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.

Wednesday, 23 March 2022			
	Session 1	**Open**	
12:00 – 12:05	Welcome by the ADG, UCN	Dr Ren Minghui	
12:05 – 12:15	Welcome by the Chair, MPAG	Dr Dyann Wirth	
12:15 – 13:15	Report from the Director, GMP	Dr Pedro Alonso	
13:15 – 13:45	Update on RTS,S and Framework for vaccine allocation	Ms Eliane Furrer	**For guidance**
13:45 – 14:15	Operational manual for subnational tailoring of malaria interventions	Dr Abdisalan Noor	
	Session 2	**Open**	
14:30 – 15:00	*Plasmodium knowlesi* disease burden and transmission: implications for WHO certification of malaria elimination	Dr Li Xiao Hong	**For decision**
15:00 – 15:30	Report of the technical consultation to review the classification of G6PD • Meeting report • Presentation	Dr Andrea Bosman	
15:30 – 16:15	Update on the WHO Guidelines for malaria • Vector control • Chemoprevention • Elimination • Treatment • Diagnosis • Dissemination	Dr Pedro Alonso Dr Jenny Stevenson Dr David Schellenberg Dr Kim Lindblade Dr Peter Olumese Dr Jane Cunningham Ms Saira Stewart	**For guidance**

WHO/UCN/GMP/MPAG/2022.03

Report from the Global Malaria Programme

Malaria Policy Advisory Group

Geneva, Switzerland

Pedro L. Alonso

Director

23 March 2022

Global **Malaria** Programme

World Health Organization

Since October …

- World malaria report 2021
- Normative guidance
- Meetings
- Country support
- Looking back
- Looking forward

History offers to the one who studies it a measure for the just and well-founded of the doings of his own time, places in his hands the thread by which he unites past conditions and efforts with those of the present, and set before him the mirror in which he may observe and compare the past and present, in order to draw therefore well-grounded conclusions for the future

Bass CC (1899) quoted by Russel P.F. (1955)

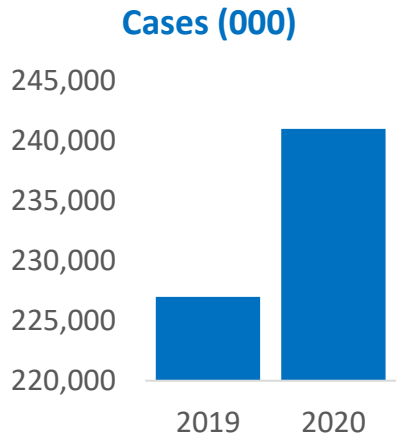
Outline of the *World malaria report 2021*

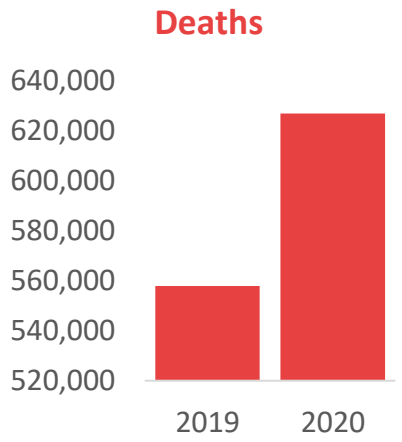
- Introduction
- Key events in 2020-2021 (including response during COVID-19 pandemic)
- Trends in burden of malaria
- Elimination
- “High burden high impact”
- Malaria financing
- Distribution and coverage of interventions
- Progress toward the milestones of the global strategy
- Biological threats
- Conclusion

Impact of disruptions during the COVID-19 pandemic

KEY MESSAGE 1: During the pandemic, malaria-endemic countries succeeded in averting the worst-case scenario of malaria deaths projected by WHO by mounting an urgent and strenuous response. Still, moderate disruptions in the delivery of malaria services contributed to the considerable increases seen in malaria cases (14 million) and deaths (69 000) between 2019 and 2020.

- About two thirds (47 000) of the additional malaria deaths were due to disruptions in the provision of malaria prevention, diagnosis and treatment during the pandemic.

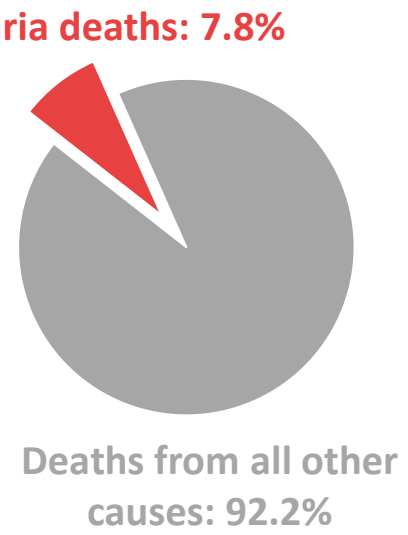




WHO methodology and global burden of malaria

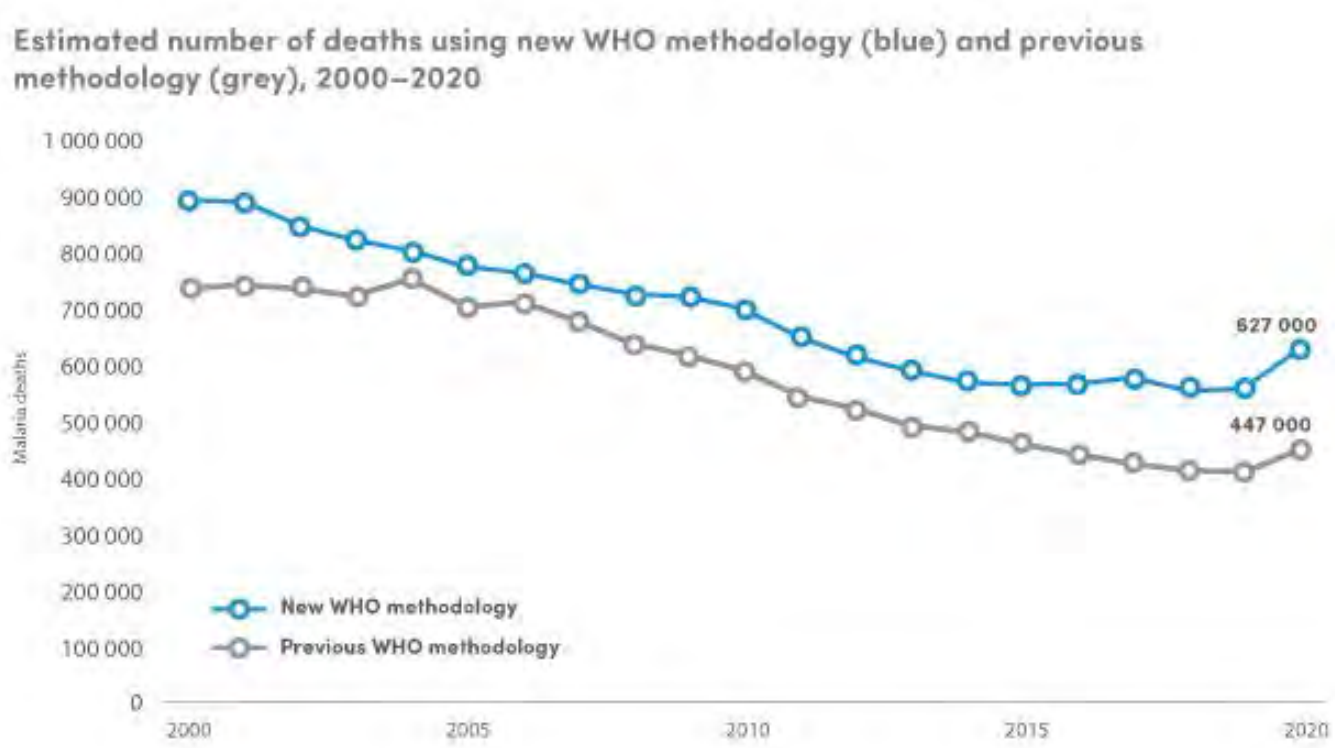
KEY MESSAGE 2: This year's *World malaria report* applied a new statistical method to calculate the number of malaria deaths among children under 5 years of age since 2000. This new methodology is being used across WHO and provides more precise cause-of-death estimates for young children for all diseases, including malaria.

- The new methodology reveals higher numbers of estimated malaria deaths across the entire period 2000–2020, compared with previous analyses.



New WHO methodology for estimating malaria deaths

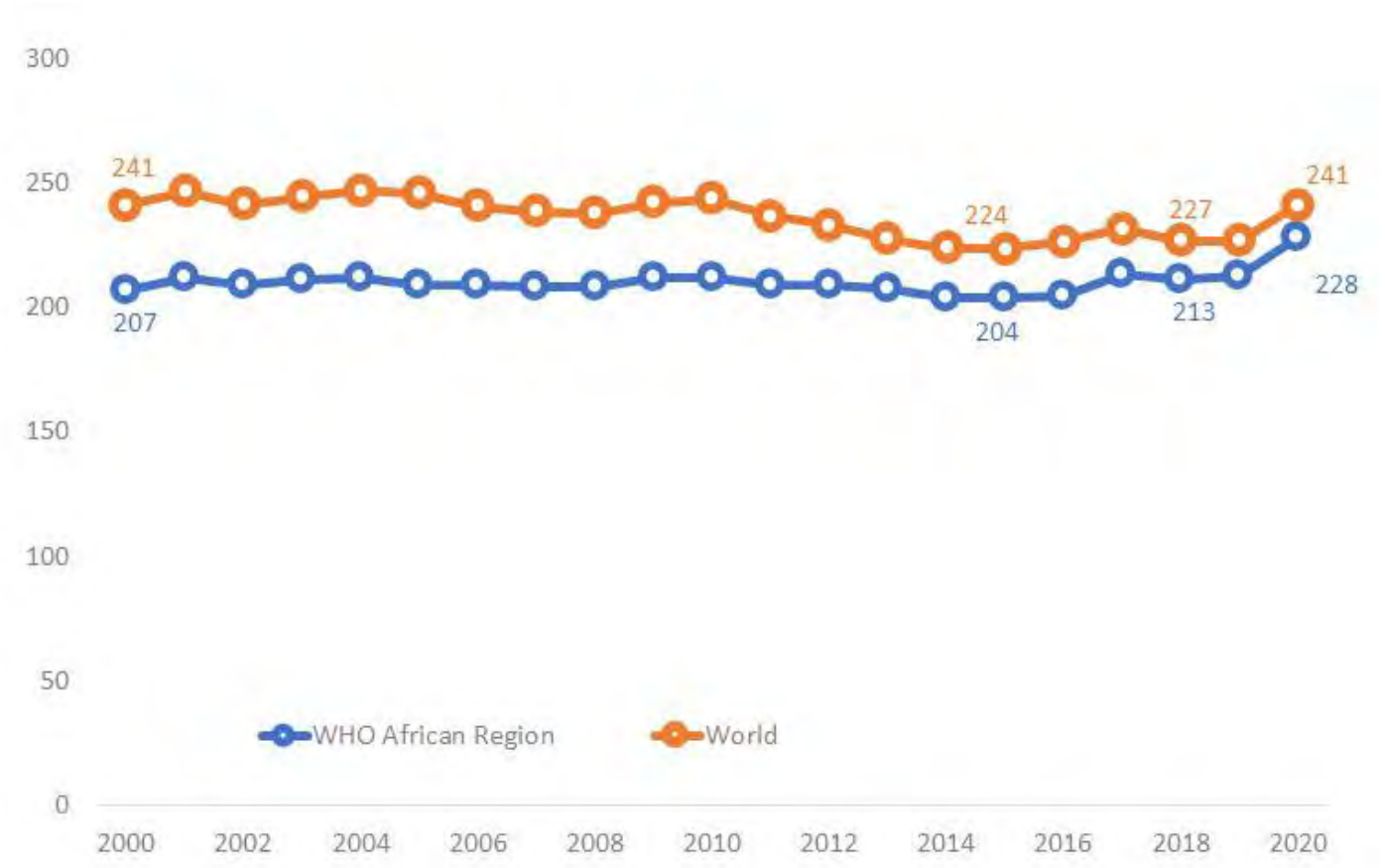
Estimated number of deaths using new WHO methodology (blue) and previous methodology (grey), 2000–2020



- Applying the new methodology, there were an estimated **627 000 malaria deaths** worldwide in 2020.

Trends in malaria cases – global and WHO African Region, 2000–2020

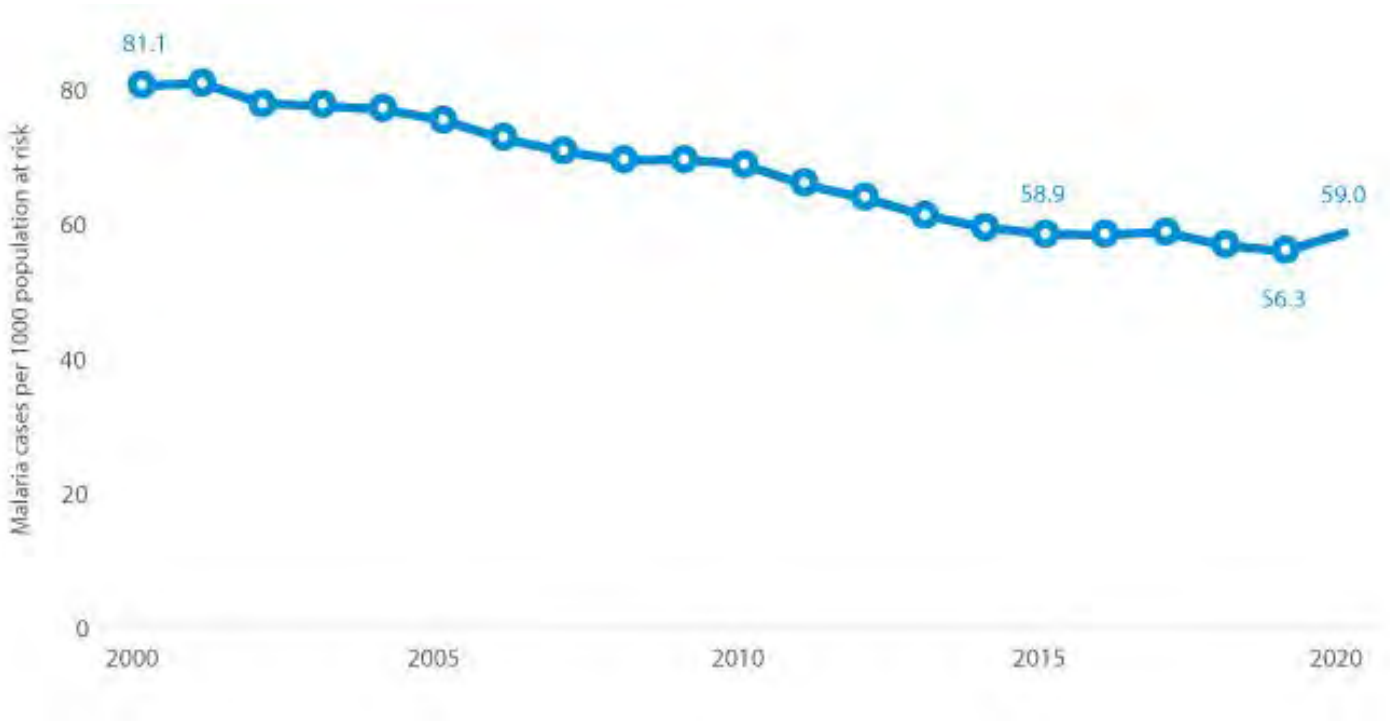
Global trends in malaria cases, 2000–2020



- Globally, an estimated 241 million malaria cases in 2000 and in 2020**, but the population in sub-Saharan Africa nearly doubled** in that period.
- WHO African Region carried about **95%** of global malaria cases in 2020.

Global malaria case incidence, 2000–2020

Global trends in malaria case incidence (cases per 1000 population at risk), 2000–2020



Despite a slowing of progress since 2015, case incidence (cases per 1000 population) was still considerably lower in 2020 than in 2000.

- **27% reduction** in case incidence from 2000 to 2020

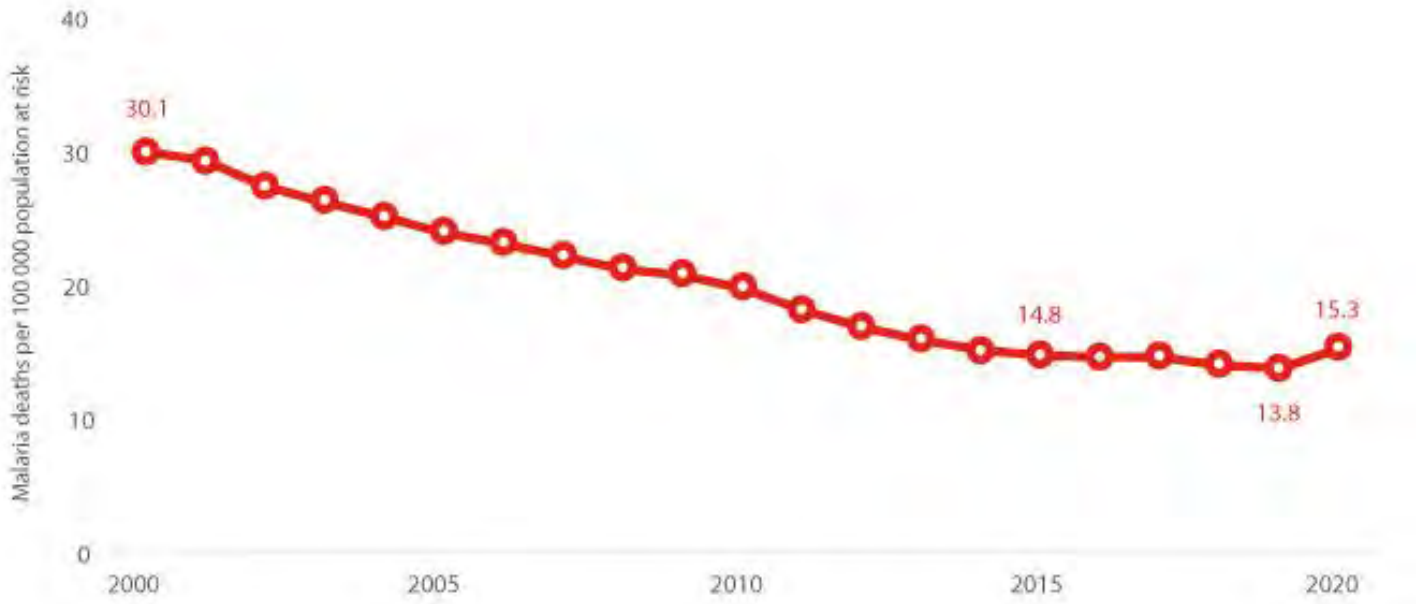
Trends in malaria deaths – global and WHO African Region, 2000–2020

Global trends in malaria deaths, 2000–2020

96% of global malaria deaths in 2020 were in the WHO African Region.

