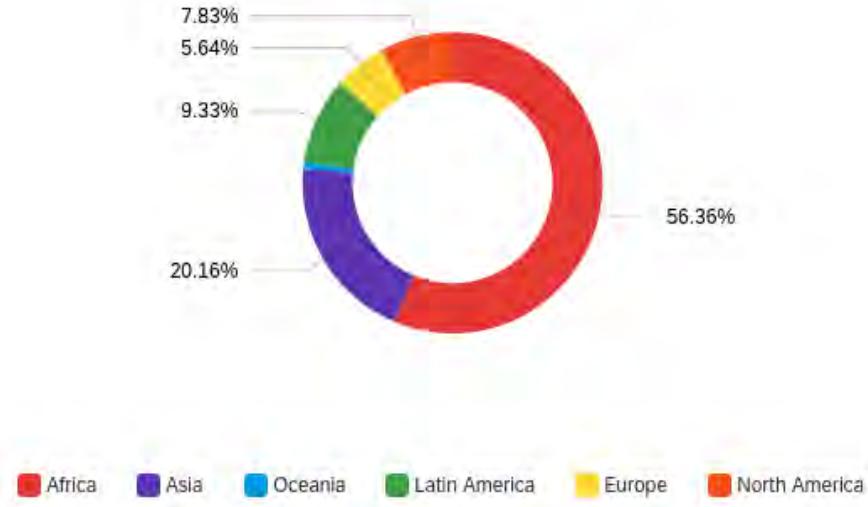
2pm–5pm CEST | 3pm–6pm EAT

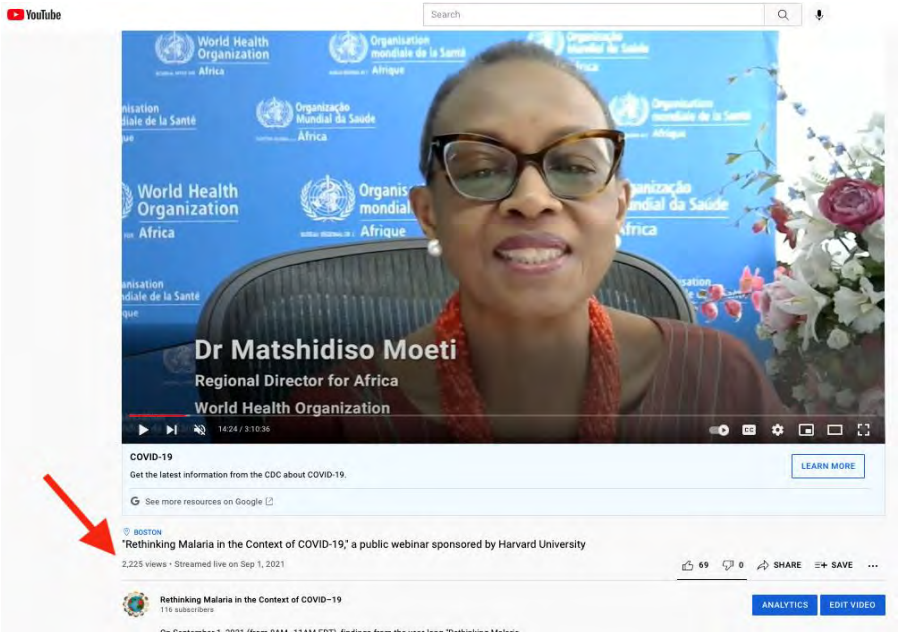
LIVE STREAMING

English | French | Portuguese | Spanish

Registered Attendees: 2,926

Regional Participation: (below)





YouTube Live Stream Views: 2,225 (to date)

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REGISTER

Rethinking Malaria in the Context of COVID-19

~ Presents a 2-Day Webinar on ~

Malaria Governance, Integrated Service Delivery for Malaria, Training & Capacity Building for Malaria

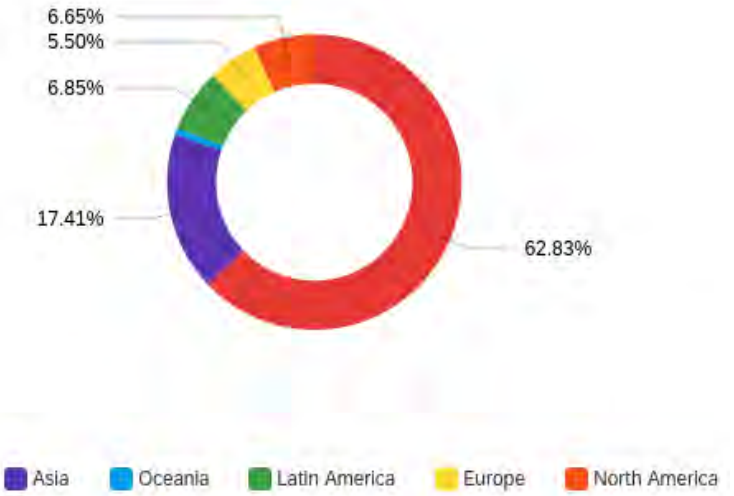
September 28-29, 2021

9:00AM-11:30AM EDT

1:00PM-4:30PM GMT | 2:00PM-5:30PM WAT | 4:00PM-7:30PM EAT

Registered Attendees: 1,999

Regional Participation: (below)



YouTube Live Stream Views: *pending/ recorded webinar available soon*

Key Messages

Why now?

- **Malaria elimination is possible** – 10 countries have been certified "malaria-free" in the past five years, including China which eliminated from 30 million cases to zero cases
- **Africa suffers 90% of the malaria burden and progress has stalled**. Today, there are 220 million cases of malaria and 435,000 deaths worldwide – this is the same level of human suffering as was the case in 2015
- COVID-19 also brought about the fastest vaccine and diagnostics in history, proving our ability to **quickly bring new/powerfully effective treatments to bear on public health challenges** – and this is exactly what's needed to end malaria
- **Lessons from COVID-19 will help us rethink malaria**—our assumptions, our approaches, etc.—and decide on the best solution for the situation
- The **COVID-19 has laid bare the limitations and inequities** of our global health systems; in particular, challenge related to governance, service delivery integration, and workforce
- The first step is to **spark change on paper, the second step is to spark action** in the community

What needs to change?

- 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
- 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 real-time data, knowledge, and information
  --**Malaria data needs to be valued and visible** and used by the public and policy makers, as has happened with COVID-19 for decision-making
- 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**

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World Health Organization

Rethinking Malaria in the Context of COVID–19

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Emeritus Professor of Immunology and Parasitology
University of Yaoundé I

Malaria Policy Advisory Group

4 October 2021

~ Backup Slides ~

External Advisory Committee

Member Names / Titles

Rethinking Malaria's External Advisory Committee

Samira Hamid Abdelrahman, Professor of Community Medicine, Faculty of Medicine, University of Gezira (FMUG)
Kesete Admasu, CEO, Big Win Philanthropy
Arti Ahuja, Additional Secretary & Director-General, Department of Health and Family Welfare, Government of India
Pedro L. Alonso, Director, Global Malaria Programme, World Health Organization
Uche Amazigo, Professor in the Department of Parasitology and Entomology, Nnamdi Azikiwe University, Nigeria
Chinedum Peace Babolaola, Professor of Pharmaceutical Chemistry and Pharmacokinetics and Vice-Chancellor of Chrisland University Abeokuta
Honorable Awa Marie Coll-Seck, Minister of State, Republic of Senegal
Kelly Chibale, Neville Isdell Chair in African-centric Drug Discovery & Development; South Africa Research Chair in Drug Discovery; and Director, H3D, University of Cape Town, South Africa
Oluwafunmilola (Lola) Dare, President, Chestrad Global, Nigeria and Board, RBM Partnership to End Malaria
Abdourahmane Diallo, Chief Executive Officer, RBM Partnership to End Malaria
Mark Dybul, Professor, Department of Medicine at the Medical Center; Co-director of the Center for Global Health **Practice and Impact**, Georgetown University

Christopher J. Flowers, Chairman & CEO, JC Flowers Foundation
Sharon Fonn, Professor, School of Public Health, University of Witwatersrand, South Africa
George F. Gao, Director-General, Chinese Center for Disease Control and Prevention (China CDC), Vice President, the National Natural Science Foundation of China (NSFC); Director and Professor, CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences; and Dean, Medical School, University of Chinese Academy of Sciences, People's Republic of China
Githinji Gitahi, Group Chief Executive Officer, Amref Health Africa
Tore Godal, Special Adviser to the Prime Minister on Global Health, Norway
Silvia Gold, President, Mundo Sano Foundation
Margaret Gyapong, Professor and Director, Institute of Health Research and Coordinator, Centre for Health Policy and Implementation Research, University of Health and Allied Sciences, Ghana
Lutz Hegemann, Group Head, Corporate Global Strategy, ESG Management & Global Health, Novartis
James (Jim) Jones, Director, Global Community Programs and Strategy, ExxonMobil Foundation
Karl W. Lauterbach, Member of the Bundestag, Social Democratic Party/SDC; Adjunct Professor, Harvard T.H. Chan School of Public Health
Nobuaki Mito, Managing Executive Officer and President, Health & Crop Sciences Sector, Sumitomo Chemical Co., Ltd.
Carlos Morel, Director, Centre for Technological Development in Health (CDTS), Oswaldo Cruz Foundation (FIOCRUZ)