Global malaria mortality rate, 2000–2020

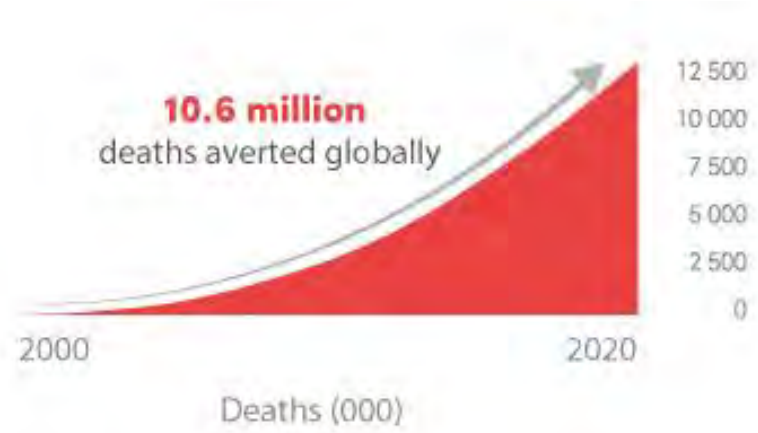
Global trends in mortality rate (deaths per 100 000 population at risk), 2000–2020

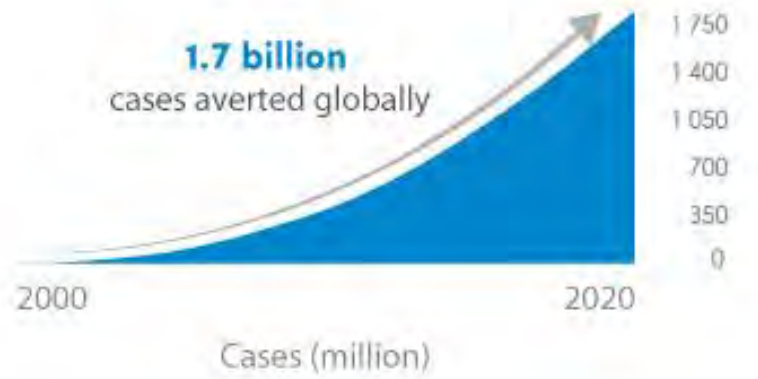


Even after applying the new methodology, the malaria death rate (deaths per 100 000 population) maintained an overall downward trend from 2000 to the present day.

- **49% reduction** in malaria mortality rate from 2000 to 2020

Global malaria cases and deaths averted, 2000–2020





Globally, 1.7 billion cases and 10.6 million deaths were averted between 2000 and 2020

- Most of the malaria cases (**82%**) and deaths (**95%**) averted over the last 20 years were in the WHO African Region

A plateau in malaria progress pre-pandemic

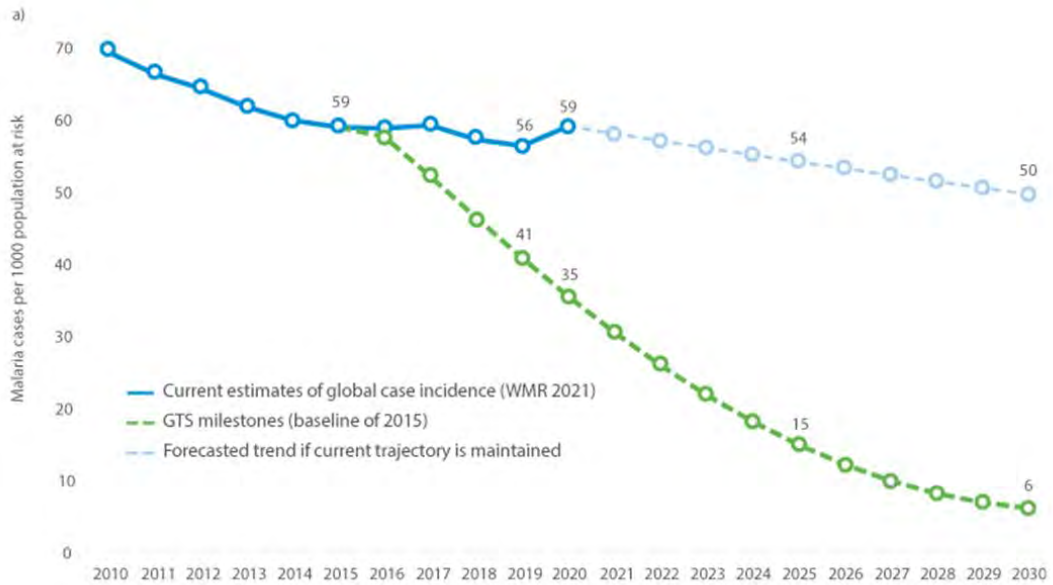
KEY MESSAGE 3: Even before the emergence of COVID-19, global gains against malaria were levelling off, and the world was not on track to reach the 2020 milestones of WHO's global malaria strategy. To reinvigorate progress, WHO and partners catalyzed a new, country-driven approach to malaria control in high-burden countries that was beginning to gain momentum when COVID-19 struck.

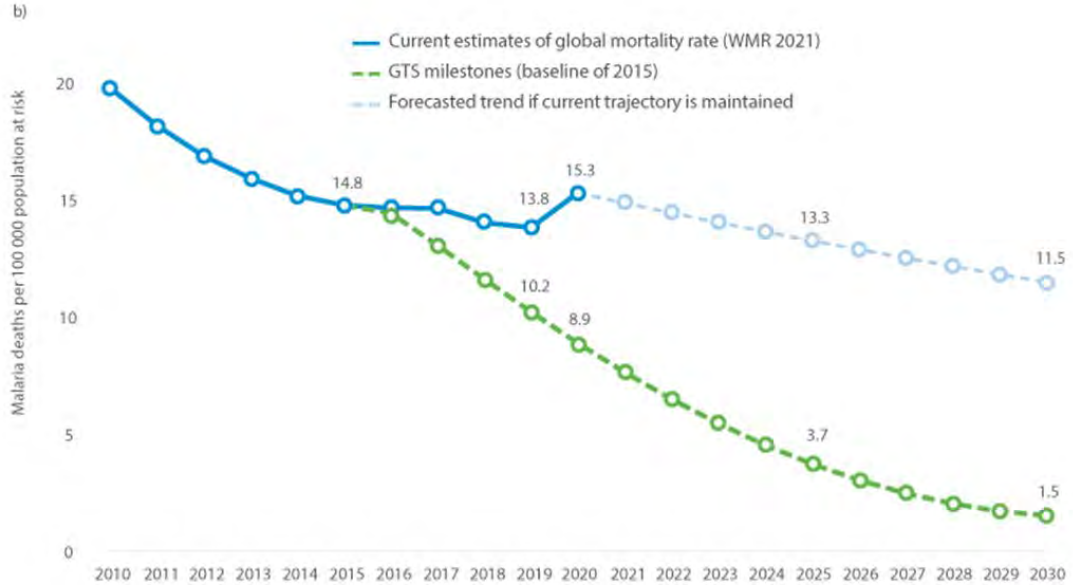
- WHO's *World malaria report 2017* warned that the global response had reached a "crossroads," and that progress towards critical targets of WHO's global strategy for reductions in disease and death was off track.

The challenge remains – reductions in cases and deaths are off-track

In 2020, global malaria case incidence was **59** cases per 1000 people at risk, against a target of **35** – putting it **off track by 40%**.

In 2020, the global mortality rate was **15.3** deaths per 100 000 people at risk, against a target of **8.9** – putting it **off track by 42%**.

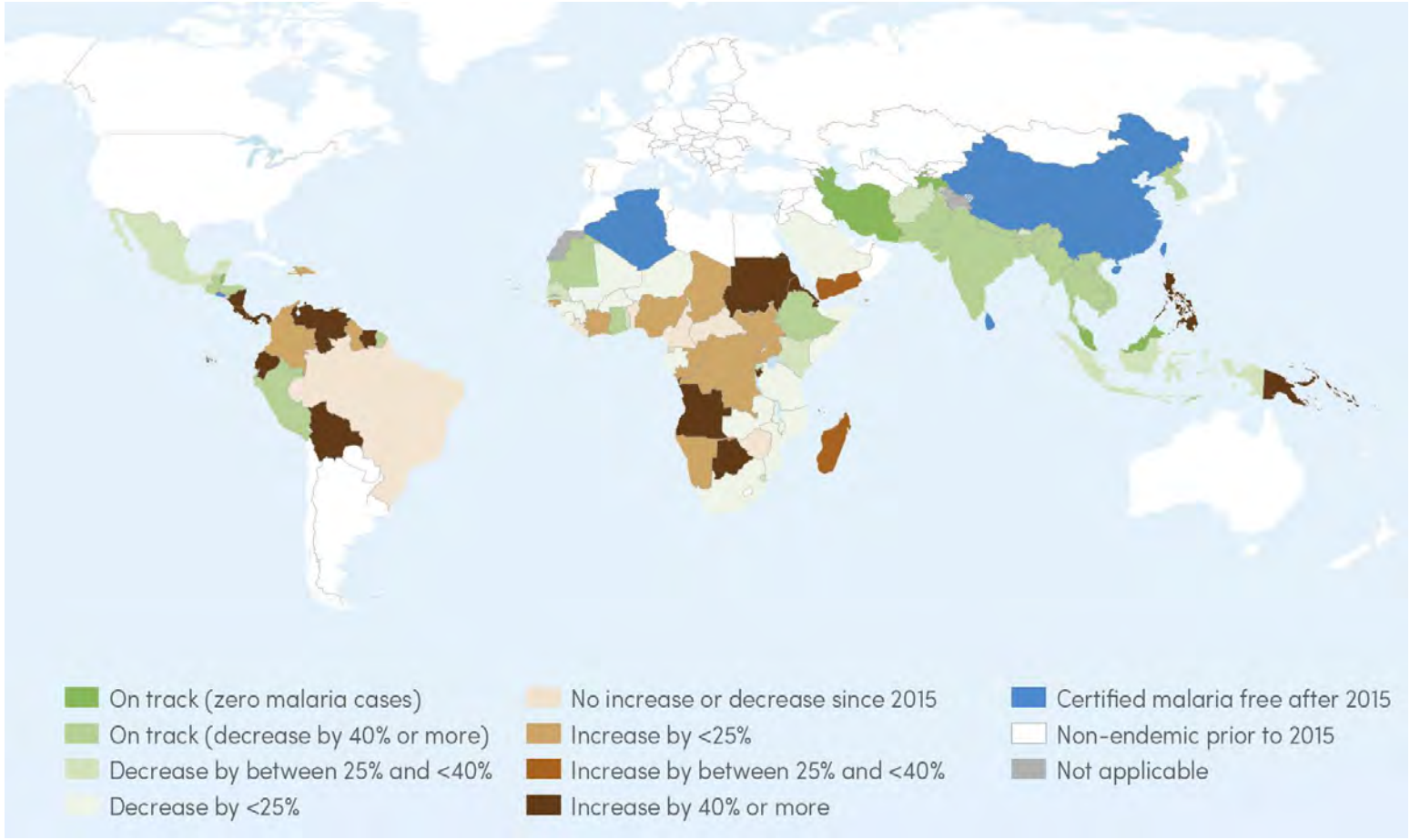




Progress on a global scale remains uneven

KEY MESSAGE 4: On a global scale, progress against malaria remains uneven. Many countries with a low burden of the disease are moving steadily towards the goal of malaria elimination. Two countries – El Salvador and China – were certified malaria-free by WHO in 2021. However, most countries with a high burden of the disease have suffered setbacks and are losing ground.

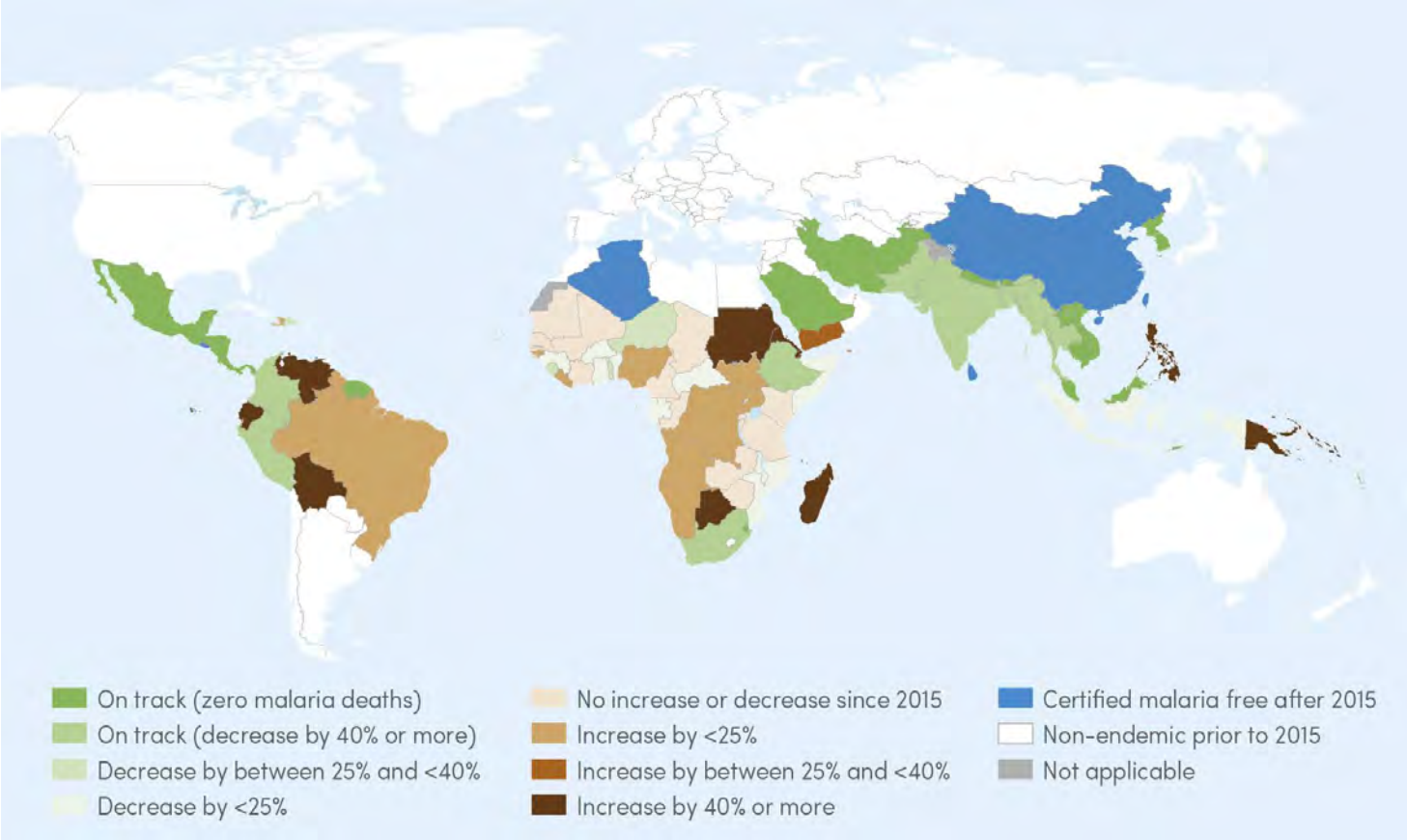
Mixed progress toward the 2020 GTS case incidence milestone, from 2015 baseline



Of the 93 countries and territories that were malaria endemic in 2015 (the baseline of the global strategy):

- **30** had achieved the GTS target of 40% reduction in malaria case incidence by 2020.
- **24** achieved reductions in malaria case incidence of less than 40%.
- **7** remained at similar levels of malaria case incidence.
- **32** countries registered *increases* in malaria case incidence

Mixed progress toward the 2020 GTS mortality milestone, from 2015 baseline

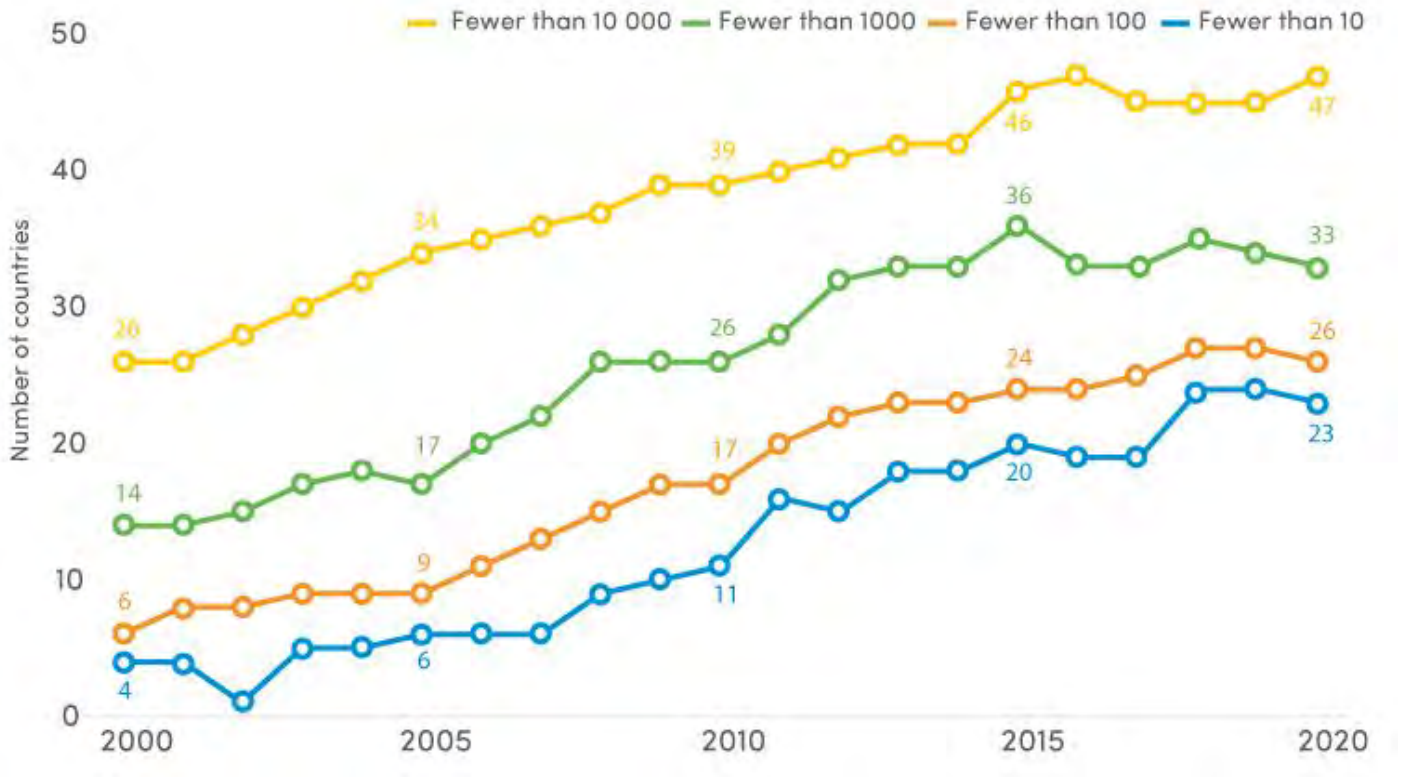


Of these same 93 countries:

- **40** achieved the target of a 40% reduction in the malaria mortality rate by 2020
- **15** achieved reductions in the malaria mortality rate of less than 40%
- **14** countries (all in Africa) remained at similar levels of malaria mortality
- **24** countries registered *increases* in malaria mortality rate

Progress in countries with a low burden of malaria

Number of countries that were malaria endemic in 2000, with fewer than 10, 100, 1000 and 10 000 indigenous malaria cases between 2000 and 2020

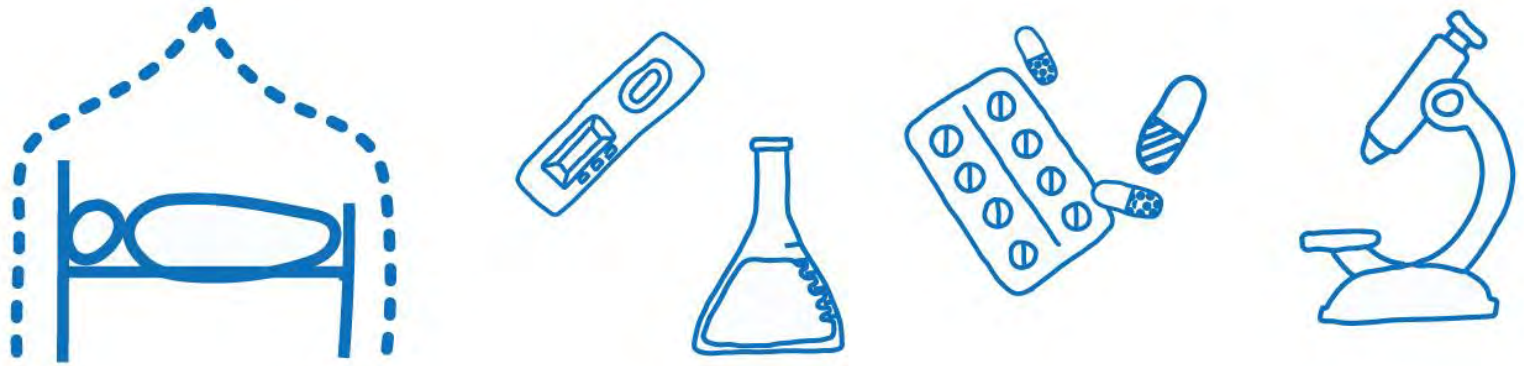


A growing number of low burden countries are moving steadily towards the goal of malaria elimination.

- More than half of the world's malaria-endemic countries (47) now have less than 10 000 cases of malaria.
- 23 countries reported fewer than 10 cases of malaria in 2020.

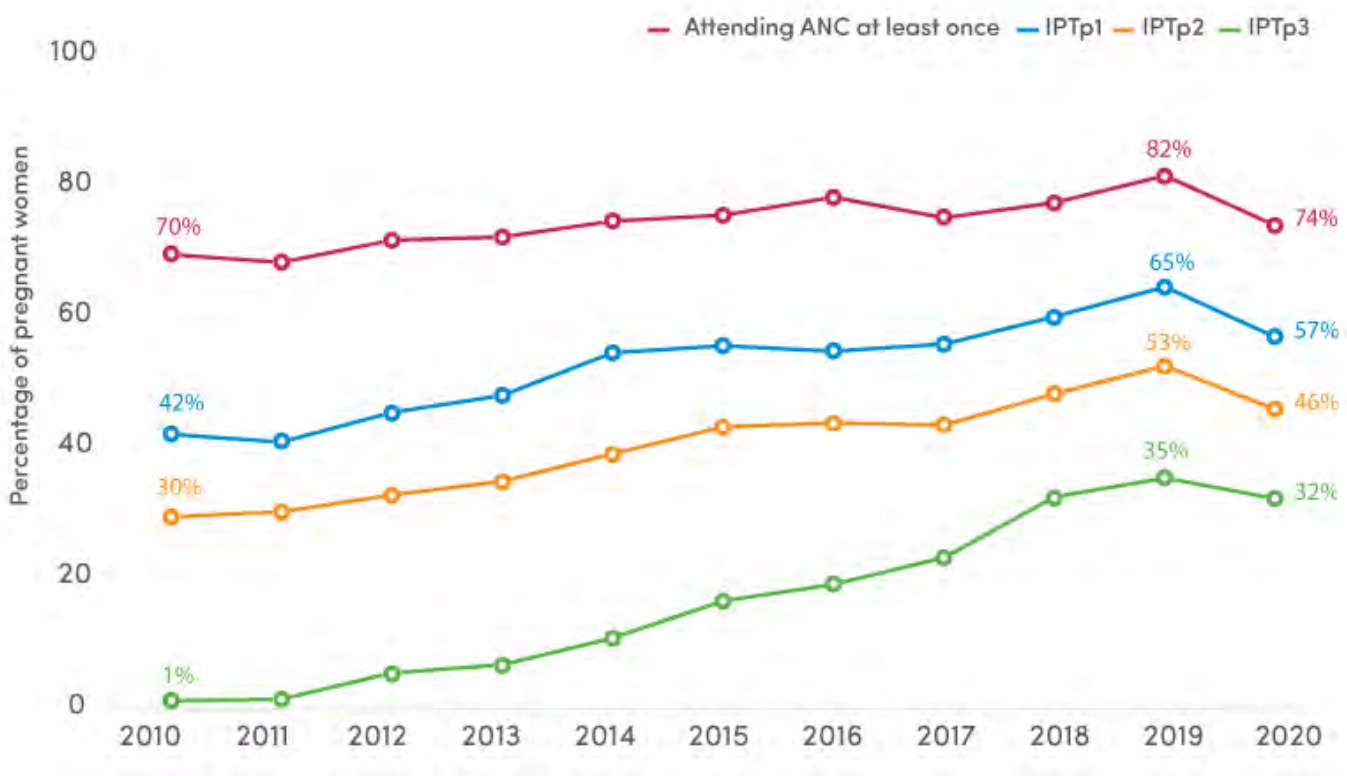
Significant and growing coverage gaps

KEY MESSAGE 5: **Global progress against malaria over the past two decades was achieved, in large part, through the massive scale-up and use of WHO-recommended malaria tools that prevent, detect and treat the disease. The most recent data demonstrate these gains, while also highlighting the significant and sometimes widening gaps in access to lifesaving tools for people at risk of malaria.**



Coverage of preventive therapy for pregnant women

Percentage of pregnant women attending an ANC clinic at least once and receiving IPTp, by dose, sub-Saharan Africa, 2010–2020



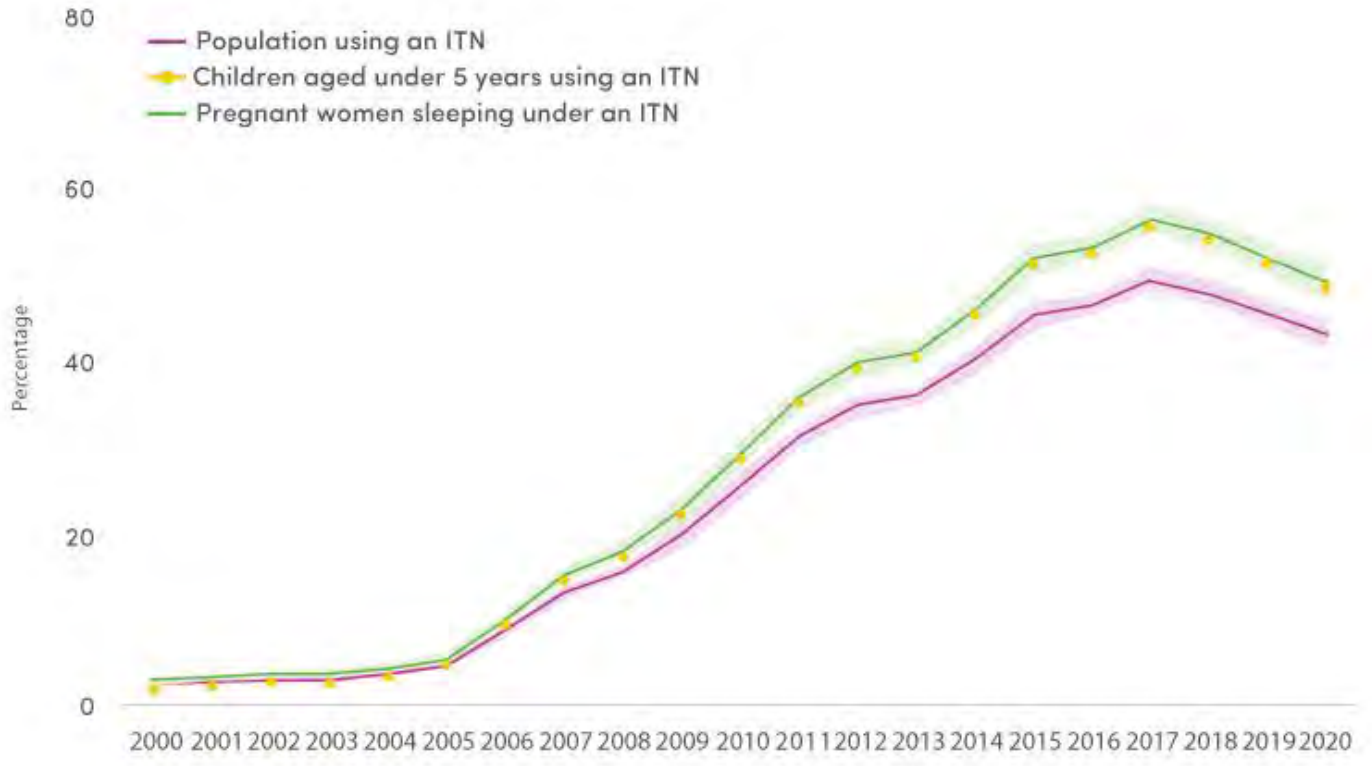
WHO recommends 3 or more doses of IPTp for pregnant women living in areas of moderate to high malaria transmission in Africa

Expanded coverage of intermittent preventive treatment in pregnancy (IPTp) since 2012, but still far below the target of universal access

- Coverage of 3 doses of IPTp3 increased from 1% in 2010 to 34% in 2019 and then fell to 32% in 2020 during the pandemic

Coverage of insecticide-treated nets

Indicators of population-level use of ITNs, sub-Saharan Africa, 2000–2020



Significant expansion in coverage of insecticide-treated nets (ITNs) in sub-Saharan Africa since 2000, but a slight decline seen since 2017

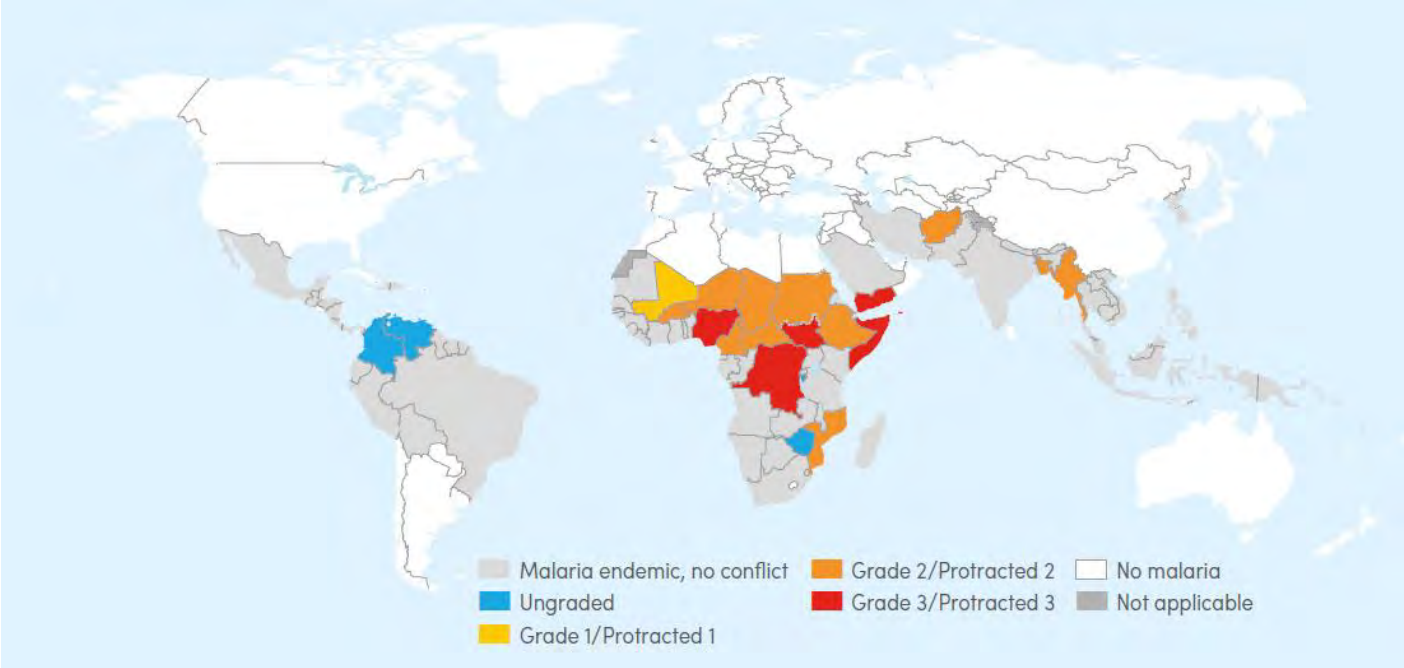
- % of pregnant women and children sleeping under an ITN increased from 2% in 2000 to 49% in 2020

A worrying situation – particularly in sub-Saharan Africa

KEY MESSAGE 6: The situation remains precarious – especially in sub-Saharan Africa, where the malaria burden remains unacceptably high and a convergence of threats poses an added challenge to disease control efforts. At the same time, the pandemic is not over, and the pace of economic recovery is uncertain. Without immediate and accelerated action, key 2030 targets of the WHO Global technical strategy for malaria will be missed, and additional ground may be lost.