Rose Gana Fomban Leke, Emeritus Professor of Immunology and Parasitology, University of Yaoundé I
Hassan Mshinda, Consultant, Botnar Foundation
John Nkengasong, Director, Africa Centers for Disease Control and Prevention
Olivia Ngou, Founder & Executive Director, Impact Sante Afrique (ISA)
Faith Osier, Executive Director, IAVI Human Immunology Laboratory, Imperial College London
Raj Panjabi, Global Malaria Coordinator, US President's Malaria Initiative
Muhammad Pate, Global Director, Health, Nutrition and Population; Director, Global Financing Facility for Women, Children and Adolescents (GFF), The World Bank
N. Regina Rabinovich, ExxonMobil Malaria Scholar in Residence, Harvard University Director, Malaria Elimination Initiative and International Scholar, Barcelona Institute for Global Health (ISGlobal)
Peter Sands, Executive Director, The Global Fund to Fight AIDS, TB, and Malaria
Susan Silbermann, Global Advisor to the Group President of Pfizer's Biopharmaceuticals Group
Leonardo Simão, Chairman of the Board of Directors, Manhiça Foundation
Keizõ Takemi, Member, House of Councillors of Japan
Philip Welkhoff, Director, Malaria Program, Bill & Melinda Gates Foundation
Dyann F. Wirth, Richard Pearson Strong Professor of Infectious Diseases, Harvard T.H. Chan School of Public Health
Rear Admiral Timothy Ziemer, Former Acting Assistant Administrator for the Bureau for Democracy, Conflict, and Humanitarian Assistance at USAID

Technical Consultation on Non-Inferiority

31 August – 2 September 2021

Recommendations to WHO

For MPAG Decision

Malaria Policy Advisor Group
Virtual Meeting
4 October 2021

Global **Malaria** Programme

World Health Organization

Background

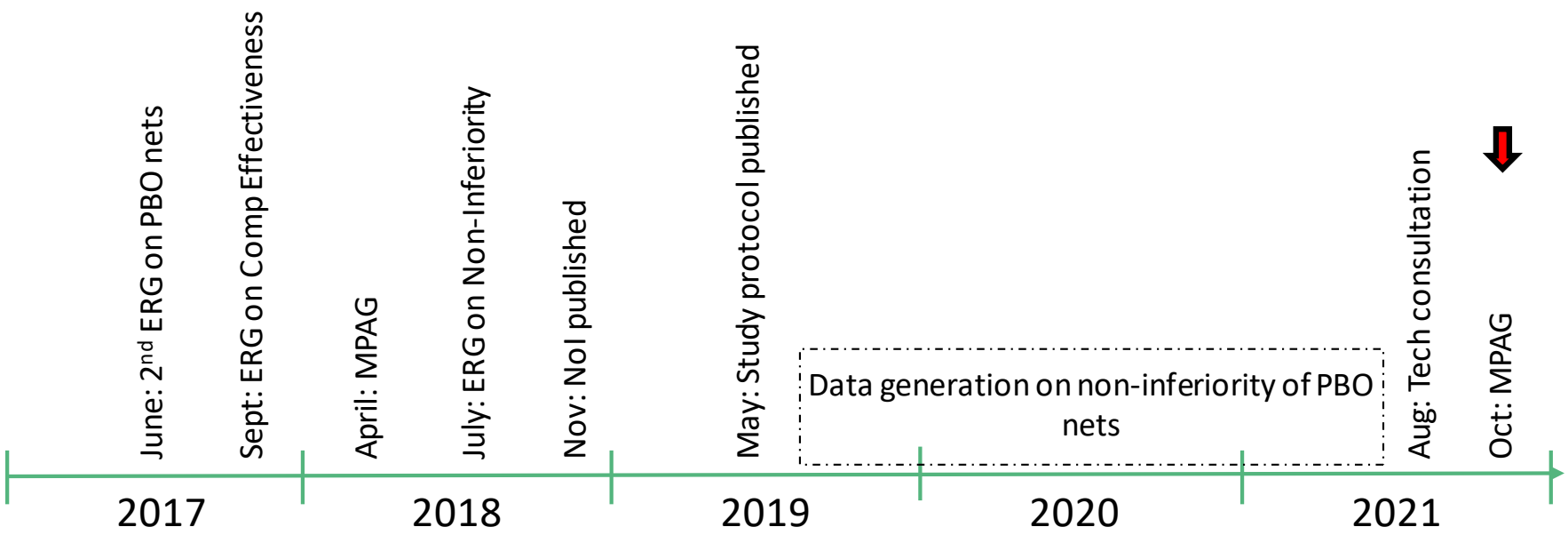
- Since the discontinuation of WHOPES in 2017, the WHO vector control evaluation process, as well as the WHO guidelines process have significantly evolved
- Explicit links between the demonstration of an intervention's public health value (= epidemiological impact) and the formulation of a WHO recommendation are now common practice
- There is a trend for vector control intervention classes to broaden, meaning that:
    - overall, fewer trials with epidemiological endpoints may be needed (≥2 / class)
    - products within a class (and hence covered by a WHO recommendation) are becoming more diverse
- In turn, the need for assurance that a WHO recommendation – formulated by drawing on epi impact data from at least two trials deploying a 'first-in-class' (FIC) product – applies to a 'second-in-class' (SIC) product has been identified
- At the request of MPAG, GMP – in collaboration with PQT and NTD – have explored non-inferiority trials using one or more entomological endpoints as a potential way to provide such assurance

https://www.who.int/publications/i/item/9789240017382

Background

- Pyrethroid-PBO nets were used as a case study to investigate the potential value of the non-inferiority method in experimental hut studies
- To date, no method to generate non-inferiority data or to translate such data into decisions has been adopted by WHO

	Session 2	Open	
14:15 – 14:45	Update on technical consultation on non-inferiority evaluation of vector control tools	Dr Jan Kolaczinski	For decision



Technical Consultation: Aim & Objectives

2nd Technical consultation held from 31 August – 2 September 2021

Aim: To formulate recommendations to WHO on next steps regarding the use of non-inferiority assessments in the area of vector control evaluation

Objectives:

1) To determine whether or not there is value in the use of non-inferiority assessments based on datasets generated for pyrethroid-PBO nets
2) To identify the advantages, disadvantages and potential challenges associated with the use of a non-inferiority study design and with the interpretation of data generated by such studies
3) Where appropriate, make specific suggestions on how the identified challenges could be addressed and on improvements to the current protocol/methods, as well as on research gaps
4) To suggest way in which non-inferiority data could be made public, if the method were to be adopted as standard practice

Summary Recommendations (1)

- Non-inferiority studies can provide the required assurance to extend a WHO recommendation to SIC vector control products and should be adopted as a general procedure.
- Mortality is to be used as the primary endpoint where the primary entomological mode of action is the killing of mosquitoes.
- Blood-feeding is to be included as a secondary endpoint, but there is no requirement for non-inferiority analysis.
- For intervention classes with other entomological modes of action other endpoints should be used to inform a non-inferiority assessment.

Summary Recommendations (2)

- For ITNs, unwashed and 20-times washed nets should be tested. The results of both should be reported; primary analysis to be performed on the combined results.
- The primary endpoint should be calculated based on data for the dominant vector species (or species complex) only.
- A minimum of two independent trials are needed, ideally from different geographical regions. Data from each trial should be analysed separately.
- Non-inferiority needs to be demonstrated in at least two trials. If results from one of the two trials are inconclusive or show inferiority, a third trial is required.

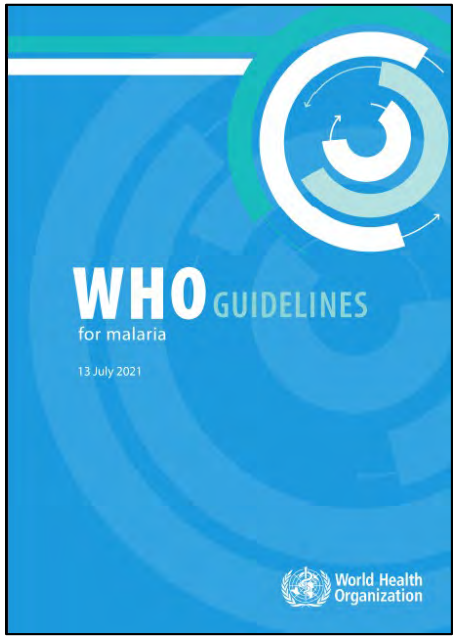
Summary Recommendations (3)

WHO should:

- Update the study protocol for ITNs / IRS
- Provide guidance to manufacturers/researchers on endpoints to evaluate non-inferiority of products in other classes.
- Develop a course on non-inferiority evaluation in the context of vector control that should be made available as an online resource.
- Promote training in appropriate statistics.
- Clearly define the process to be used for non-inferiority assessments and who within WHO will be responsible for overseeing it.
- Ensure alignment/complementarity with the data requirements and data generation for the WHO prequalification process.
- Develop a new or expand an existing online platform to facilitate non-inferiority trial data entry, sharing of results and secondary analysis by third parties.

Conclusions

- Based on the above criteria, all of the pyrethroid-PBO net products evaluated in the two non-inferiority trials – namely PermaNet 3.0, Tsara Boost and Veeralin – are considered to have met the requirement of demonstrating non-inferiority to Olyset Plus.
- WHO should consider all of these products as part of the same intervention class and as covered by the conditional recommendation for pyrethroid-PBO nets published in the consolidated guidelines for malaria (https://app.magicapp.org/#/guideline/5438).