Humanitarian and health emergencies – beyond COVID-19

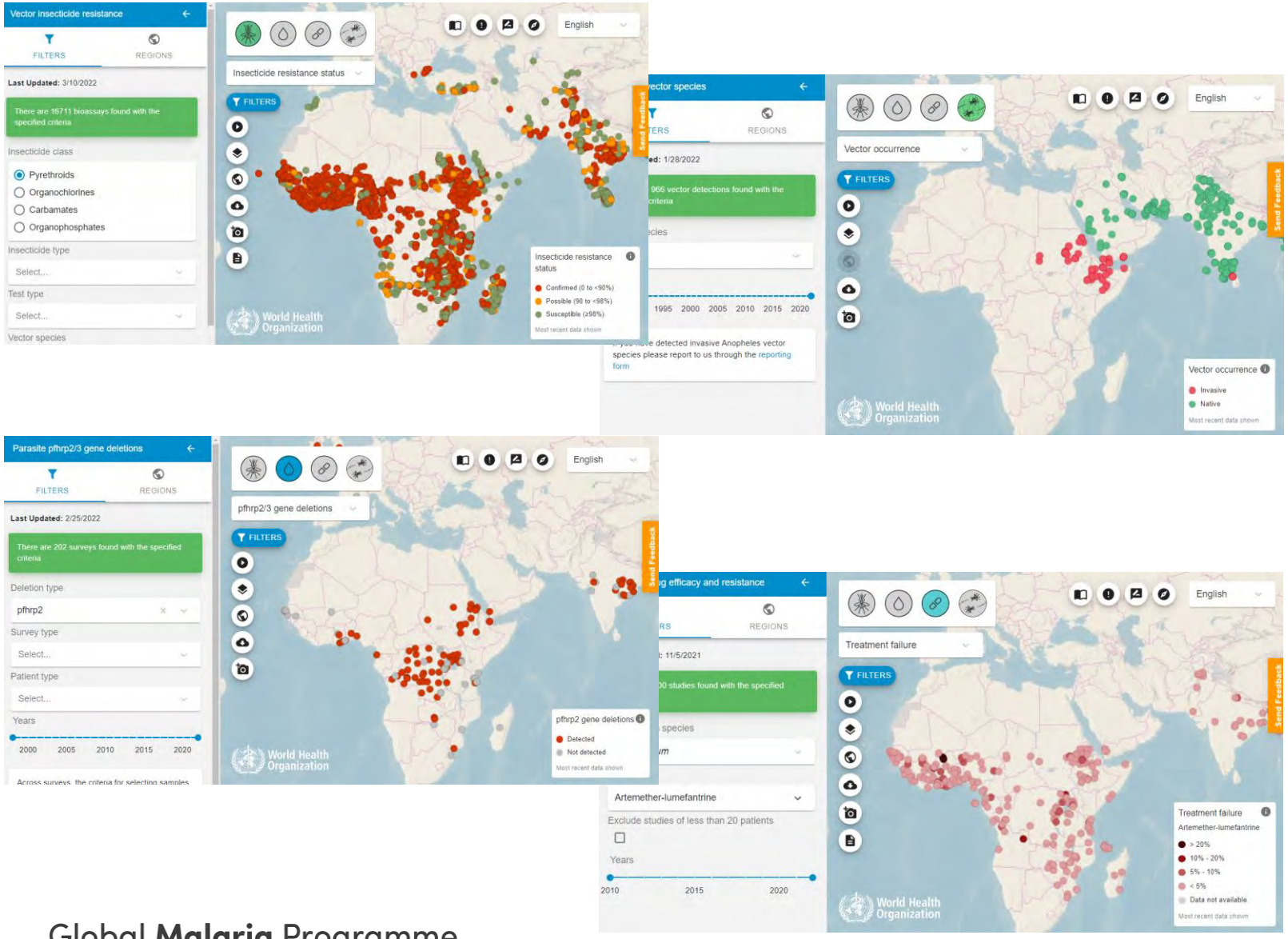
Map of ongoing armed conflicts as of October 2021



122 million people in 21 malaria-endemic countries needed assistance due to health and humanitarian emergencies in 2020–2021, not including the COVID-19 pandemic

- Ebola outbreaks in DRC and Guinea
- Armed conflicts
- Flooding

A convergence of biological threats in sub-Saharan Africa



A convergence of threats in sub-Saharan Africa:

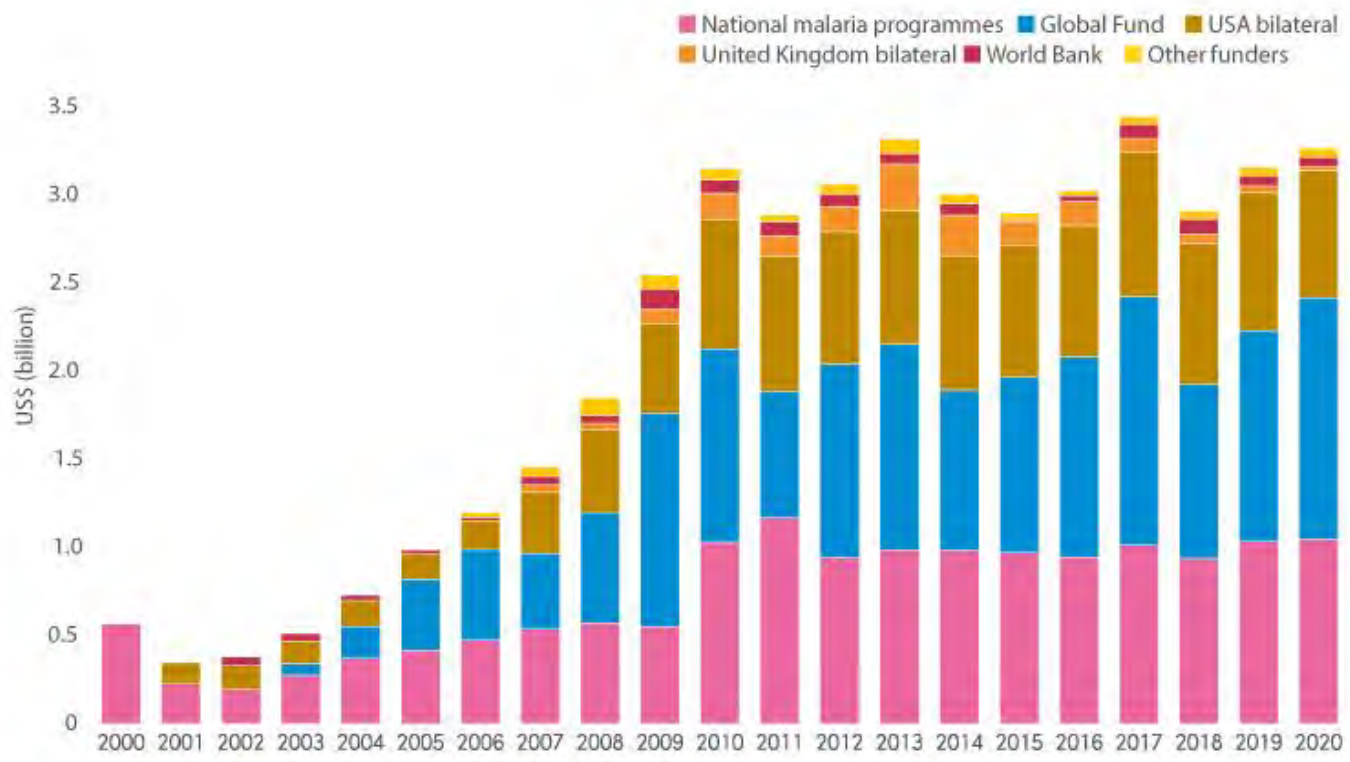
- Antimalarial drug resistance in East Africa
- HRP2 gene deletions
- Mosquito resistance to insecticides
- Invasive vector species (*Anopheles stephensi*) in Horn of Africa
- Latest data on these 4 biological threats can be found in WHO's Malaria Threats Map

What is needed to reach global malaria targets

KEY MESSAGE 7: **In 2021, WHO updated its global malaria strategy to reflect lessons learned over the past five years. Meeting the strategy's goals, including a 90% reduction in global malaria incidence and mortality rates by 2030, will require new approaches and greatly intensified efforts aided by new tools and the better implementation of existing ones. Stepped-up investment is also essential.**

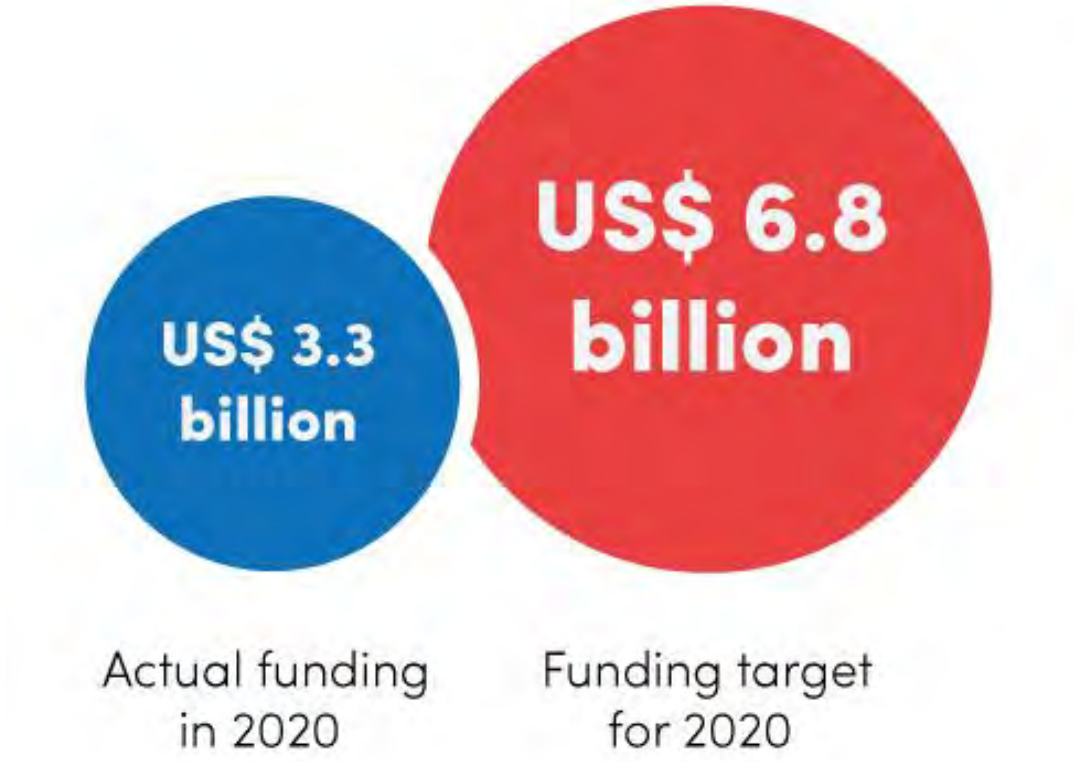
Global malaria funding, 2000–2020

Funding for malaria control and elimination, 2000–2020, by channel (constant 2020 US$)



- **US$ 44.5 billion** invested globally since 2000
- **US$ 15.2 billion** from governments of malaria endemic countries (mostly patient care costs)
- **US$ 15.4 billion** through the Global Fund
- **US$ 10.5 billion** through US bilateral channels

Funding gap continues to widen



A total of US$ 3.3 billion invested globally in malaria control and elimination in 2020 against a target of US$ 6.8 billion

- To reach global malaria targets, annual investments will need to more than triple by 2030 – to **US$10.3 billion** per year.

Our normative work

Information note on the use of rectal artesunate

- Countries that have not yet introduced pre-referral RAS but are considering doing so should withhold implementation and await further guidance from WHO on the criteria that need to be met to ensure the safe and efficacious use of RAS.
- Countries that have already adopted and are deploying pre-referral RAS should urgently review in detail the conditions under which it is currently being used. This includes all three steps along the cascade of care:
  i. Diagnosis and administration of RAS;
  ii. Immediate referral; and
  iii. Complete treatment with at least 24 hours of injectable artesunate and a 3-day ACT.

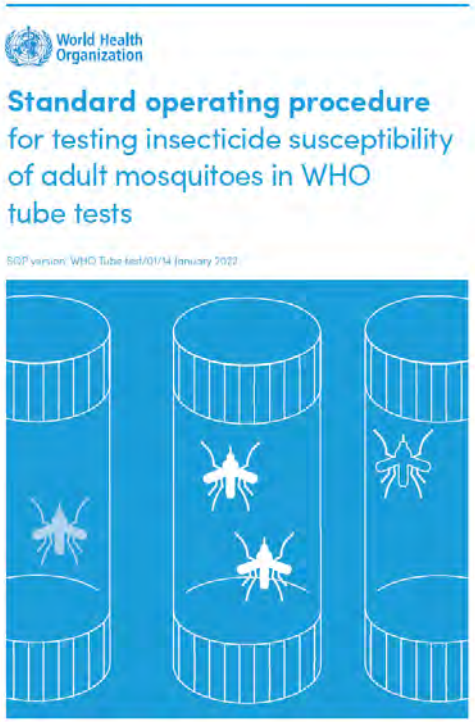
  Countries that have already adopted RAS are encouraged to withhold further expansion of its use until further guidance from WHO.

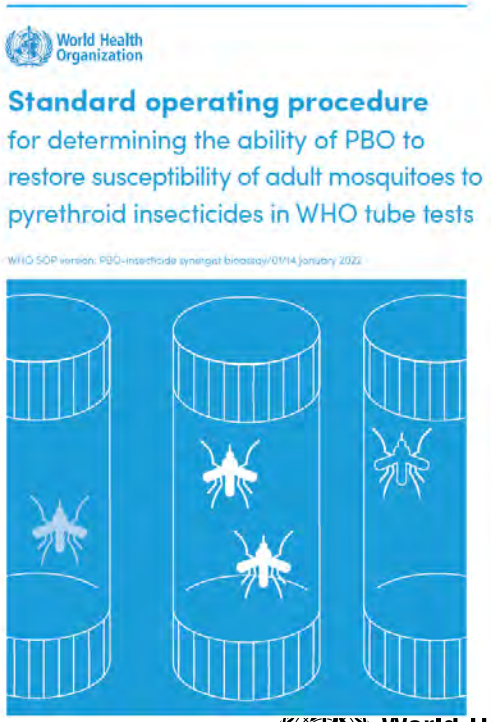
Malaria vaccine recommendation published in WHO Guidelines for malaria

- Malaria vaccine recommendation published on 18 February in the WHO Guidelines for malaria
- Malaria vaccine: WHO position paper – March 2022

New SOPs to monitor insecticide resistance in mosquito vectors

- New WHO bottle bioassays procedures
- New discriminating concentration for Anopheles against transfluthrin, clothianidin, flupyradifurone and chlorfenapyr
- Updated discriminating concentration for Anopheles against alphacypermethrin and pirimiphos-methyl
- New procedures for testing mosquito resistance to pyriproxyfen





Publications in 2022

- Manual for monitoring insecticide resistance in mosquito vectors and selecting appropriate interventions (April 22)
- WHO Vector control evaluation process (video) (Feb 22)
- Meetings of the malaria elimination certification panel (MECP) (Feb 22)
- MALVAC meeting on PPCs for malaria vaccines (Feb 22)
- Technical consultation on the use of economics in insecticide resistance management for malaria vector control (Jan 22)
- 2nd focused review meeting by the MEOC (Dec 21)
- 15th mtg of WHO VCAG – (Dec 21)
- Workshop on external competence assessment and national competence assessment for malaria microscopists (Dec 21)
- Technical consultation on determining non-interiority of vector control products (Nov 21)
- Informal consultation on methodology to distinguish reinfection from recrudescence in high malaria transmission (Nov 21)

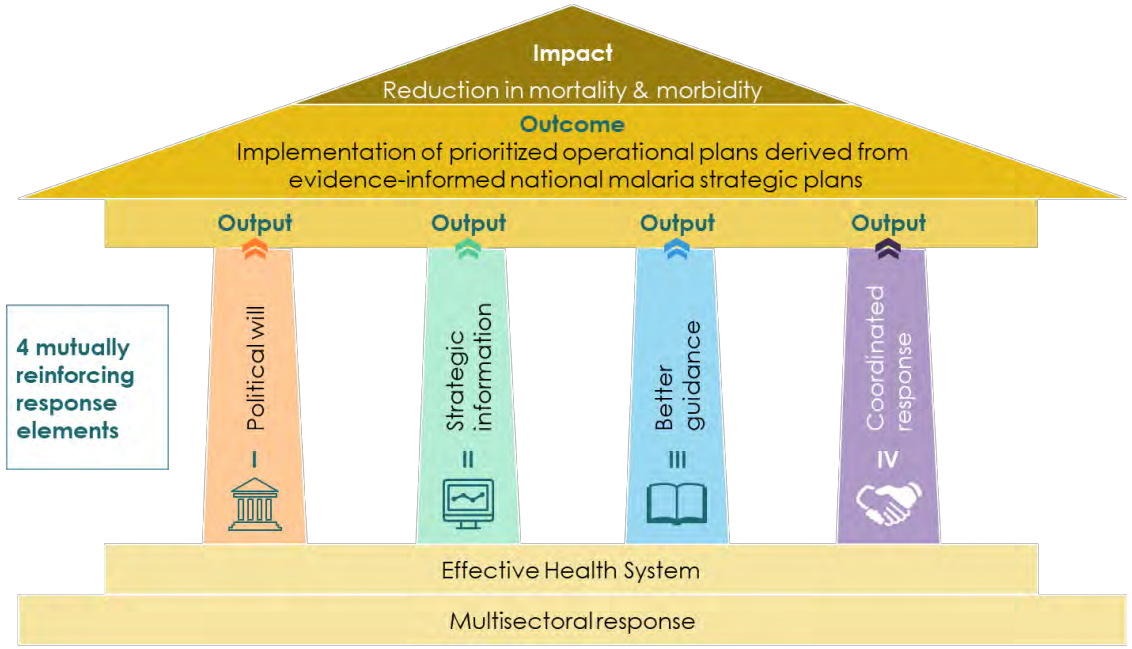
Smart data-driven public health: moving away from a one size fits all

Tendency to extrapolate elsewhere a success from a specific region … the one size fits all approach

In the study of malaria problems and in the formulation of control programmes, ***action based on generalizations is likely to be followed by the most disastrous consequences****. It has been well said that the most hazardous of human tendencies is the drawing of general conclusions from limited experience, and in no instance it is more applicable than in the planning of malaria control measures*.

Sir Gordon Covell (1948) Lectures on Malaria (4th edition)

Operational Manual for subnational tailoring of malaria interventions



Work started during the phase 1 of the HBHI approach

Key challenges in the process were:

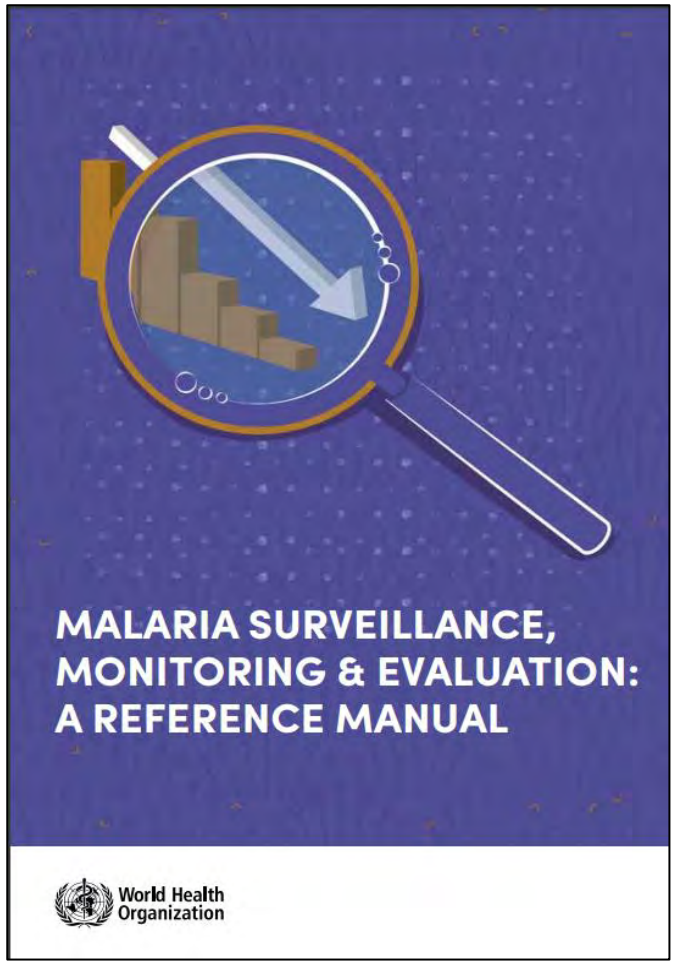
- inflexibility of some of the WHO recommendation
- Complex decision-making process where alignment with NSPs was professed and often not acted on
- no specific guidance on subnational tailoring

The SNT operational manual benefits from

- The HBHI experience
- Clarity in new policy recommendations (some still awaiting approval)
- The Framework on malaria in urban areas
- The strong push for data and subnational tailoring in the updated GTS, the new GF, RBM and PMI strategies

Launch: June 2022

Surveillance, Monitoring & Evaluation Reference Manual – 2022 update



- Launched in March 2018
- Combined epidemiological, entomological, resistance, epidemics and M&E in one document
- Widely used as basis for training in countries and in academia for postgraduate training
- Will be updated this year to:
  - To align with new WHO recommendations
  - To expand the section of assessment of surveillance systems with the launch of the new surveillance assessment toolkit
  - To include in the annexes the links to all digital solutions for malaria
  - To introduce a new chapter on data to action that is linked with the subnational tailoring manual

WHO Framework for Response to Malaria in Urban Areas

Consultation launched on 22nd September by

Mayor of Freetown, Hon. Yvonne Aki-Sawyerr

Five thematic groups established:

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

Thematic groups discussions were held from October – December 2021

Meetings in 2022 – Quarter 1

- Review of classification of G6PD (25-27 January)
- Informal Dissemination Taskforce (8-9 February)
- TPPs for G6PD testing (21, 23 & 25 February)
- 10th meeting of the Malaria Elimination Certification Panel (3 March)
- Malaria Vaccine Advisory Committee (MALVAC) (7 March)
- Technical consultation on the malaria rebound phenomenon (21-22 March)
- 16th meeting of the Vector Control Advisory Group (28-30 March)
  - Sessions on ATSBs, Housing modifications and Gene drive

Country support

High Burden to High Impact approach

- Evaluation of HBHI Approach jointly with RBM just started
- Evaluation objectives:
  - To review progress in operationalizing the HBHI approach, identify solutions to key challenges, and document best practices and lessons learned
  - To improve the approach based on the findings and recommendations
- The evaluation report will be one of the background documents for the Africa Malaria Stakeholders meeting being organized by AFRO, EMRO and GMP before the end of Q2
- HBHI will be a major agenda in the meeting; it will be an opportunity to advocate for expansion of HBHI to other countries that GMP and Regional Offices have tentatively identified
- HBHI evaluation in India will be part of MPR this April; the findings and recommendations are expected to inform the development of new Malaria NSP 2023 – 2027

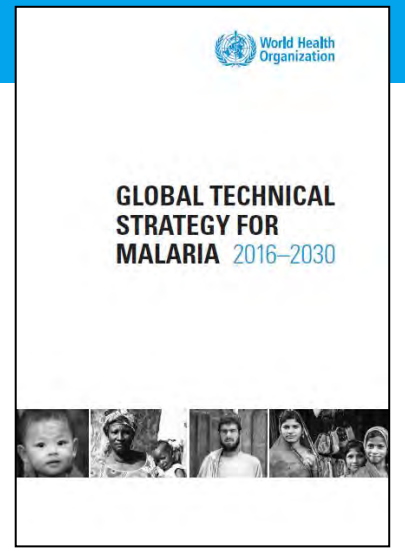
A Look back

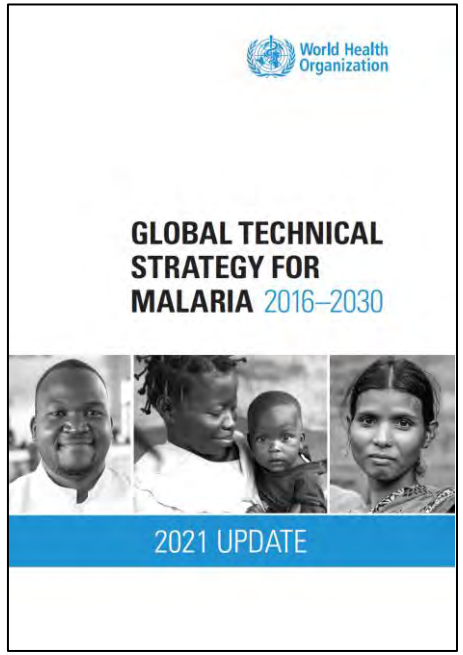
Global Technical Strategy for Malaria 2016 - 2030

- The Global Technical Strategy for Malaria was first endorsed by the 68th WHA in 2015
- GTS Review and update with a new resolution adopted by the 74th WHA in 2021

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





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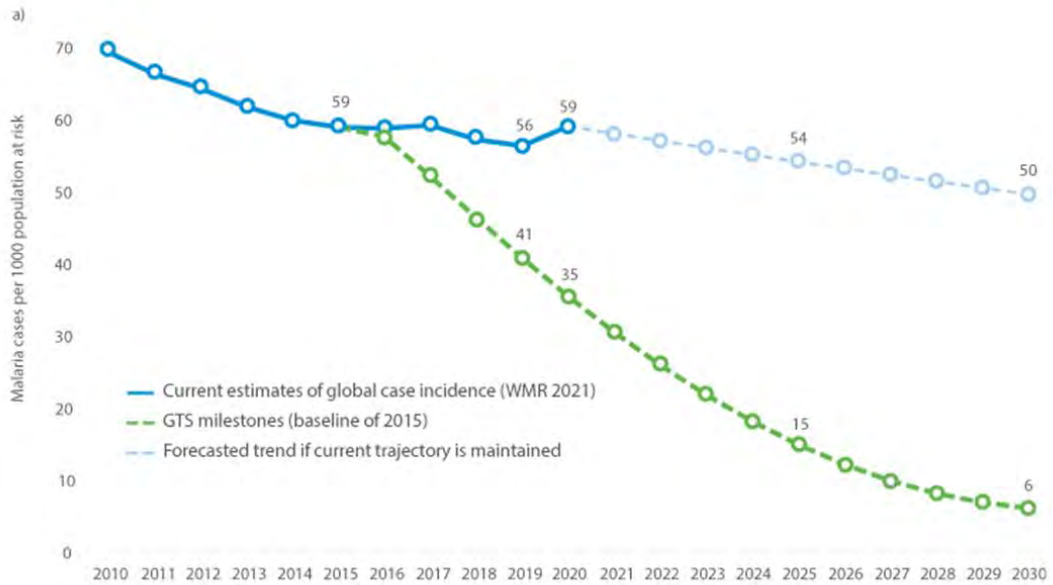
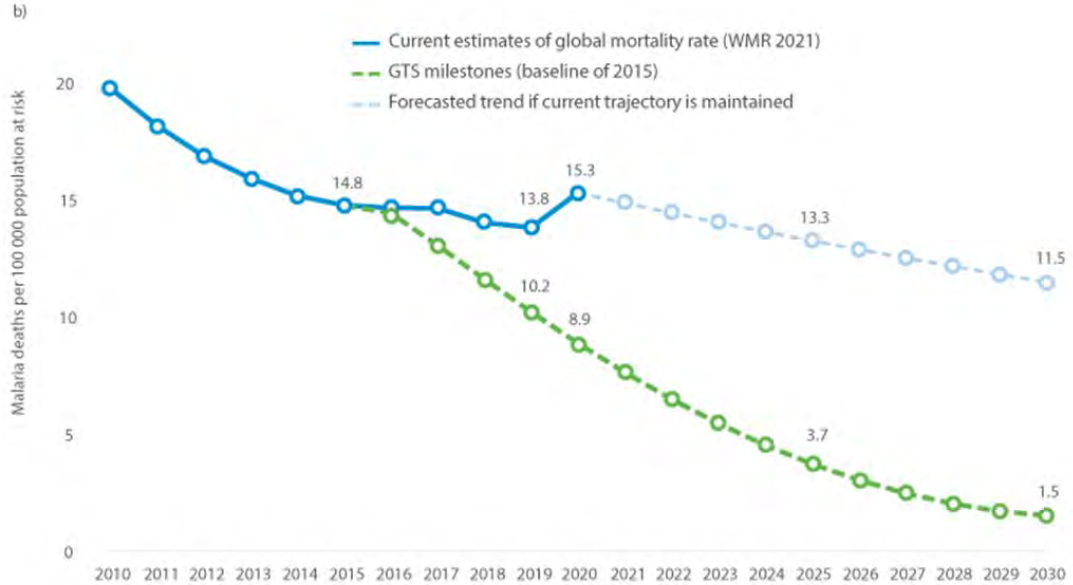
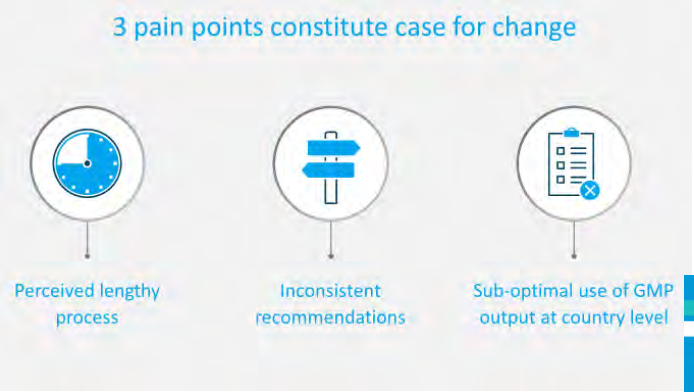
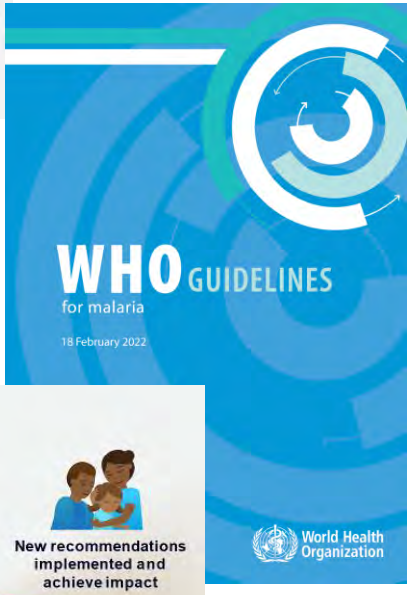
In 2020, the global mortality rate was **15.3** deaths per 100 000 people at risk, against a target of **8.9** – putting it **off track by 42%**.

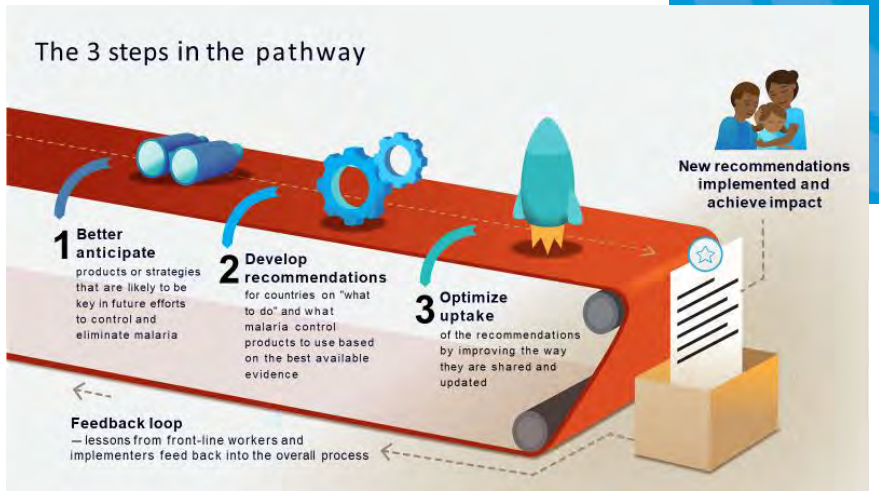




Reforming the process to develop WHO Guidelines for malaria







- In May 2018, GMP launched a review of its recommendation development process
- 3 pain points constitute the case for change: perceived lengthy process, inconsistent recommendations and sub-optimal use of GMP output at country level
- Since then, 5 technical areas are undergoing technical reviews and updates – consolidated into the WHO Guidelines for malaria
- Improved dissemination

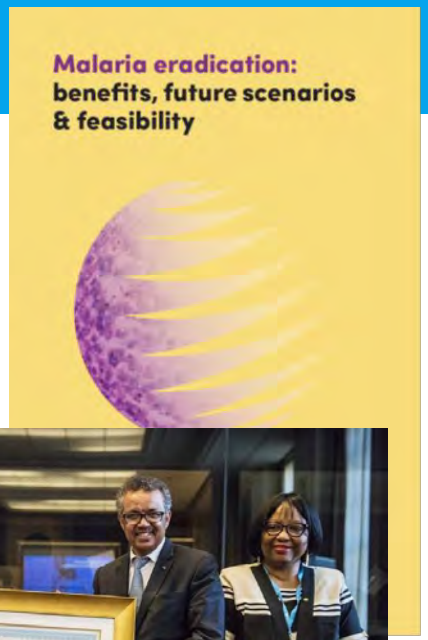
Catalyzing the High Burden to High Impact approach

- In November 2018, WHO and RBM spearheaded the launch of HBHI
- Built on 4 key elements:
  - Political will
  - strategic information to drive impact
  - better guidance, policies and strategies
  - a coordinated national malaria programme
  - Under 2 platforms:
    - strong health systems
    - a multi-sector response

Supporting countries with low burden through E-2020 & E-2025 initiatives

- From 2017 to 2020, WHO supported a group of 21 malaria-eliminating countries through the E-2020 initiative.
- By 2020, 8 of those countries reported zero indigenous cases of malaria
- The 2020 GTS milestones for elimination and prevention of reintroduction were met
- In 2021, WHO launched the E-2025 initiative to support 26 countries with the potential to eliminate malaria by 2025

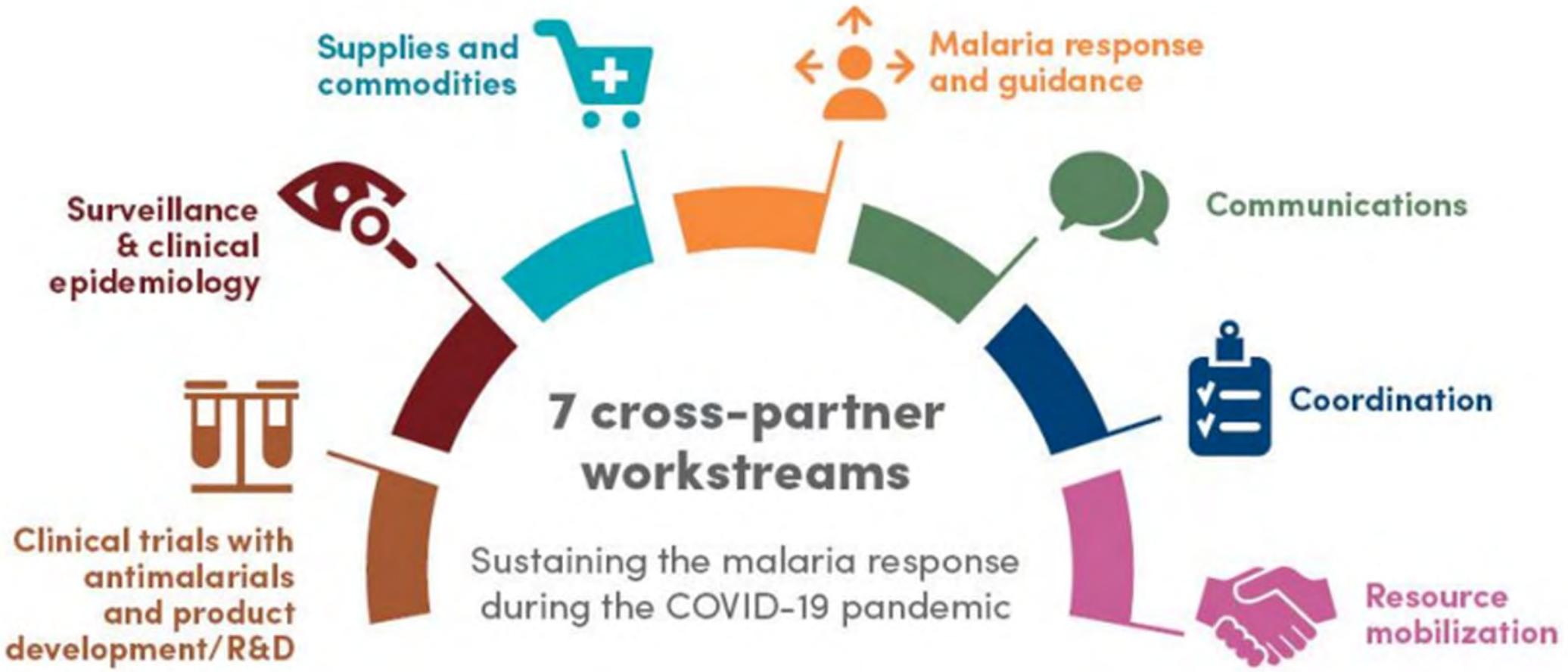
Certification of malaria-free status and the SAGme