Research Gaps

Measurement of endpoints

- Understand how deterrence should be better measured and interpreted and how the phenomenon influences the assessment of ITN effectiveness.
- Performance of pyrethroid-PBO nets in West Africa: Pyrethroid-PBO nets showed relatively poorer performance in the West African trial. A randomized controlled trial may need to be performed in West Africa to assess the impact of these nets in the region.

Durability

- How should durability of products under field conditions be factored into the evaluation?

Malaria Policy Advisory Committee Meeting

4—7 October 2021, Geneva, Switzerland
Background document for Session 2

Technical consultation on determining non-inferiority of vector control products within an established class

31 August–2 September 2021, Geneva, Switzerland, virtual meeting

Advance copy prepared for the 20th meeting of the Malaria Policy Advisory Group – the final report will be published in the coming weeks.

Contents

Acronyms

AI	active ingredient
EHT	experimental hut trial
FIC	first-in-class
GLP	Good Laboratory Practice
GMP	Global Malaria Programme
ITN	insecticide-treated net
MFO	mixed function oxidase
MPAG	Malaria Policy Advisory Group
PBO	piperonyl butoxide
PQT/VCP	(WHO) Prequalification Team for Vector Control Products
SIC	second-in-class
WHO	World Health Organization

Opening remarks and welcome

Dr Pedro Alonso, Director of the World Health Organization's Global Malaria Programme (WHO GMP), welcomed participants and observers to this important meeting. He highlighted that determining the non-inferiority of vector control products continues to be an important topic on the agenda of the Malaria Policy Advisory Group (MPAG). The importance lies in providing reassurance that second-in-class (SIC) products perform at least as well as the first-in-class (FIC) products for which epidemiological impact data informed WHO's original recommendation for that intervention class. At its biannual meeting in April 2021, MPAG highlighted the need for continued investigation into the potential value of non-inferiority study.

Dr Alonso thanked all those serving as members and temporary advisors in the technical consultation for their support of WHO's work.

Declarations of interest

Prior to the meeting, Dr Jan Kolaczinski, Head of the Vector Control & Insecticide Resistance Unit of GMP, assessed the Declarations of Interest submitted by members of the technical consultation. Based on the assessment, it was decided that none of the declarations constituted conflicts of interest in this context and that the considered experts could participate in the meeting, subject to the public disclosure of their interests. The Statement of Declarations of Interest was read out at the meeting and is provided here in Annex 1.

Proceedings of the meeting

The technical consultation was convened from 31 August to 2 September 2021, virtually on the MS Teams platform. The meeting was attended by eight members, six participants and 11 observers, plus WHO staff. The open sessions of the meeting (Days 1 and 2) were open to all meeting participants. During the open sessions, results of the trials in question were presented and deliberated, as was secondary analysis based on these trial results. The secondary analysis was performed with the aim of responding to specific questions regarding the design and analysis of non-inferiority trials that would benefit from additional clarity and/or guidance from WHO. The final day of the meeting was a closed session, attended only by technical consultation members and the WHO Secretariat.

Background, objectives and expected outcomes

The WHO vector control evaluation process transitioned from WHOPES to the Prequalification Team for Vector Control Products (PQT/VCP) in 2017. The evaluation process has continued to evolve, with the latest guidance published in late 2020 in the form of a document entitled *Norms, standards and processes underpinning development of a WHO recommendation on vector control.* [1] This document outlines the two parallel pathways of the process: One is designed to assess new (FIC) interventions and guide the generation of epidemiological impact evidence to enable such assessment. The other pathway is designed

[1] Norms, standards and processes underpinning development of a WHO recommendation on vector control. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/bitstream/handle/10665/338030/9789240017382-eng.pdf).

to confirm the safety, quality and entomological efficacy of all vector control products, irrespective of whether they are FIC or SIC, with the aim of supporting WHO prequalification and an associated listing.

SIC interventions are not required to demonstrate epidemiological impact, and hence it remains unclear whether their impact in the field against the target disease(s) is at least equivalent to that of the FIC product that established the intervention class. MPAG therefore requested WHO to investigate whether assessments of non-inferiority of SIC products based on entomological endpoints could provide some form of reassurance that impact under field conditions is likely to be as good as that of the product for which epidemiological impact data are available.

In late 2018, WHO published a notice of intent on the potential introduction of non-inferiority assessment as part of the vector control evaluation process and posted a draft protocol for public consultation. This study protocol was designed to generate data to inform an assessment of the potential value of non-inferiority trials as part of the vector control evaluation process. Based on public feedback, the study protocol was finalized in early 2019 and trials were conducted thereafter.

The goal of the present meeting was to evaluate the data generated by these two trials and to formulate a recommendation to WHO on the next steps regarding the use of non-inferiority assessments in the vector control evaluation process. The recommendations will be presented to MPAG for their decision in October 2021. The meeting objectives were to:

- determine whether there is value in the use of non-inferiority assessments based on the datasets generated for pyrethroid-piperonyl butoxide (PBO) nets;
- identify the advantages, disadvantages and potential challenges associated with the use of a non-inferiority study design and with the interpretation of data generated by such studies;
- where appropriate, make specific suggestions on how the identified challenges could be addressed and on improvements to the current protocol/methods, as well as on research gaps;
- suggest ways in which non-inferiority data could be made public, if the method were to be adopted as standard practice.

Particular points for discussion that were identified prior to the meeting are listed below. A summary of the discussions around each of these points is presented in Part II of this report.

- In the case of pyrethroid-PBO nets, should mosquito mortality **and/or** mosquito blood-feeding inhibition be adopted as study endpoints?
- Should these endpoints be measured and evaluated using unwashed (new) nets, nets that have been washed 20 times (as per standard WHO requirements), or a combined measure using washed and unwashed nets?
- What statistics are best used to assess outcomes against the established non-inferiority margin: odds ratio, relative risk, absolute differences in risk, or a combination/sequence of these measures?
- What should be the criteria and/or process to pool data derived from different study sites?
- What should be the process to ensure sufficient statistical power in the study, e.g., interim, blinded analyses?
- How should durability of products under field conditions be factored into the evaluation?

Part I: Presentations of data on pyrethroid-PBO nets

PQT/VCP review and analysis of the chemistry and manufacturing of pyrethroid-PBO nets

The PQT/VCP provided an update on the status of the product review and some key findings from the analysis. The prequalified products reviewed included six ITNs containing a pyrethroid co-formulated with the synergist PBO. These products were also included as part of the non-inferiority experimental hut trials (EHTs). Interceptor G2 and Royal Guard were also included in the product review, along with relevant submissions currently under assessment (DuraNet Plus 2.0).

The product review was initiated in March 2020 with the purpose of complementing other ongoing efforts in the sector to investigate/research the performance of these specific ITNs. One example is the non-inferiority pilot.

The first phase of the PQT/VCP review of these products focused on the formulation chemistry and manufacturing processes used in the development of these vector control tools. An ITN is a complex product that combines a specific chemical formulation with a delivery mechanism (net), which is then subjected to harsh conditions and relatively uncontrolled processes from the time of manufacture through to distribution to communities and long-term use in the field. Formulation chemistry, manufacturing processes and information on the materials used in the product manufacture are key elements informing the performance of ITNs. Understanding the chemistry and manufacturing information provides the baseline data/information necessary to define the products and address any issues, such as perceived product failure, quality control issues, chemical and physical durability, etc. Historically, the WHO assessment of chemistry and manufacturing data and information has been limited to the evaluation of data to establish product specifications.

The product review involved an assessment of all relevant data submitted previously to WHO, e.g., WHOPES reports, and the additional data requested in the data call-in letter sent by PQT/VCP to manufacturers in March 2020.

The assessment focused on the description of the manufacturing process, identifying the steps that are critical to the product manufacture and assessing the details provided with respect to the chemical formulation (including active ingredient [AI] sources), masterbatch formulations and process of applying the chemical formulation to the net material. Details of the processes in place, data requested and assessment findings are available in the presentation.

The next step in the product review will be to link the information gleaned from this assessment to bioefficacy data requirements and combine these into data requirements that provide a better understanding of the mechanisms involved and the product performance, both from a chemical and physical perspective.

This product review will inform a number of ongoing projects involving ITNs, namely the development of ITN guidelines, revised data requirements, testing methods, quality assurance/quality control, specification development, post-marketing surveillance, inspections, enhanced use of products in the field, clarity on appropriate transport and storage conditions, differentiation of product shelf-life and intended useful life, and the non-inferiority pilot.

Presentations of non-inferiority trial data from experimental hut trials

The assessment of pyrethroid-PBO nets in two EHTs included a number of net products (the same products were evaluated in both studies). The nets were assessed in two sites: Ifakara, United Republic of Tanzania and Mbe, Côte d'Ivoire. The study protocol guiding both studies was published in 2019.[2]

Role in comparison	Net name	Manufacturer	Chemistry	Trials
Untreated control				United Republic of Tanzania & Côte d'Ivoire
Pyrethroid control	Olyset	Sumitomo	Permethrin	United Republic of Tanzania only
Pyrethroid PBO – A	Olyset Plus	Sumitomo	Permethrin + PBO	United Republic of Tanzania & Côte d'Ivoire
Pyrethroid PBO – B	Tsara Boost	Moon Netting	Deltamethrin + PBO	United Republic of Tanzania & Côte d'Ivoire
Pyrethroid PBO – C	PermaNet 3.0	Vestergaard	Deltamethrin + PBO	United Republic of Tanzania & Côte d'Ivoire
Pyrethroid PBO – D	Veeralin	VKA Polymers	Alphacypermethrin + PBO	United Republic of Tanzania & Côte d'Ivoire

Sarah MOORE presented the non-inferiority trial conducted in the United Republic of Tanzania. Having outlined the study design, she detailed the specific approach taken to allow nets to regenerate after washing, how nets were stored, and the verification of net efficacy using the cone bioassay and tunnel test prior to the start of the study.