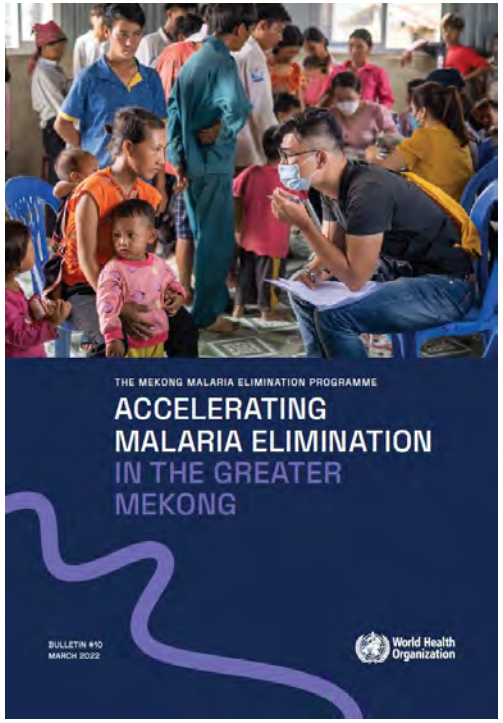
- The Strategic Advisory Group on Malaria Eradication highlighted 6 areas that would underpin a successful malaria eradication effort after a 3-year study

- Countries certified malaria-free
  - China (June 2021)
  - El Salvador (Feb 2021)
  - Algeria (2019)
  - Argentina (2019)
  - Uzbekistan (2018)
  - Paraguay (2018)
  - Kyrgyzstan (2016)
  - Sri Lanka (2016)
  - Maldives (2015)

Responding to the challenges of the COVID-19 pandemic to malaria



Tackling drug-resistant malaria in the GMS – nearing elimination



2021 GMS DATA AT A GLANCE (JUL-SEP)*

17 386 cases

1 169 837 tests conducted

-48% tests compared to the same period in 2020

-39% cases compared to the same period in 2020

-72% *P. falciparum* + mixed cases compared to the same period in 2020

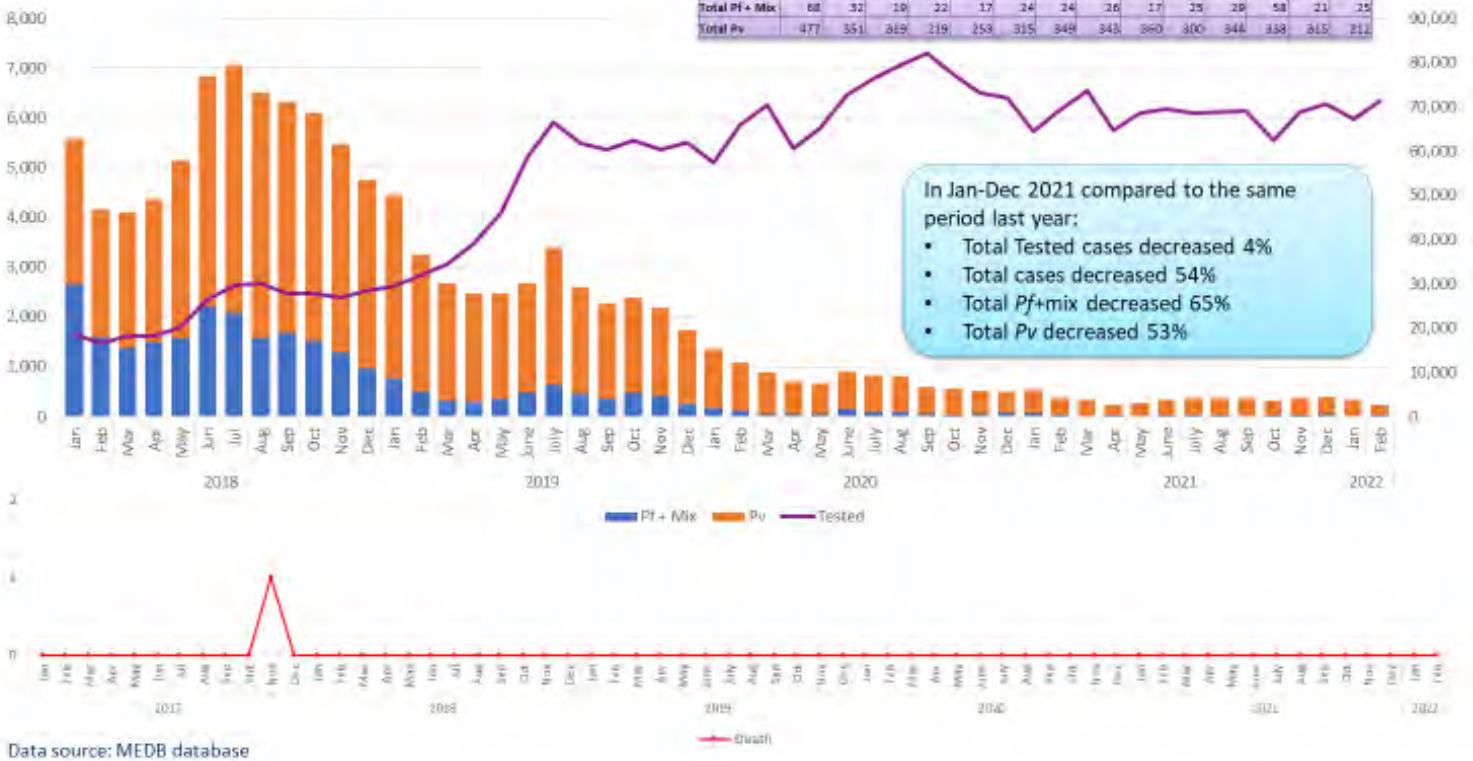
-28% *P. vivax* cases compared to the same period in 2020

2021 QUARTER 3 OVERVIEW

With support from WHO and partners, the GMS has achieved a dramatic reduction in cases from an estimated 650,000 in 2012 to 82,000 cases in 2020

Cambodia

Data	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22
Total Tested	64,563	69,240	73,576	64,750	68,811	69,435	68,631	68,928	68,965	62,412	68,951	70,691	67,502	71,288
Total Pf + Mix	68	32	19	22	17	24	24	26	17	25	29	58	21	25
Total Pv	477	351	319	219	253	315	349	343	360	300	344	338	315	212



In Jan-Dec 2021 compared to the same period last year:

- Total Tested cases decreased 4%
- Total cases decreased 54%
- Total *Pf*+mix decreased 65%
- Total *Pv* decreased 53%

Data source: MEDB database

Global **Malaria** Programme

World Health Organization

Looking forward

- Africa
- Biological threats
- Smarter data driven public health
- UHC & inequalities
- Country ownership
- R&D

"…The history of special antimalarial campaigns is chiefly a record of exaggerated expectations followed sooner or later by disappointment and abandonment of the work. This record of failure and disappointed hopes makes it clear that the only prospect of real progress lies in renewed activity in the continuous study of the disease in all its aspects…"

Malaria Commission (1927) Principles and Methods of Antimalarial Measures in Europe. 2nd General Report of the Malaria Commission of the League of nations, Geneva.

WHO (1948 – 2018)

7 decades supporting countries fighting malaria

Malaria: a problem to be solved,

not simply a task to be performed

For guidance: Draft Framework for allocation of limited malaria vaccine supply

World Health Organization

Due to limited time today: additional written comments from MPAG members welcome, please address to MalariaVaccineConsultation@who.int or WHO Secretariat by 30 March

Presentation to Malaria Policy Advisory Group

Virtual meeting 23 March 2022

Initial malaria vaccine supply expected to be insufficient to meet the needs

Demand

- WHO recommendation in October 2021 - Over 25 million children are born each year in regions with medium to high malaria transmission
- Financing approved by Gavi in December
- African leaders calling for rapid access, demand expected to be high
- **Could exceed 80-100 million doses/year** (based on Gavi's latest forecast)

Supply[1]

- 1 vaccine, single manufacturer
- Production currently ramping up; GSK **commitment of up to 15 million doses per year** until 2028
- Ongoing product transfer of RTS,S antigen to Bharat BioTech (AS01 will continue to be provided by GSK)
- 2nd vaccine (R21/MM) in phase III, could become available within 5 years

1/ WHO Malaria Vaccine Global Market Study, available: https://www.who.int/publications/m/item/who-malaria-vaccine-global-market-study-september-2021

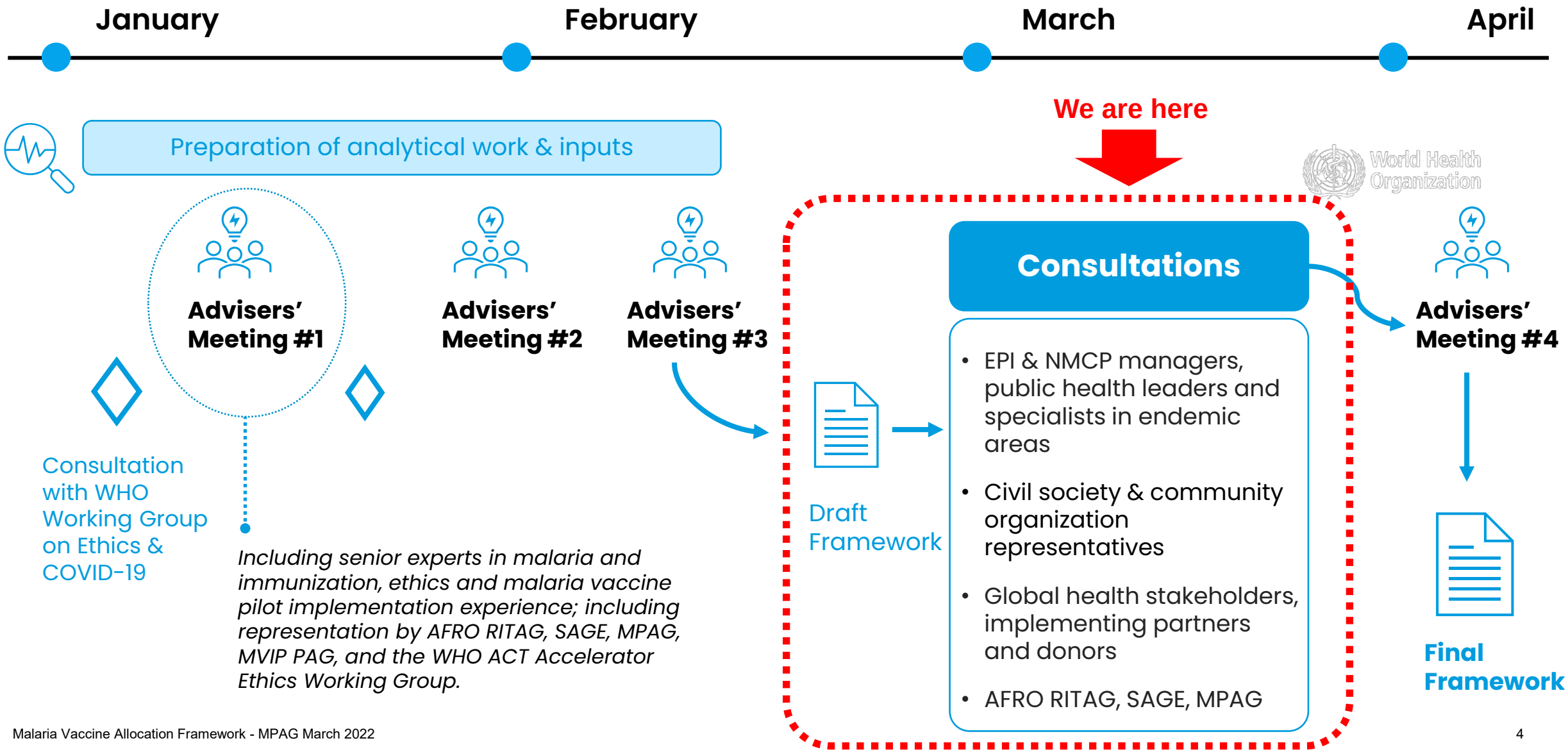
Intention of the Framework

The Framework aims to offer guidance globally on the allocation of RTS,S/AS01, and other malaria vaccines as they become available, between countries, and to offer guidance on prioritization of areas for vaccination within countries until supply constraints can be resolved.

- Details of in-country deployment should respect sovereign decision-making and align with the High Burden to High Impact (HBHI) approach to sub-national tailoring of malaria interventions

The intended audience of the Framework are global and national decision-makers involved in making allocation and prioritization decisions about malaria vaccines, including policy makers in malaria-endemic countries, the manufacturer(s), Gavi, the Vaccine Alliance and other funding, implementing and technical partners.

Process for the development of the Allocation Framework



The draft Framework

World Health Organization

Governance principles	Ethical principles for allocation	Key considerations / side-constraints
Transparency **Inclusiveness & participation** **Accountability**	**First priority principle: Greatest need** Allocate the vaccine to those countries at greatest need, where the disease burden and risk of progression to severe disease or death is highest **Second priority principle: Maximize health impact** Allocate the vaccine to countries for use in areas where the expected health impact is greatest **Third priority principle: Equity (Equal Respect)** Prioritize countries that commit to fairness and addressing the needs of marginalized individuals and communities in their malaria vaccination programmes **Tie-breaker principle: Reciprocity** If everything else is equal, the country with a prior contribution to the vaccine's development should get priority	 Honour commitments to pilot countries: pilot areas continue to get priority access to vaccine  Ensure continuity / sustainability of access to vaccine once a programme has started  Avoid sub-optimal use of vaccine / minimize risk of vaccine wastage  Allocation should not perpetuate pre-existing structural injustices

Substantive values

Thinking as a community and standing in solidarity with those most in need

- **The target population are children living in regions with moderate to high malaria transmission**, primarily on the African continent.
- It is thus important that an allocation framework resonates with the **ethical values common to African peoples**.
- **Communitarian values**, such as solidarity, sharing, and harmony, alongside individual rights and duties, occupy a central role in African normative frameworks.
- A **solidaristic approach** is required to ensure, in this initial phase, highest priority is accorded to saving the most lives and prioritizing the needs of children at greatest risk of severe disease and death.

Substantive values

Thinking as a community and standing in solidarity with those most in need

Governance principles

- **Refer to how this Framework is being developed and how the resulting decisions should be made, communicated and monitored**

Transparency

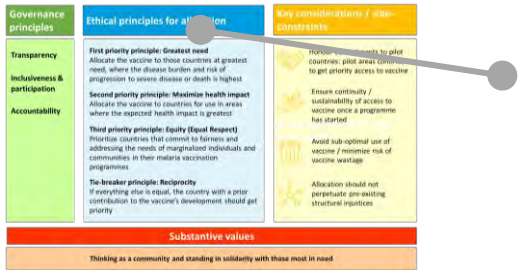
- Make information publicly available in an honest, straightforward manner – including allocation decisions and their justifications, the practical implications, and reasons for scarcity, and actions taken to address

Inclusiveness & participation

- Those affected by vaccine allocation decisions – including individuals, communities and countries – should be able to exert some influence
- Expert advisers provide guidance, most live in or work with malaria affected countries
- Broad stakeholder consultation process (ongoing)

Accountability

- Decisions made with clearly defined objectives, processes, roles and responsibilities – important role for Gavi Alliance
- Recipient countries should also be held accountable regarding criteria for internal allocation and actual delivery of vaccines
- Periodic reviews of Framework, updates if needed



Ethical principles for allocation

First priority principle: Greatest need
Allocate the vaccine to those countries at greatest need, where the disease burden and risk of progression to severe disease or death is highest

- Proposed proxy measure: composite index that combines levels of *P. falciparum* parasite prevalence rate (PfPR) in children and under-five all-cause mortality rate (U5MR)

Second priority principle: Maximize health impact
Allocate the vaccine to countries for use in areas where the expected health impact is greatest

- Drop-out rate between DTP3 and MCV1 **preferably <10%** to minimize sub-optimal vaccine use and wastage

Third priority principle: Equity (Equal Respect)
Prioritize countries that commit to fairness and addressing the needs of marginalized individuals and communities in their malaria vaccination programmes

- Take into account the vulnerabilities, risks and needs of communities who, because of underlying societal or geographic factors, are at risk of experiencing greater burdens from malaria
- Many countries have areas with similarly high needs – as a consequence, phased sub-national vaccine implementations will be required

Tie-breaker principle: Reciprocity
If everything else is equal, the country with a prior contribution to the vaccine's development should get priority

Key considerations / side-constraints

Honour commitments to pilot countries: pilot areas continue to get priority access to vaccine

- Since 2019, nearly 1 million children reached across Ghana, Kenya and Malawi; some areas have been serving as comparator (without vaccine) for the purpose of the pilot evaluation

Ensure continuity / sustainability of access to vaccine once a programme has started

- Essential principle upheld by national immunization programmes and global partners; important for trust in public services
- Withdrawal in the setting of ongoing stable transmission would likely be followed by an increase in severe disease cases and death similar to those seen before vaccine introduction

Avoid sub-optimal use of vaccine / minimize risk of vaccine wastage

Allocation should not perpetuate pre-existing structural injustices

- When aiming to maximizing health impact or to reduce suboptimal vaccine use or vaccine wastage, care must be taken not to perpetuate or exacerbate pre-existing structural injustices
- Every effort should be made to provide resources and technical assistance to remove barriers to access

Framework implementation

- **Implementation is a shared responsibility**
  To achieve its objectives, this Framework should, as much as possible, be adhered to by all relevant stakeholders - decision-makers in malaria endemic countries, the Gavi Alliance in its prioritization of support and vaccine procurement, manufacturer(s) and other partners as they consider their financial and technical support

- **Phased sub-national malaria vaccine implementation will be required**

- **Potential caps on vaccine doses in each phase**
  An upper limit (cap) for the number of vaccine doses provided to each country for each phase of prioritization might need to be implemented by Gavi in order to ensure that more countries with areas of highest need that want to implement the vaccine can have access to the vaccine.

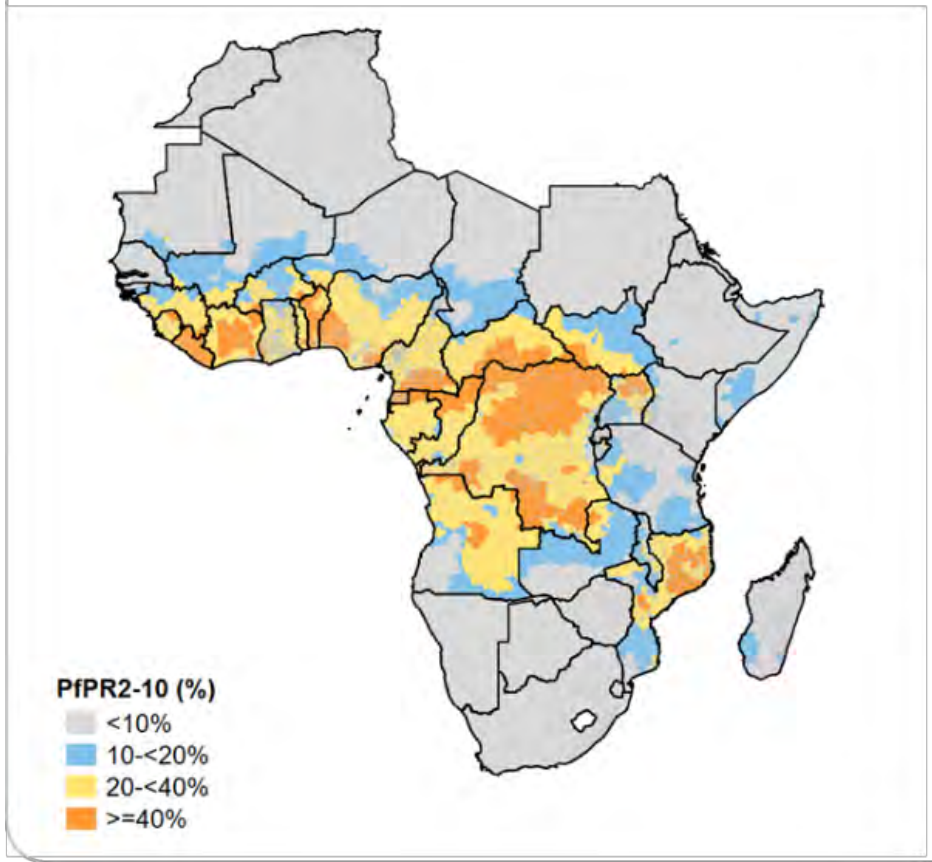
- **Proxy measure for greatest need**
  At global level, to enable across country comparison: composite index of *P. falciparum* parasite prevalence rate and under-five all-cause mortality rate. Countries may use locally available data to determine areas of greatest need, including potentially other measures of malaria risk, such as malaria incidence data.

- **Monitoring and periodic reviews**

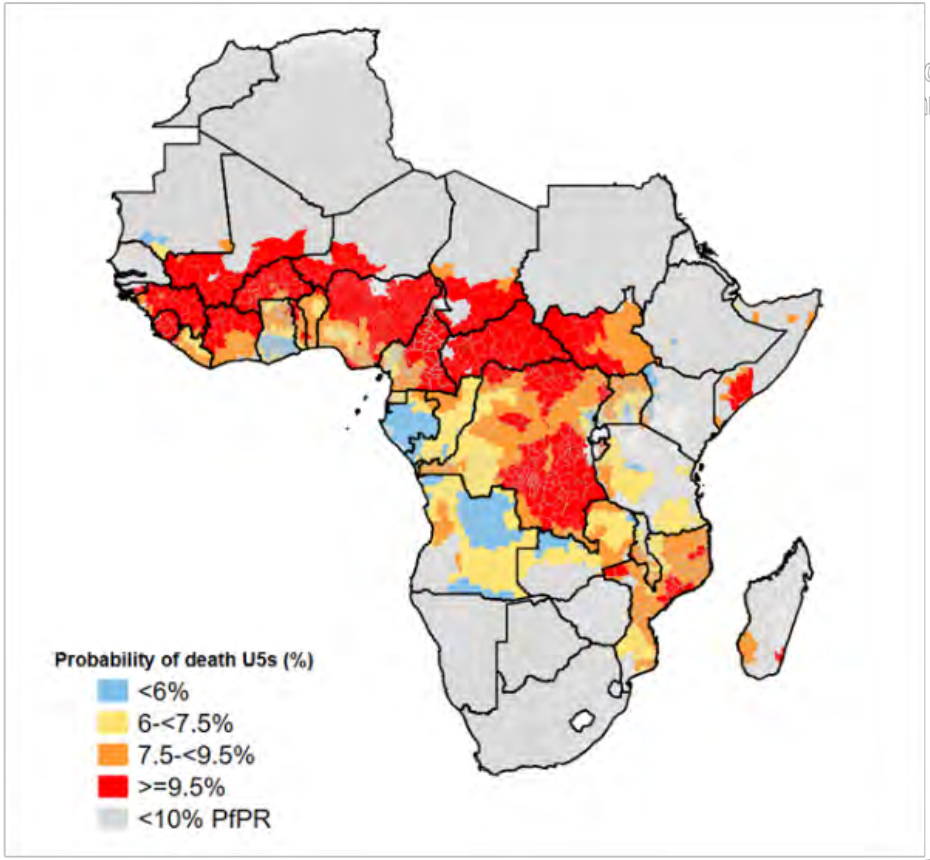
Illustration of “need” classification

World Health Organization

Estimated prevalence of *P. falciparum* infections in children aged 2-10 years

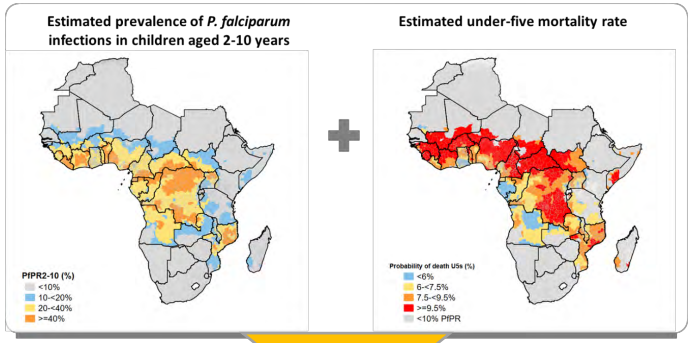


Estimated under-five mortality rate



Sources:
District level mean estimates of *Pf*PR in 2-10 year old children in 2019 (Malaria Atlas Project)
District level mean estimates probabilities of death from all-causes before the age of 5 in 2015 (IHME)

Illustration of “need” classification

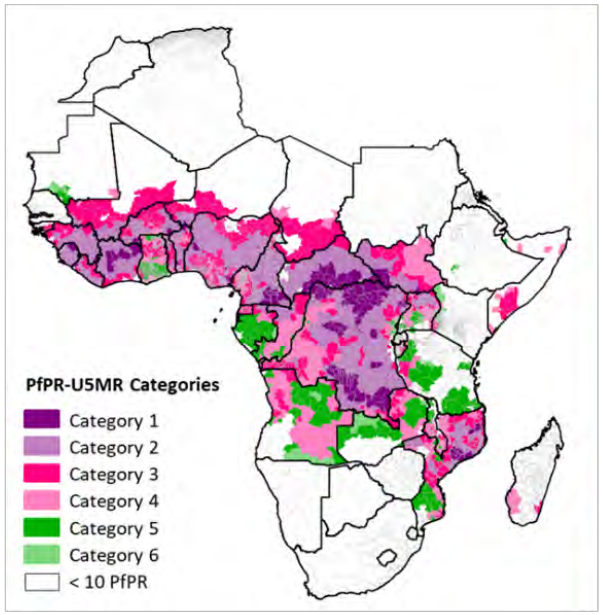


World Health Organization

Composite classification of malaria prevalence and all-cause under-five mortality as proxy for “need”

Maps are illustrative based on global estimates. Countries will identify areas of highest burden and need within its own borders based on best available local evidence and the broader context of sub-national tailoring of malaria interventions

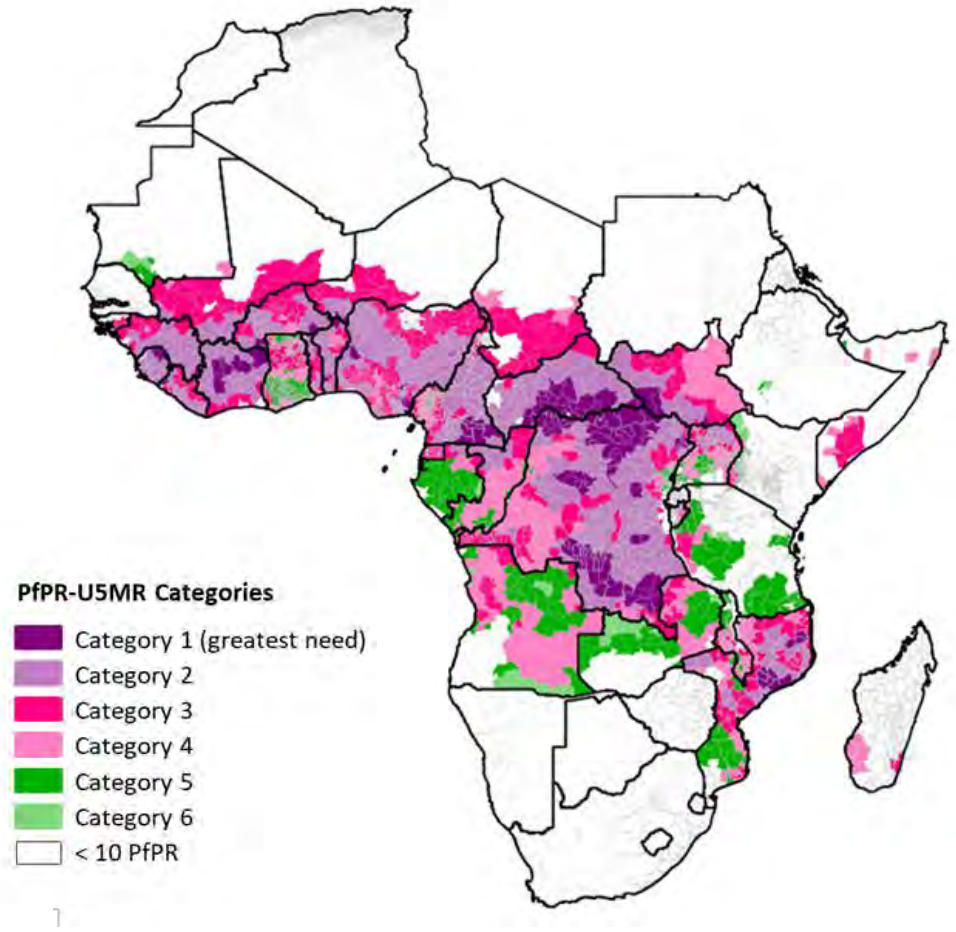
Composite classification of malaria prevalence and all-cause under-five mortality as proxy for “need”



Category	Possible combinations	
	Malaria prevalence	All-cause under-five mortality
1 Greatest need	PfPR >=40%	& U5MR >=9.5%
2	PfPR 20-<40%	& U5MR >=9.5%
	PfPR >=40%	& U5MR 7.5-<9.5%
3	PfPR 10-<20%	& U5MR >=9.5%
	PfPR 20-<40%	& U5MR 7.5-<9.5%
	PfPR >=40%	& U5MR 6-<7.5%
4	PfPR 10-<20%	& U5MR 7.5-<9.5%
	PfPR 20-<40%	& U5MR 6-<7.5%
	PfPR >=40%	& U5MR <6%
5	PfPR 10-<20%	& U5MR 6-<7.5%
	PfPR 20-<40%	& U5MR <6%
6	PfPR 10-<20%	& U5MR <6%

World Health Organization

Illustration of "need" classification



Supply availability	Category of need (order of prioritization)	Target children per year (births in 2023)	Vaccine doses required per year (assuming 100% coverage and 4 dose schedule)
	Pilot areas in Ghana, Kenya & Malawi	**~900,000**	**~3,600,000**
	Category 1 Greatest need, highest priority	1,200,000	4,800,000
	Category 2	6,700,000	26,900,000
	Category 3	7,800,000	31,100,000
	Category 4	4,500,000	17,800,000
	Category 5	2,300,000	9,400,000
	Category 6	1,600,000	6,500,000
	TOTAL	**25,000,000**	**100,100,000**

Map production: Global Malaria Programme (GMP), World Health Organization (WHO)
Disclaimer: The designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Next steps to finalize the Framework

Target timelines

- Written feedback welcome (for MPAG members by 30 March)
- 30 March: presentation to AFRO RITAG members for guidance
- Analysis and summary of feedback from consultations to advisers, for their consideration
- 20 April: Final meeting of advisers to finalize the Framework
- **By end May:** Framework completed

Thank you!

Credit: WHO/Neil Thomas.

Temporary Advisers

Drawing expertise from the AFRO Regional Immunization Technical Advisory Group (RITAG), the Strategic Advisory Group of Experts on Immunization (SAGE), the Malaria Policy Advisory Group (MPAG), the Malaria Vaccine Implementation Programme Advisory Group (MVIP PAG), the WHO ACT Accelerator Ethics Working Group, CSOs and pilot implementation countries

Professor Helen Rees (Co-Chair)	Chair of AFRO Regional Immunization Technical Advisory Group (RITAG) & Executive Director, Wits RHI, University of the Witwatersrand, Johannesburg, South Africa
Professor Rose Leke (Co-Chair)	Emeritus Professor of Immunology and Parasitology and Fellow of the Cameroon Academy of Sciences CAS, the African Academy of Science (AAS) and The World Academy of Science, (TWAS), Université de Yaoundé, Cameroon
Professor Brieger William	Member of AFRO RITAG & Professor, Health Systems Program, Department of International Health, The Johns Hopkins Bloomberg School of Public Health
Dr Folake Olayinka	Member of AFRO RITAG & Immunization Team Leader, U.S Agency for International Development
Professor Richard Adegbola	Member of AFRO RITAG & Research Professor & Consultant, Nigerian Institute of Medical Research
Professor Alejandro Cravioto	Chair of the Strategic Advisory Group of Experts on Immunization (SAGE) & Affiliated with the Faculty of Medicine of the Universidad Nacional Autónoma de México (UNAM)
Professor Dyann Wirth	Chair of the Malaria Policy Advisory Group (MPAG) & Director, Defeating Malaria: From the Genes to the Globe, Harvard University and Faculty Director, Harvard Integrated Life Sciences Ph.D. Programs
Dr Fredros Okumu	Member of MPAG & Public Health Researcher and Director of Science at Ifakara Health Institute, Tanzania
Professor Evelyn Korkor Ansah	Member of MPAG & Director, Center for Malaria Research, University of Health and Allied Sciences, Ghana
Dr Bvudzai Magadzire	Senior Technical Advisor for Research & Advocacy at VillageReach, based in Cape Town, South Africa; Gavi Alliance Alternate Board member representing Civil Society Organizations
Dr Caesar Atuire	Senior Lecturer, Department of Philosophy and Classics, University of Ghana, Accra, Ghana & Member of the WHO ACT Accelerator Ethics Working Group
Professor Fred Binka	Expert from MVIP Pilot country (Ghana) & Professor of Epidemiology and the Vice Chancellor of the University of Health and Allied Sciences Ho, Ghana
Dr Rose Jalang'o	Expert from MVIP Pilot country (Kenya) & Strategic Information Management and Communications Officer in the National Vaccines and Immunization Program, within the Kenya Ministry of Health
Professor Peter Smith	Chair of MVIP Programme Advisory Group (PAG) & Professor of Tropical Epidemiology, London School of Hygiene and Tropical Medicine (LSHTM), UK
Dr Eusebio Macete	Co-Chair of MIVP Programme Advisory Group (PAG) & Director, Farmácias de Moçambique SA, Mozambique
Professor Keymanthri Moodley	Distinguished Professor in Department of Medicine and Director of the Centre for Medical Ethics and Law, Stellenbosch University, South Africa and Adjunct Professor, Department of Social Medicine, University of North Carolina- Chapel Hill, USA

Tailoring the malaria response to subnational context: an operational manual

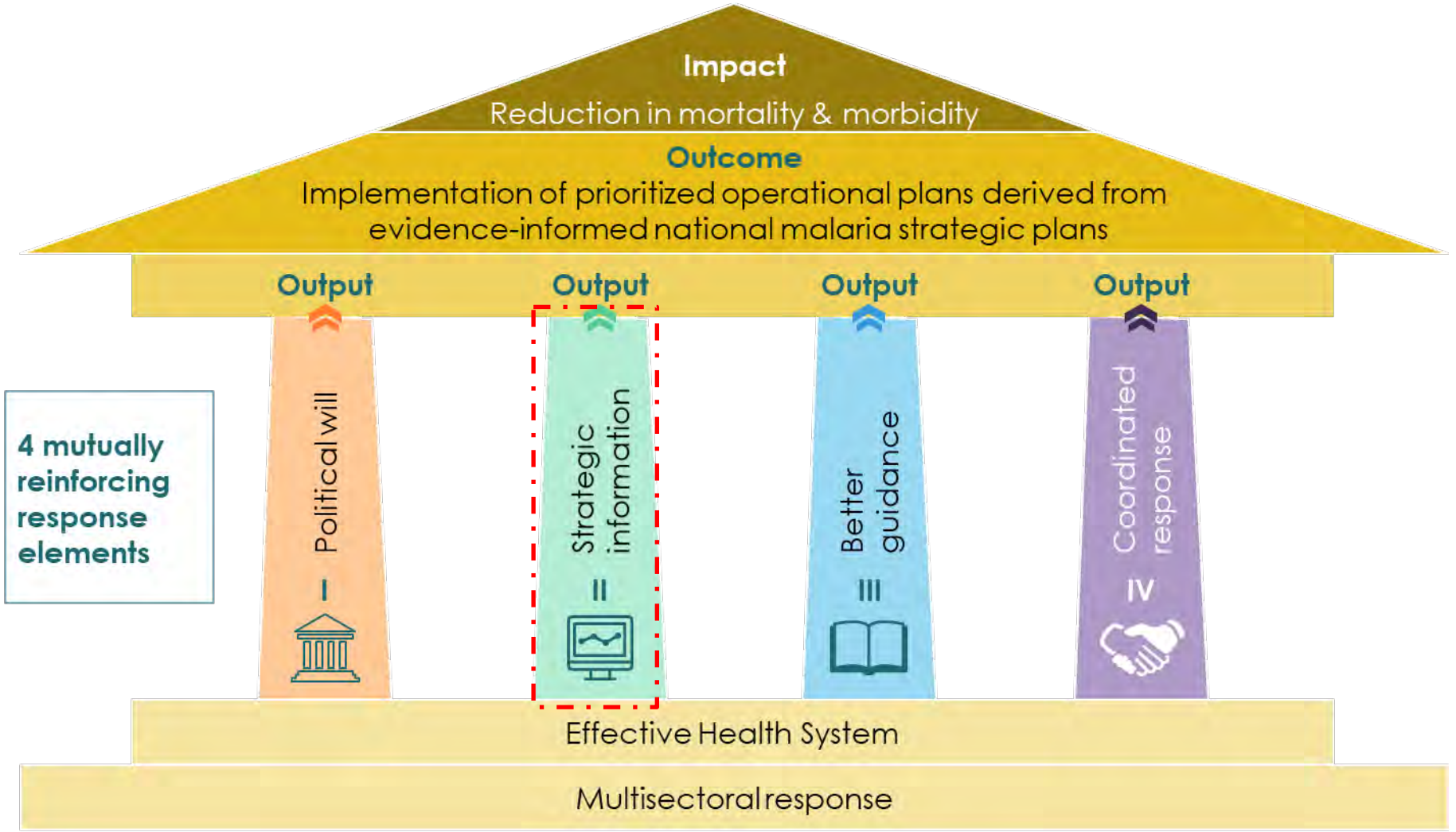
Dr Abdisalan Noor
Head, Strategic Information for Response Unit

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

Global **Malaria** Programme

World Health Organization

High Burden to High Impact (HBHI) approach



Anchored in broad health priority setting

National malaria strategic plans should ideally be nested within the broader national health sector planning...