The EHT tested the non-inferiority of each candidate PBO net relative to the FIC, Olyset Plus. The six treatment arms were evaluated over 36 nights in 24 huts. Unwashed and washed nets of each arm were paired and allocated to two hut pairs, and volunteers were also paired. Two huts per net condition were used. Measures were taken throughout the study to reduce bias, which included concealment, randomization (random allocation then sequential rotation of treatments), investigator bias (by using a predefined analysis plan), and study conduct (two huts per treatment arm, and study oversight by an independent quality assurance team). Data were entered weekly, with double data entry to ensure consistency.

The study investigated two primary endpoints: the proportion of mosquitoes dead after 24 hours, and the proportion that were blood-fed. Secondary endpoints investigated in the study included induced exophily, deterrence, personal protection, and blood-fed and alive (combined measure of feeding and mortality). A priori estimates of statistical power were met by obtaining more than 20 mosquitoes per hut per night. The dominant species was *Anopheles arabiensis*, which was the focus of these analyses, but *An. funestus* also contributed a small proportion. An analysis combining both species was later presented (see Part II of this report).

[2] Data requirements and protocol for determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established WHO intervention class. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/rest/bitstreams/1161935/retrieve).

For the mortality endpoint, all of the candidate PBO nets were shown to be non-inferior to Olyset Plus, for both the washed and unwashed time points. Odds ratios were in the direction of higher mortality for candidate nets. With regard to blood-feeding inhibition, all treated nets reduced blood-feeding rates to less than 6% compared to the rate for the untreated net of 20%. However, none of the candidate nets were shown to be non-inferior to Olyset Plus; all confidence intervals crossed the non-inferiority margin. The large confidence intervals resulted from the small number of blood-fed mosquitoes collected (itself a sign of efficacy), which made it more difficult to attain success. However, relative to the untreated net, an over 70% reduction in blood-feeding occurred in both the pyrethroid-only arm and the pyrethroid-PBO arms.

Overall, the trial demonstrated that it was possible to complete non-inferiority assessments of multiple nets in an EHT in 36 nights by using 24 experimental huts. Results of the trial showed evidence of non-inferiority of the candidate PBO nets to the FIC and enhanced mosquito mortality in all PBO arms, both unwashed and 20-times washed. Therefore, the results support the conclusion of public health value based on epidemiological data on PBO nets from randomized controlled trials.

Raphael N'GUESSAN presented the equivalent results from the non-inferiority trial conducted in Mbe, Côte d'Ivoire. The study site represents a large rice-growing area, which is productive throughout most of the year. The main malaria vector in the area is *An. coluzzii*. These populations are highly resistant to pyrethroids, DDT, organophosphates and carbamates, with intensity of resistance to deltamethrin showing 160-fold resistance.

The study investigated the same two primary endpoints as the trial in the United Republic of Tanzania, yielding estimates of the proportion of mosquitoes dead after 24 hours and the proportion that were blood-fed. The study had 11 treatment arms, tested within a simple Latin Square design, which required 11 weeks to perform one full rotation. Due to an observed low number of mosquitoes during the first rotation, the blinded data were sent to Imperial College for assessment of statistical power. With only ~six mosquitoes/hut/night observed after the first rotation, it was determined that another full rotation was needed to have enough statistical power for the study. Following the completion of the two rotations, mean numbers of mosquitoes rose to just above 10. Blood-feeding inhibition levels by PBO nets varied from 46% to 74%. Resistance of *An. coluzzii* in the Mbe area impacted the overall killing power of all PBO-based nets (<22% mortality).

Supplementary assays were completed, including cylinder tests of the constituent AIs in the ITNs with and without PBO, as well as the WHO cone bioassay before and after the hut trials. The cylinder assay confirmed that there was significant resistance to pyrethroids at the Mbe site, with PBO only restoring pyrethroid activity from 6–9% to 22–34% mortality of mosquitoes.

Similar to the study in the United Republic of Tanzania, results demonstrated that none of the candidate nets were shown to be non-inferior to Olyset Plus on the blood-feeding inhibition endpoint. Only after 20 washes was Veeralin deemed non-inferior to the active comparator, Olyset Plus. By contrast, mosquito mortality induced by the unwashed candidate nets was comparable, and all were deemed non-inferior. For washed nets, only Veeralin was non-inferior; inconclusive results were obtained for the other candidate nets.

Part II: Lessons learned from non-inferiority trials and discussion on the potential utility of the method

Overview of lessons learned from non-inferiority trials

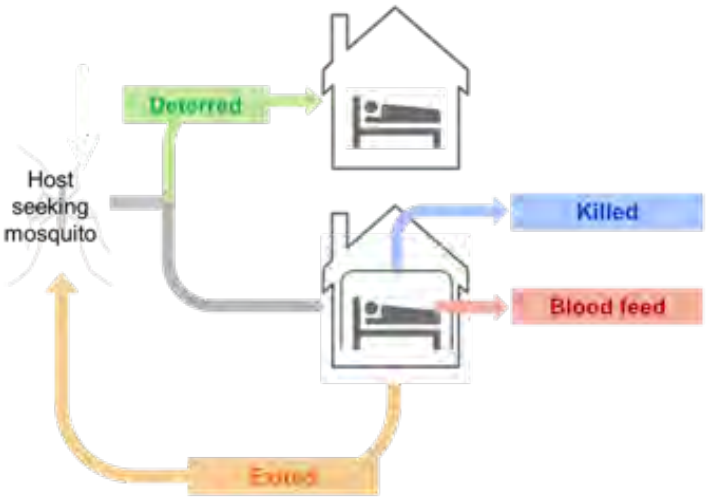
Joseph CHALLENGER presented a secondary analysis of the data obtained from the trials in both the United Republic of Tanzania and Côte d'Ivoire. Outcomes considered in these studies were whether mosquitoes were killed, blood fed, or deterred from hut (see Fig 1.). The analysis was conducted to gain a broader understanding of the variability in the observations, statistical power achieved, and overall implications for the adoption of non-inferiority studies for vector control interventions, using PBO nets as the first example. The analysis considered the following factors:

- number of mosquitoes entering the huts over the course of the trial
- trial duration (number of data points per arm)
- magnitude of sources of variation present (between-hut variation)
- the non-inferiority margin selected.

Data related to unwashed nets, washed nets, and both estimates combined, were analysed for the four treatment arms. The analyses showed consistent trends (with minimal aberration) in the point estimates of the results for each net type, indicating that washed nets had a lower efficacy (expectedly). This finding was consistent across studies, despite the different numbers of mosquitoes collected.

A meta-analysis of 10 trials was performed to try to understand the sources of variation. Sources of variation included the huts and sleepers rotating between the huts each night. Additionally, non-specified variance (i.e., variation that cannot be accounted for by any of the variables in the model) was also considered. This source of variation was the greatest.

Fig. 1. Schematic illustration of the possible outcomes for host-seeking mosquitoes in the EHTs (Credit: Tom Churcher, Imperial College London)



The study in the United Republic of Tanzania employed 24 huts to conduct four simultaneous 6x6 Latin Squares. The study achieved 90% statistical power to be able to detect non-inferiority (should it exist), with a mean of more than 20 mosquitoes collected per hut per night. For the study in Côte d'Ivoire, the

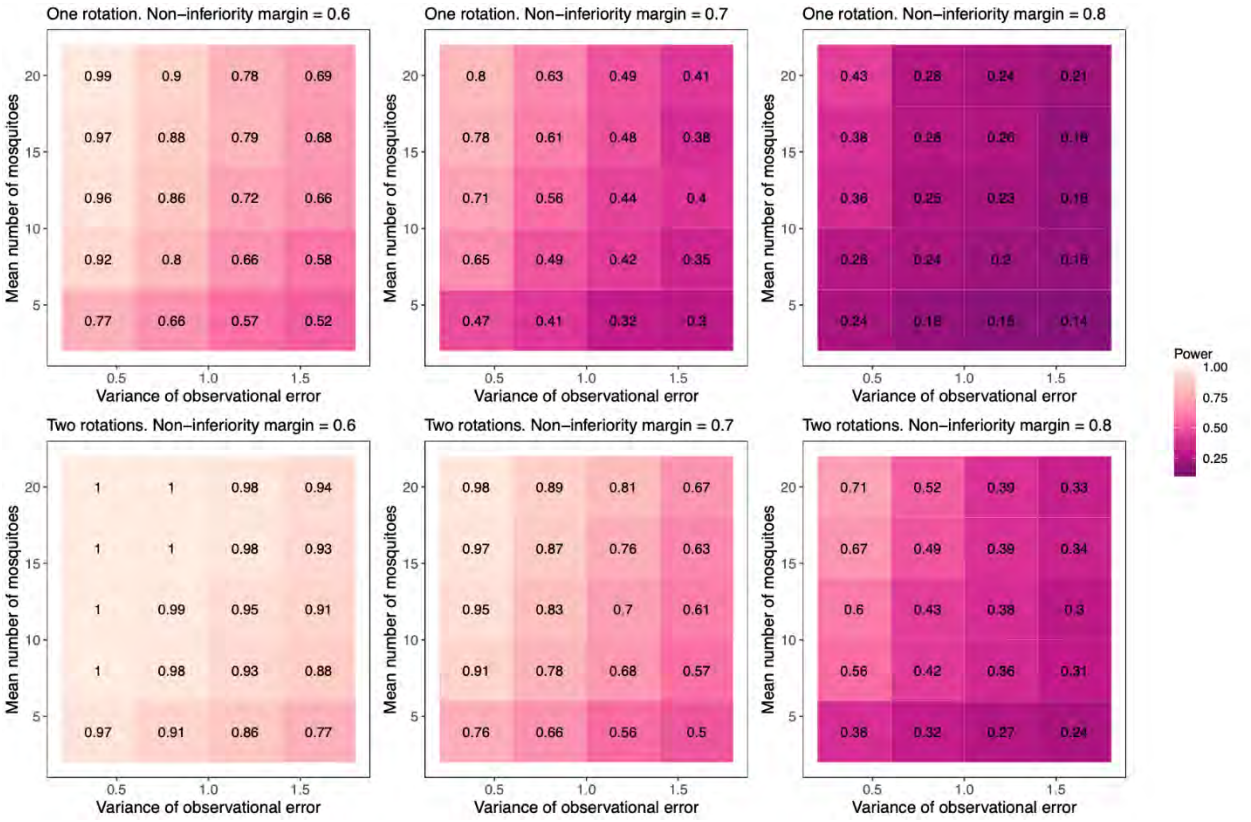
study required two rotations of the Latin Square, given that there were fewer mosquitoes entering the huts in this study (<10 per hut per night). The second rotation enabled the study to sustain 89% power to detect non-inferiority.

Higher mortality was noted in the Tanzanian dataset than in the Ivorian dataset. This could be attributed to a different representation of species, different resistance profiles between the sites and/or differences in hut design. Combining the data from both sites, all candidate arms of the trials were deemed non-inferior with respect to mortality.

Overall, the study in Côte d'Ivoire saw higher blood-feeding than the one in the United Republic of Tanzania. When looking at blood-feeding inhibition as the endpoint, combined data from the two sites showed that no candidate could be identified as being non-inferior to the active comparator. Indeed, due to Olyset Plus's high efficacy in relation to blood-feeding inhibition, the active comparator generally had lower blood-feeding compared to all candidate nets.

It was observed that because of the wide confidence intervals for the odds ratios in relation to mortality and blood-feeding inhibition, some studies could have been underpowered to detect true differences. A simulation was conducted to illustrate how changing several variables (one/two rotations, non-inferiority margin from 0.6 to 0.8, mean number of mosquitoes ranging from five to 20 and variance in observational error) can cause the power to fluctuate from 0.14 to 1.0 (see Fig. 2). The simulation illustrates how easy it is to drop from acceptably powered studies to those that are unacceptable, with only minor changes to these factors.

Fig. 2. Simulation of resulting power estimates in EHTs when multiple factors are allowed to vary, including the non-inferiority margin, variance in observational error, number of rotations, and mean number of mosquitoes captured per hut per night. Numeric values for the power estimates will further depend on experiment-specific factors such as the trial design and the magnitude of mosquito mortality observed (Credit: Joseph Challenger, Imperial College London)



It was emphasized that power assessment of an EHT can be repeated during the first few weeks of the trial in order to make an on-the-spot decision as to whether more time is needed to assess the efficacy of the treatment arms. Making the decision to prolong the trial while it is underway may reduce costs overall and simplify the analyses, compared to having to initiate another trial (starting over, rewashing nets, etc.) and needing to control for this as a variable in the final analysis of the intervention. Such an analysis can be performed effectively while the trial is still being conducted, *without* unblinding the trial.

Tom CHURCHER walked the participants through some of the implications that one must consider in relation to the implementation of non-inferiority assessments. Questions were posed in light of what considerations might be necessary moving forward, and how the implementation of non-inferiority assessment would impact changes in policy, bearing in mind that the protocol of the two trials was indeed a provisional protocol. These trials were intended to be the foundation for discussion, leading potentially to the refinement of the protocol for non-inferiority assessments.

It was highlighted that over the last 30 years, observations of mortality in trials have decreased[3] (likely as a result of increased prevalence of insecticide resistance in mosquito populations). By contrast, similar changes in blood-feeding inhibition have not been observed over this time; this observation is possibly impacted by the long-term practice of making artificial holes in the netting in order to assess mosquito feeding capacity. It therefore does not reflect the personal protection one receives from a new net and is unlikely to accurately reflect the durability of a net overall.

The question was then raised of which endpoints should be used to measure the efficacy of nets. To illustrate the potential for variation in this measure, a comparison of the data from the two trials in question was presented. Both studies demonstrated data that were consistent in direction, but the magnitude of the reduced impact following 20 washes differed among nets.

Given the high bar set by Olyset Plus in terms of personal protection from blood-feeding, candidate SIC nets were challenged to demonstrate non-inferiority against the active comparator. It becomes difficult to certify the non-inferiority of an intervention against a high-performing FIC intervention when odds ratios are used, and small differences observed are indeed unlikely to have a significant epidemiological impact. Alternatively, one could employ the relative risk or absolute differences in risk, or even set a post-estimate threshold that cannot be exceeded to be deemed non-inferior. Programmatically, the personal protection offered by the candidate SIC nets was actually very good, and there would be little difference in terms of operational importance whether one is selected over another.

There was discussion of variation in study sites, in terms of East and West African geography and associated species composition and epidemiology, and how one should interpret the results of discordant trials in terms of net efficacy when it comes to making procurement decisions. Differences in species between sites could also influence results. Breaking down the data, one could consider species-specific effects that could explain site-specific variation, but, in doing so, one would also lose statistical power. The question was raised of whether trials should be repeated in the event of negative outcomes or whether an overall positive result could be identified following pooling, and how this might influence any potential requirements for repeating studies. Repeating studies while trying to reach the desired outcome could be viewed as cherry-picking results.

In preparing for the trial, obtaining the active comparator for assessment may not always be possible. The FIC intervention might be hard to source for reasons of availability or more likely competition, if the manufacturer is unwilling to see its product tested against other products. Alternative options for using SIC active comparators were offered, and the benefits and challenges of each option were noted. The major issue is that if one is free to choose the active comparator, it will be beneficial to always select the lowest performing comparator, thus making it easier to determine non-inferiority.

Two factors influencing the likelihood of determining non-inferiority were also raised. The first was related to the number of mosquitoes captured per hut per night, because smaller numbers increased the confidence intervals of the odds ratios, making it harder to clearly designate a candidate net as being non-inferior. Related to this point, the second issue raised was that of mosquito deterrence from huts. Where the presence of a net actually deters a mosquito from entering a hut, the nightly capture rate will be

[3] Nash RK, Lambert B, Guessan RN, Ngufor C, Rowland M, Oxborough R. Systematic review of the entomological impact of insecticide-treated nets evaluated using experimental hut trials in Africa. Diseases. 2021;1:100047. doi:10.1016/j.crpvbd.2021.100047.
https://www.sciencedirect.com/science/article/pii/S2667114X21000418?via%3Dihub

lower, making it more difficult to have high enough numbers to reduce the confidence intervals. This latter point warrants further investigation of how deterrence can be more effectively measured in future EHTs.

With the necessity of having sufficient numbers of mosquitoes to reach statistical power requirements, it was suggested that a study be continued until a minimum threshold of mosquitoes has been reached. As presented above, interim calculations were indeed performed in the Côte d'Ivoire study while the data were still blinded, which allowed the duration of the study to be extended to increase the sample size. Such routine interim calculations could avoid issues of insufficient power in assessing non-inferiority.

Open discussion on the utility of non-inferiority trials to differentiate vector control products

The chair guided the meeting participants through a discussion on the multiple issues that had been raised in previous sessions, seeking viewpoints from all parties.

Study endpoints

The discussion of endpoints raised numerous views, some of them mixed. Several important points included the pertinence of two endpoints for the vectorial capacity equation, in that, the higher mortality of vectors has a greater impact on R_0 than blood-feeding; therefore, mortality should be a priority. Given that the primary mode of action of PBO is to increase killing, the assessment of the non-inferiority of pyrethroid-PBO nets should not exclude this endpoint. Practically, it is simpler to power studies to address a single endpoint, bearing in mind that secondary endpoints are not invisible and that these can have additional weight when procurers are selecting their products.

Alternative approaches suggested to the group included an "either/or" approach, in which a product could be deemed non-inferior to the active comparator in either blood-feeding inhibition or mortality. Further to this, it was suggested that, as pyrethroids affect blood-feeding inhibition, the mortality endpoint should be compared to other PBO nets, whereas the impact on blood-feeding of a pyrethroid-PBO net should be compared to a pyrethroid-only net. Finally, it was also suggested that a combined measure of mortality and blood-feeding could be devised (weighted or otherwise), thereby allowing a single measure and easier calculations of sample size.

At the same time, the point was made that it is mosquito biting that has a direct relevant impact on public health because without biting, transmission cannot occur. It was also noted that adherence to net usage by the public is strengthened by the personal desire for protection again bites.

Active comparators: What if the FIC is not available, what do we do?

When there is more than one net in an intervention class, it will be necessary to determine which net(s) can be used to determine non-inferiority moving forward. The risk is that if the active comparator changes each time, for each consecutive assessment, the bar changes (normally being lowered). Therefore, it is better to have the same comparator used across the board. However, the accessibility of the nets could be a challenge. All manufacturers are encouraged to make their nets available for testing, rather than obstructing the potential for more products to become available on the market, which is in the global interest. FIC nets clearly offer the ultimate comparator, as they are the nets that have demonstrated epidemiological evidence against the target disease. If this FIC net is not available, an SIC net that has epidemiological evidence associated with it should be the next best option. For example, PermaNet 3.0 also has epidemiological data associated with it, so it would be the next best option.

Using best in class nets is also an option in the case that an SIC net has actually outperformed the FIC. However, if the best in class was actually superior to the FIC, it would be (perhaps unfairly) hard for

suppliers to demonstrate non-inferiority if they were unable to get hold of the FIC. Therefore, it was suggested that the most similar net to the FIC should be an option for the alternative.

Pooling of data

Discussion was held about when it is acceptable and practical to pool data in relation to species data, data related to washed and unwashed nets, and data from different trial sites.

Species: For species data, given the different compositions of species at sites, profiles of resistance and mechanisms, there was a push to avoid pooling data. Current recommendations are to test the dominant vector, but this may pose problems when molecular characterization is necessary and in places where there are numerous dominant vectors. Therefore, an overall estimate of efficacy by pooling species data also holds value.

Sites: For study site data, numerous participants shared the view that, given the differences between sites, one should always view the data from a trial by itself as a standalone result, before any consideration is given to pooling data. This is especially true when trials show opposing trends between sites. Alternatively, those in favour of pooling argued that pooling allows one to more easily generalize results as to the efficacy of the net. Discussion followed that any pooling of data could be performed in a formal meta-analysis, and weighted means were considered so that smaller trials would contribute appropriate weight.

Another point raised was on the issue of site selection, as it is also key that the site should have pre-exposure assay data available; the Côte d'Ivoire site had strong recent indications of mixed function oxidase (MFO)-driven resistance before the trial started – based on overexpressed CYP6P3. Considering such information in site selection could aid in the determination of efficacy.

Washed and unwashed nets: For washed and unwashed data, participants again felt that each measurement in and of itself provided valuable information and so should not be automatically combined, despite the increased power that this would provide for the trial. Nevertheless, considering the lifespan of a net, having an overall estimate of how it performs at the start and at the end of its life was deemed more representative of how it might perform in the field. The decision of whether to report pooled or individual data for the unwashed/washed nets will influence power calculations.

PQT data assessments currently use only the performance of nets following 20 washes, and so such consistency between requests for data should be considered.

Odds ratios for non-inferiority criteria

The issue of non-inferiority assessments using odds ratios was raised in light of the high benchmark for blood-feeding inhibition set by Olyset Plus, although this applies to any non-inferiority assessment in which the reference arm is very high or very low. When the standard set by the FIC arm is high (whether it be for mortality, blood-feeding or another endpoint), the probability of the SIC candidate passing will be influenced; as such, use of the odds ratio may not be ideal. Alternative statistics discussed by the group as being potentially acceptable were prevalence ratios or setting a standard cut-off that the SIC candidates must pass.

Regeneration time of nets following washing

The difference in regeneration time between nets was considered an important factor in planning an EHT using washed nets. The compositions of nets differ with respect to both the AIs and the chemistry. As

such, it is important to ensure that one allows sufficient regeneration time to maximize the efficacy of the nets after each wash.

Blood-feeding and mortality estimates may also be altered because the migration of each chemical back to the surface of the netting may differ. It was also discussed whether the rate of regeneration within a net may change over time as a result of depleted reservoirs within the material; in effect, migration time could increase as the net ages (or if it is washed more).

Where adoption of any non-inferiority assessment occurs, the testing protocol should ensure that instructions are provided (perhaps this should be the responsibility of manufacturers) to ensure that the investigators testing the nets employ the correct regeneration time for each net. Applying a strict seven-day regeneration time for all nets means that it would take six months to one year to do a study; however, if there are no nets that take seven days to regenerate included in the study, there should be no need to require this seven-day regeneration time. This may encourage manufacturers to consider how to optimize the migration of chemicals back to the surface to reduce regeneration time.

Usefulness of the process on non-inferiority

Overall, it was deemed that non-inferiority assessments have value. End-users felt that it was a straightforward assessment using existing methods and a priori consideration of power estimates is valuable to ensure high-quality data. It was mentioned that the protocol would benefit from being adapted to ensure guidance on powering trials well. The weight of evidence for other endpoints should also be considered.

Further to this point, guidance could be included in the protocol or more generally using an online platform (such as MTM), or regular training on appropriate statistics could be offered to make sure that all investigators are able to analyse the trials appropriately. This would also help build capacity at the sites. Otherwise, collaborations could be sought.

Capacity-building

Should there be a WHO requirement for all SIC nets to undergo non-inferiority assessment (and perhaps expanded to other intervention classes beyond nets), there would be a need to ensure that the infrastructure was adequate. General capacity-building at the level of hut construction and maintenance was discussed, with the recognition that more huts would enable larger trials (whether this means more arms to a trial, or fewer rotations with a smaller number of arms) and more rapid results. The added benefit of this is that shorter trials are also less subject to temporal fluctuations in mosquito density or species composition over a season.

Statistical support, whether it be in the form of supporting collaborations or online platforms, to support the automation of appropriate statistical approaches was also discussed. Regular training or workshops could be developed and offered to investigators, designed with specific curriculum relevant to their trials.

Part III: Conclusions and recommendations in the closed session

The closed sessions of the meeting involved only the designated members of the technical consultation, exclusive of all industry observers and temporary advisors. The members reviewed and deliberated on the points from the previous days' discussions and agreed on the following formal recommendations on the value of non-inferiority assessments for SIC products within an established intervention class.

Major recommendations

Value of non-inferiority studies

- Non-inferiority studies have value in determining whether SIC products should be covered by a WHO recommendation formulated for an FIC product. The approach should be adopted as a general procedure across vector control interventions, not limited to pyrethroid-PBO nets.
- To implement the approach routinely, however, the non-inferiority protocol will need updating to reflect the specific points outlined below.

Endpoints

- Mortality is to be used as the primary endpoint for pyrethroid-PBO nets and for other products whose primary entomological mode of action is the killing of mosquitoes. Mortality results should be used to make the ultimate decision regarding non-inferiority of a product and its inclusion under a WHO recommendation for an intervention.
- For this and other intervention classes with similar entomological modes of action, blood-feeding is to be included as a secondary endpoint to assist in informing programmatic and procurement decisions. For the secondary endpoint, there is no requirement for the use of a non-inferiority margin or for non-inferiority analysis. The investigators should report the percentage of blood-fed mosquitoes for each net, with a confidence interval and p-value. A comparison to a standard reference product (in this case a pyrethroid-only net) should also be presented. This information will enable the reader to interpret these results in the context of the non-inferiority results for the primary endpoint.
- For intervention classes with other entomological modes of action, such as sterilization, other endpoints should be used to inform a non-inferiority assessment. WHO should provide guidance to manufacturers/researchers on what endpoints are relevant to evaluate the non-inferiority of products in other classes.
- For ITNs, unwashed and 20-times washed nets should be tested. The results of both should be reported, with the primary non-inferiority analysis performed on the combined results of both time points.
- The primary endpoint should be calculated based on data for the dominant vector species (or species complex) only. A secondary analysis should be performed on data pooling all species.

Number of trials

- A minimum of two independent trials are needed, ideally from different geographical regions. Data from each trial should be analysed separately.
- To be classified as non-inferior, the candidate product must be deemed non-inferior in at least two trials. If results from one of the two initial trials are inconclusive or if one of the trials demonstrates inferiority, a third trial should be conducted to inform a final decision regarding the inclusion/exclusion of a product within an intervention class. If a candidate product does not demonstrate non-inferiority in two out of three trials it will be deemed to not meet the non-inferiority criterion compared to the FIC product and should not be considered as covered by a WHO recommendation for the applicable intervention class.

Non-inferiority margin

- Analyses of non-inferiority for the primary endpoint should be calculated using odds ratios of the proportion of mosquitoes killed. In the case of pyrethroid-PBO nets, the candidate net should be compared to the FIC net (or a suitable alternative [see below]), using a non-inferiority margin of 0.7 for the odds ratio, reported with the corresponding 95% confidence interval.

Selection of active comparator

- Primary option: the FIC product, if it can be sourced (e.g., Olyset Plus for evaluation of pyrethroid-PBO net products).
- Second-best option: any SIC product for which epidemiological evidence is available (e.g., PermaNet 3.0 for evaluation of pyrethroid-PBO net products).
- Third-best option: a product that has shown superiority to the FIC in the primary endpoint. If superiority is shown by any SIC product, it would be acceptable as an active comparator.
- Fourth-best option: In the event that no SIC product has shown superiority to the FIC product, the best performing product among the SIC products should serve as the comparator.
- The study report must provide a justification for why a specific comparator product was used in the trials.

Statistics

- To ensure valuable return on investment, statistics support will need to be sought for development of the detailed study protocol and for data analysis.
- Statistical analysis of the data must be done using a logistic regression model with fixed effects for the brand of net, hut, sleeper, night and number of washes.
- A priori power calculations are required.
- It is strongly recommended to conduct at least one blinded interim analysis to assess if the assumptions underlying the power calculations are verified. If the assumptions are not verified, the planned size of the study may need to be adjusted. A suitable point for an interim analysis would generally be after one full rotation of products and sleepers. Investigators planning to conduct an interim analysis should include reference to this in their study protocol.
- Simulations using mathematical modelling may be used to support study design.
- It is recommended that WHO develop a course on non-inferiority evaluation in the context of vector control evaluation. The course should be made available as an online resource to support investigators in the design and analysis of these types of trials.
- Lastly, WHO should promote training in appropriate statistics for the analysis of data from this type of experimental design.

Non-inferiority and prequalification assessments

- WHO should clearly define the process to be used for non-inferiority assessments and who within WHO will be responsible for overseeing it. Alignment/complementarity with the data requirements and data generation for the WHO prequalification process is needed.

Minor recommendations

General

- The protocol will need to be adapted for interventions with different entomological modes of action (e.g., change in endpoints used to determine non-inferiority).

Registration of trials

To avoid cherry-picking of positive trial results, all trials should be registered in a registry prior to starting.

- Proposal: Tests can only be done at Good Laboratory Practice (GLP)-accredited sites or, in the interim, performed according to GLP standards at sites undergoing certification. Sites are responsible for registering studies in their own registry in an attempt to avoid failure to report negative trial outcomes. Other mechanisms to provide such transparency should be explored, analogous to the requirement for registration of clinical trials.
- Selection of test sites: Sites should be appropriate for the question being asked. Site selection should be justified based on a baseline assessment of class-relevant parameters (e.g., P450 resistance mechanisms in the case of pyrethroid-PBO nets). These should be articulated in the registry a priori and in the report. For all vector control interventions, the mosquito species composition and its insecticide resistance profile are the minimum requirements to be reported; however, these details may need to be supplemented with class-specific background information, as indicated in the example above.

Infrastructure and capacity-building

- Investment in infrastructure and training according to GLP is needed to expand site capacity in order to ensure that non-inferiority (and other) entomological studies are conducted on time and to a high standard.
- If the non-inferiority process is adopted, investment in more sites, more huts at existing sites and maintenance of sites will be necessary to support the process (not just for PBO assessments, but for other nets and other interventions as appropriate).

Data availability and sharing

- Data should be made available in sufficient detail to enable independent verification of the results reported.
- It is also recommended that WHO develop or expand an existing online platform to facilitate non-inferiority trial data entry and secondary analysis by third parties.
- WHO should investigate this in more detail (including issues relating to legalities).

Regeneration time of nets between washes

- Manufacturers need to generate this evidence as part of the data package for WHO evaluation of a vector control intervention and submit the results as part of that package.
- Regeneration time for each product should be determined at a GLP-accredited laboratory and provided as a standard for non-inferiority studies. Regeneration times already generated for the pyrethroid-PBO nets evaluated to inform the present deliberations should be used for future studies, where relevant.
- The washing interval should correspond with the regeneration time for the net in question, not a standardized seven days.

Research gaps

Measurement of endpoints

- Understand how deterrence, currently measured based on the number of mosquitoes entering intervention experimental huts relative to untreated net control huts, should be measured and interpreted and how the phenomenon influences the assessment of ITNs' effectiveness.
- Performance of pyrethroid-PBO nets in West Africa: Pyrethroid-PBO nets showed relatively poorer performance in the West African trial. The synergistic effect of PBO was also much lower in bioassays. The available evidence of the improved epidemiological effect of pyrethroid-PBO nets has so far been generated only in East Africa. There are concerns that these nets may have a different outcome in West Africa, considering the historically higher levels of pyrethroid resistance and poor synergistic effect of PBO in the region. A randomized controlled trial may need to be performed in West Africa to assess the impact of these nets in the region.

Final conclusions

Based on the above criteria, all of the pyrethroid-PBO net products evaluated in the two non-inferiority trials – namely PermaNet 3.0, Tsara Boost and Veeralin – are considered to have met the requirement of demonstrating non-inferiority to Olyset Plus.

It is recommended that WHO consider all of these products as part of the same intervention class and thus as covered by the conditional recommendation for pyrethroid-PBO nets published in the consolidated guidelines for malaria (https://app.magicapp.org/#/guideline/5438).

Annex 1. Declarations of Interest

The Malaria Vector Control and Insecticide Resistance Unit of the Global Malaria Programme held a technical consultation from 31 August to 2nd September 2021 on assessing the value of determining non-inferiority of vector control products within an established class. The meeting was a follow-up to an Expert Review Group on the same topic held by WHO on 5–6 July 2018 at the request of MPAG. The detailed deliberations of the earlier meeting, including a study protocol to guide data collection to inform further discussion on non-inferiority determination in the area of vector control, are available at:

1) https://apps.who.int/iris/bitstream/handle/10665/276038/WHO-CDS-GMP-2018.21-eng.pdf?ua=1

2) https://www.who.int/publications/i/item/WHO-CDS-GMP-2018.22

As part of the consultation conducted in 2018, WHO published a notice of intent to introduce partners to the organization's exploratory work in this area and the potential for non-inferiority determination to be adopted as standard practice in the area of vector control evaluation:

https://www.who.int/malaria/publications/atoz/non-inferiority-notice-intent-nov2018.pdf

The present meeting was convened as a follow-up to the work in 2018 to review non-inferiority datasets from two field studies on pyrethroid-PBO nets, and to formulate recommendations to WHO on whether and how to proceed. The recommendations formulated at the technical consultation will be presented to MPAG at its October 2021 meeting.

This technical consultation consisted of four categories of invitees, namely: i) 'members', including the chair, who formulated the recommendations to WHO and were each required to complete a Declaration of Interest (DOI) and Confidentiality Undertaking form; ii) participants, which in this case were the investigators who conducted the research studies or researchers who conducted additional analyses of these data; iii) observers, such as industry partners and donors; and iv) WHO staff. All invitees were able to attend the open sessions of the meeting, while only members and WHO staff were allowed to participate in the closed session.

DECLARATIONS OF INTEREST

All members completed and submitted their DOI and Confidentiality Undertaking forms. The review of the completed DOI forms identified one member as having a potential conflict of interest. The interest and its management by GMP are outlined below.

Dr Corine Ngufor is employed by the Centre de Recherche Entomologique de Cotonou, Benin, and the London School of Hygiene and Tropical Medicine. She declared receiving research support for testing of vector control products from Shobikaa Impex Private Limited, which ended in 2018, and from Moon Netting and Tainjin Yorkool International, both of which ended in 2020.

Conclusion: Given that no active research support was declared or otherwise identified by WHO and that past support was not related to the topic of discussion at the present meeting, the declared potential conflict of interest was judged to not present an actual conflict with respect to the content of the present meeting.

Annex 2. Meeting agenda

Day 1 - Tuesday 31 August 2021 3 hours		
Open Session (TC Members, Participants & WHO Staff)		
14:00 - 14:10	Opening remarks and welcome	Dr Pedro Alonso
14:10 - 14:15	Declarations of Interest	Dr Jan Kolaczinski
14:15 - 14:25	Background, objectives and expected outcomes	Dr Jan Kolaczinski
Part I: Presentation data on pyrethroid-PBO ITNs		
Open Session (TC Members, Participants & WHO Staff)		
14:25 - 15:00	PQT/VCP review and analysis of the chemistry and manufacturing of pyrethroid-PBO nets	Dr Marion Law
15:00 - 16:00	Presentation of non-inferiority trial data from United Republic of Tanzania	Dr Sarah Moore
16:00 - 17:00	Presentation of non-inferiority trial data from Côte d'Ivoire	Dr Raphael N'Guessan
Day 2 - Wednesday 1 September 2021 3 hours		
Open Session (TC Members, Participants & WHO Staff)		
Part II: Lessons learned from non-inferiority trials and discussion on the potential utility of the method		
14:00 - 15:00	Combined estimate of data from both Côte d'Ivoire & United Republic of Tanzania and possible hypotheses for differences should they appear	Dr Thomas Churcher
15:00 - 16:00	Overview of lessons learned from non-inferiority trials	Dr Joseph Challenger
16:00 - 17:00	Discussion on the utility of non-inferiority trials to differentiate vector control products within the same intervention class	Chair
Day 3 - Thursday 2 September 2021 3 hours		
Closed Session (TC Members & WHO Staff)		
Part III: Conclusions & recommendations		
15:00 - 18:00	Finalization of meeting conclusions & formulation of recommendations to WHO	Chair

Annex 3. List of participants

LIST OF PARTICIPANTS

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Discussion on malaria rebound

Malaria Policy Advisory Group (MPAG) meeting
4th October 2021

Proposed technical consultation on malaria rebound phenomenon

A period of increased malaria risk after time-limited protection from malaria (e.g., after chemoprevention, vaccination, vector control), relative to individuals of the same age who did not receive the intervention.

- Interesting immunological phenomenon, public health relevance unclear.

Investments into the development of new tools would benefit from:

- Clear expectations around the evaluation of rebound
- An agreed, standardized approach

Objectives of the review

1. Literature review of studies having evaluated rebound, drawing attention to:

    - definitions used,
    - interventions,
    - target age groups,
    - methods,
    - follow-up periods ,
    - presence/absence of rebound for different outcomes

2. Inform the discussion of how to incorporate the measurement of rebound in the design of studies evaluating new strategies or interventions.

Previous definitions that have been used:

1. Higher susceptibility to severe malaria among the recipients of a malaria-control intervention when the intervention is withdrawn as compared to contemporaneously-followed individuals in the same population who did not receive the intervention *(Joint Technical Expert Group on Malaria Vaccines, September 2015).*

2. An increase in the incidence of malaria after a period when effective malaria control has been achieved (by any means) above the incidence which would have occurred if the intervention had not taken place *(Implementation workshop on Seasonal Malaria Chemoprevention, February 2017).*

Question to be answered in the review

What happens to the rate of acquisition of naturally acquired immunity (NAI, measured through different clinical endpoints) in individuals that have been receiving a time-limited malaria control intervention when that intervention is withdrawn?

Different from "Age shift": Impact of a permanent reduction in transmission intensity on the age-pattern and clinical presentation of malaria cases.

Inclusion criteria

- Follow-up period post-intervention: at least 6 months
- Outcomes: mortality, clinical cases, severe malaria, hospital admissions

Keywords for literature search:

- rebound
- “age-shift”
- intervention “withdrawal”, “cessation”, “discontinuation”
- others?

Interventions

01 | Chemoprophylaxis
02 | SMC
03 | IPTi
04 | MDA
05 | Chemoprevention in school-aged children
06 | ITNs
07 | IRS
08 | RTS,S/AS01

Study designs

01 | Randomized controlled trials
02 | Non-randomized studies
03 | Modelling

Some examples of studies to be reviewed:

Chemoprophylaxis

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1995) 89, 629–633

Mortality and morbidity from malaria after stopping malaria chemoprophylaxis

B. M. Greenwood[1], P. H. David[2], L. N. Otoo-Forbes[1], S. J. Allen[1], P. L. Alonso[1], J. R. Armstrong Schellenberg[2], P. Byass[1], M. Hurwitz[2], A. Menon[1] and R. W. Snow[1] [1]*Medical Research Council Laboratories, Fajara, P.O. Box 273, Banjul, The Gambia;* [2]*London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK*

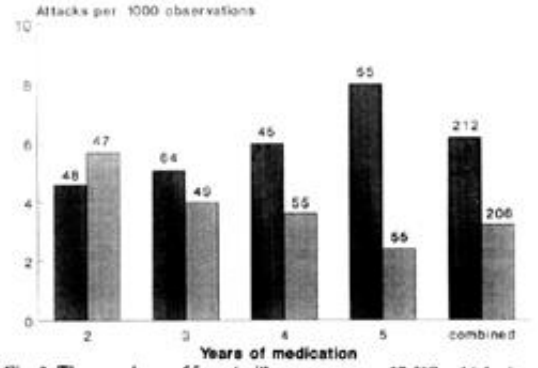

Fig. 3. The prevalence of fever (axillary temperature 37·5°C or higher) accompanied by malaria parasitaemia ('Attacks') in children visited weekly between the ages of 5 and 6 years who had received either chemoprophylaxis with Maloprim® (dark bars) or placebo (light bars) for the previous 2–5 years. Figures above the bars indicate the number of children in each group.

Fig. 1. The probability of dying from birth to the age of 7 years in a cohort of children who received chemoprophylaxis with Maloprim® (×) or placebo (+) from the age of 3 months to 5 years.

Chemoprophylaxis

THE LANCET

Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants

Clara Menendez, Elizeus Kahigwa, Rosmarie Hirt, Penelope Vounatsou, John J Aponte, Fidel Font, Camilo J Acosta, David M Schellenberg, Claudia M Galindo, John Kimario, Honorathy Urassa, Bernard Brabin, Tom A Smith, Andrew Y Kitua, Marcel Tanner, Pedro L Alonso

OPEN ACCESS Freely available online PLOS MEDICINE

Age Interactions in the Development of Naturally Acquired Immunity to *Plasmodium falciparum* and its Clinical Presentation

John J. Aponte[1,2*], Clara Menendez[1,2], David Schellenberg[1,3], Elizeus Kahigwa[3], Hassan Mshinda[3], Penelope Vountasou[4], Marcel Tanner[4], Pedro L. Alonso[1,2]

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"After the end of the intervention period, children who had received malaria chemoprophylaxis had higher rates of severe anaemia and malaria than non-chemoprophylaxis groups (relative risks 2·2 [1·3–3·7] and 1·8 [1·3–2·6])."

...and others.

SMC

OPEN ACCESS Freely available online PLoS one

Morbidity from Malaria in Children in the Year after They Had Received Intermittent Preventive Treatment of Malaria: A Randomised Trial

Amadou T. Konaté[1], Jean Baptiste Yaro[1], Amidou Z. Ouédraogo[1], Amidou Diarra[1], Adama Gansané[1], Issiaka Soulama[1], David T. Kangoyé[1], Youssouf Kaboré[1], Espérance Ouédraogo[1], Alphonse Ouédraogo[1], Alfred B. Tiono[1], Issa N. Ouédraogo[1], Daniel Chandramohan[2], Simon Cousens[3], Paul J. Milligan[2], Sodiomon B. Sirima[1], Brian M. Greenwood[2], Diadier A. Diallo[2]*

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Conclusion: IPT with SP+AQ was associated with a small increase in the incidence of clinical malaria in the subsequent malaria transmission season.

OPEN ACCESS Freely available online PLoS one

Malaria Morbidity in Children in the Year after They Had Received Intermittent Preventive Treatment of Malaria in Mali: A Randomized Control Trial

Alassane Dicko[1]*, Amadou Barry[1], Mohamed Dicko[1], Abdoulbaki I. Diallo[1], Intimbeye Tembine[1], Yahia Dicko[1], Niawanlou Dara[1], Youssoufa Sidibe[1], Gaoussou Santara[1], Toumani Conaré[2], Daniel Chandramohan[3], Simon Cousens[3], Paul J. Milligan[3], Diadier A. Diallo[3], Ogobara K. Doumbo[1], Brian Greenwood[3]

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Conclusion: IPTc with SP+AQ was not associated with an increase in incidence of malaria episodes, prevalence of malaria infection or anaemia in the subsequent malaria transmission season.

IPTi

Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials

Lancet 2009; 374: 1533–42

John J Aponte, David Schellenberg, Andrea Egan, Alasdair Breckenridge, Ilona Carneiro, Julia Critchley, Ina Danquah, Alexander Dodoo, Robin Kobbe, Bertrand Lell, Jürgen May, Zul Premji, Sergi Sanz, Esperanza Sevene, Rachida Soulaymani-Bechelkh, Peter Winstanley, Samuel Adjei, Sylvester Anemana, Daniel Chandramohan, Saadou Issifou, Frank Mockenhaupt, Seth Owusu-Agyei, Brian Greenwood, Martin P Grobusch, Peter G Kremsner, Eusebio Macete, Hassan Mshinda, Robert D Newman, Laurence Slutsker, Marcel Tanner, Pedro Alonso, Clara Menendez

"A pooled analysis for a possible rebound effect was done for those trials with extended follow-up periods (Ifakara, Manhiça, Lambaréné, and Navrongo); outcomes did not differ between IPTi and placebo groups in the 11-month period starting 35 days after the last dose."

...and others.

MDA

OPEN ACCESS Freely available online

PLoS one

The Potential Contribution of Mass Treatment to the Control of *Plasmodium falciparum* Malaria

Lucy C. Okell[1]*, Jamie T. Griffin[1], Immo Kleinschmidt[2], T. Déirdre Hollingsworth[1], Thomas S. Churcher[1], Michael J. White[1], Teun Bousema[3], Chris J. Drakeley[3], Azra C. Ghani[1]

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Burnet Institute
Medical Research. Practical Action.

Impact of declining transmission on immunity and risk of malaria rebound

Utilising data from malaria intervention trials in the Greater Mekong region, we seek to quantify the impact of malaria control measures including MDA (and therefore potential elimination) on malaria immunity within communities and how this predicts epidemiological patterns of disease over time.

Timeline

Jan 2015 – Feb 2023

...and others.

Chemoprevention in school-aged children

- **Maiga et al., Tropical Med and Inf Dis 2020**, Impact of Three-Year Intermittent Preventive Treatment Using Artemisinin-Based Combination Therapies on Malaria Morbidity in Malian Schoolchildren
- Effectiveness and Safety of Intermittent Preventive Treatment for Malaria Using Either Dihydroartemisinin-piperaquine or Artesunate-amodiaquine in Reducing Malaria Related Morbidities and Improving Cognitive Ability in School-aged Children in Tanzania (**InSMART-school**)
- **…and others**

IRS

- **Raouf et al., Clin Infect Dis. 2017**, Resurgence of malaria following discontinuation of indoor residual spraying of insecticide in a previously high transmission intensity area of Uganda
- **Okullo et al., Malaria J 2017**, Malaria incidence among children less than 5 years during and after cessation of indoor residual spraying in Northern Uganda
- **…and others**

RTS,S/AS01

Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children

Ally Olotu, Ph.D., Gregory Fegan, Ph.D., Juliana Wambua, M.Sc., George Nyangweso, B.Sc., Amanda Leach, M.R.C.P.C.H., Marc Lievens, M.Sc., David C. Kaslow, M.D., Patricia Njuguna, M.Med., Kevin Marsh, F.R.C.P., and Philip Bejon, Ph.D.

Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial

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Seasonal Malaria Vaccination (RTS,S/AS01) and Seasonal Malaria Chemoprevention (SP/AQ) Extension Study (RTSS-SMC)

ClinicalTrials.gov Identifier: NCT04319380

Recruitment Status : Active, not recruiting
First Posted : March 24, 2020
Last Update Posted : September 8, 2021

Objectives of the technical consultation

- **Review existing evaluations** of the rebound phenomenon
    - Draw attention to differences in definition and approach to measuring
- Consider **to what extent rebound could be a public health problem**
- Agree on the **key issues in the design of studies** evaluating new strategies or interventions
- Consider **approaches to ameliorate** the effects of rebound

Comments?
Suggestions?