- to relate the most important citizens' health needs and demands, as identified in a situation analysis, to the best options for addressing those needs and demands;
- to ensure that programmes and interventions are evidence-based, cost-effective and fairly distributed, addressing health needs of all population groups, particularly the most vulnerable segments of society;
- to inform national strategies and resource allocation of the public purse;
- to provide key reference information and evidence for policy-making, and monitoring and evaluation.

Anchored in value-based health services (VBHS)

The principles of value-for-money

Economy: addresses whether inputs (staff, consultants, raw materials and capital that are used to produce outputs) are purchased at appropriate quality and at the right price. In the case of malaria intervention, this will entail the collection of unit cost data for human, material and financial for all activities.

Efficiency: links inputs to outputs and measures, for example, whether quality malaria interventions are delivered at the right quantity and right timing to those populations that need them the most.

Effectiveness: how well are the outputs from an intervention achieving the desired outcome on the burden of malaria (measured as malaria infection, morbidity and all-cause mortality).

Equity: degree to which the results of the intervention are equitably distributed

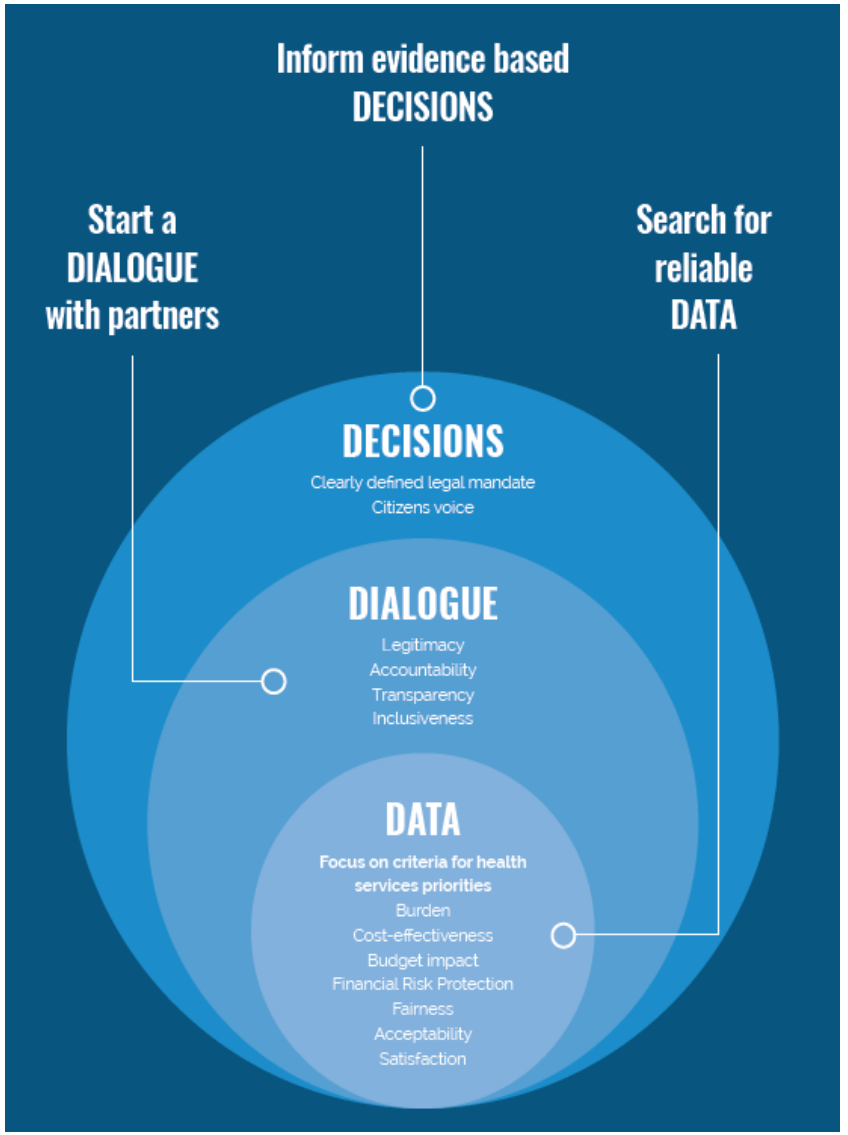
Cost-effectiveness: the relationship between economic inputs and

Value for money is generally quantified by the application of an economic evaluation methodology, such as cost-effectiveness analysis. However, value for money in the decision-making process alone is not sufficient to ensure that the anticipated value is seen at the service delivery level.

Anchored in value-based health services (VBHS)

To deliver value-based health services (VBHS) a deep understanding of what patients and communities value the most is required. This means shifting the focus away from “what is the matter with people” to “what matters to people”, placing people at the centre of care.

As such, VBHS requires that value for money estimation results in value that is passed on to patients and communities and corresponds to their interpretation of value. This could include ensuring health improvement at the patient level, responsiveness of the health system to patient needs, financial protection, efficiency and equity.



Anchored in the Paris Declaration & the Accra Agenda for Action

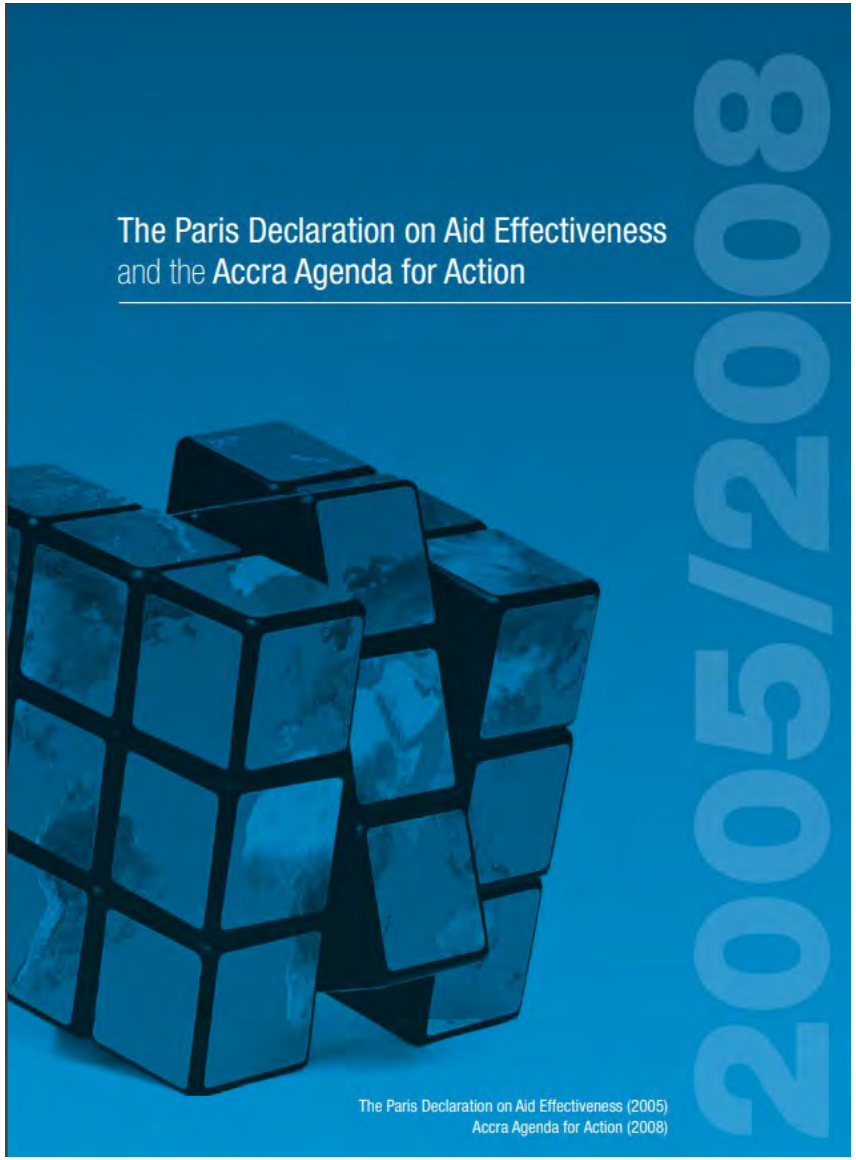
Ownership: countries set their own strategies
Alignment: Donors align behind these objectives and use local systems.

Inclusive partnerships: All partners - including participate fully.

Delivering results: focused on real and measurable impact on development.

Harmonisation: Better coordination and efficiency

Mutual accountability: Donors and partners are accountable for development results.



Target audience & structure of manual

Target audience

- National malaria programmes and their implementation partners
- Subnational entities responsible for coordination of implementation activities and engagement with communities on health priority setting
- Technical experts supporting countries in subnational tailoring of interventions
- Funders

Structure

PART 1: Principles of and metrics for subnational tailoring of malaria interventions

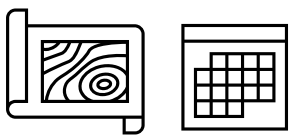
PART 2: WHO recommended malaria interventions and strategies: practical applications

PART 3: Understanding baseline and current transmission and their determinants

PART 4: Defining optimal intervention mixes

PART 5: Prioritizing interventions within a budget

PART 1: Principles of and metrics for subnational tailoring of malaria interventions



- **Malaria is geographically heterogeneous**, with transmission intensity and burden varying sub-nationally, even in high burden countries.
- These variations are not only **geographic but also temporal** (seasonal and secular trends)
- This **heterogeneity is a function of variations in climatic and ecological factors** such as temperature, rainfall and humidity **but also** modulated by anthropogenic factors such as malaria interventions, health system performance, movement and migration, urbanization, agriculture, mining and other factors.
- Current malaria interventions are highly cost-effective but have **variable impact on the main burden endpoints** (infection, mild disease, severe disease and death). All the prevention interventions have **modest efficacy,** their effectiveness changes in space and time.
- Therefore, the best pathway to impact (depending on the desired burden endpoint) is **through optimized and prioritized combinations** (or intervention mixing).
- It **defines universal coverage** not to mean everything everywhere, but matching interventions to need driven by a desire to achieve the biggest possible impact with available resources.
- This must be **driven by the best possible subnational data**, and that the evidence informs **a nationally owned and governed approach to decision-making**, recognizing that social justice and equity are not secondary but primary considerations in the decision-making process.

SNT – what are the key questions?

Where do we intervene?

Which interventions (or strategies) should we use?

Which interventions can we afford and how do we prioritize?

How and when do we deliver interventions?

How do we monitor their impact?

PART 1: Principles of and metrics for subnational tailoring of malaria interventions

Sub-national tailoring of malaria interventions – the use of **local data** and **contextual information** to determine the appropriate **mixes of interventions**, and in some cases **delivery strategies**, for a given area, such as a district, health facility catchment or village, for **optimum impact on transmission and burden of disease**.

Stratification - the process of geographically (and temporally) classifying **malaria risk** and **its determinants** into **meaningful categories** to inform the **tailored targeting** of the intervention under consideration. Eventually, this process leads to intervention (and strategy) mixes for each subnational unit. **Geospatial analysis/modeling** approaches are useful for stratification.

Optimization – national malaria strategic plans **ought to reflect the ambition of a country in its fight against malaria**. These targets are linked to overall **national health and development targets**. Therefore, the mix of interventions and strategies in these plans focus on what a country needs to do to achieve its targets and **not always constrained by the resources that are likely to be available** at the time of strategy development. *Optimization* was the process of ensuring that the interventions and strategies selected for NSP are most likely to lead to best possible **impact toward national targets**. These analyses should ensure that system-wide synergies are considered. **This is the basis of NSP costing**.

Prioritization – often, the **resources required** to fully implement national malaria strategic plans **are not available**. The SNT *prioritization* process aims to provide the right evidence to inform the **hard decisions countries need to make to prioritize investments for impact**, social justice and equity. The difference between the NSP costing and the prioritized plan is the resource gap. As new resources become available and context changes, the prioritization analysis will require revisions even with the lifespan of the NSP.

Metrics

Environmental covariates
- Rainfall
- Temperature
- Altitude
- Topology and other geographical covariates determining amenability to standing water
- Land use

Entomological measures
- Mosquito species & density
- Entomological Inoculation Rate (EIR)

Infection prevalence
- Demographically representative population-based surveys
- Surveys of populations of interest
- Prevalence from pregnant women attending Antenatal Care (ANC) facilities

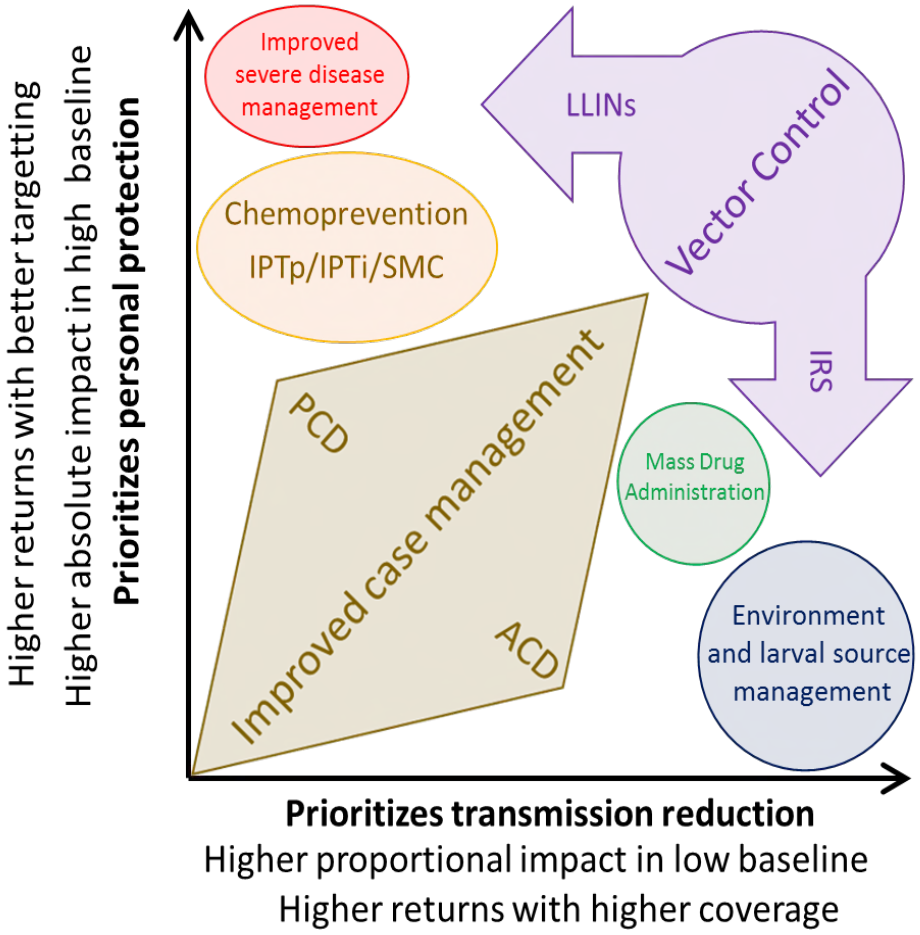
Cases
- Cases and case incidence
- Severe malaria
- Fever positivity rate

Other metrics
- Under 5 mortality

Demographic
- Population (location, count, gender, age)

Foundational
- Subnational boundaries
- Geocoded health facilities
- Settlements and urban extents

PART 2: WHO recommended malaria interventions and strategies: practical applications



Different interventions implemented at the same coverage in the same place are also likely to have strikingly different effects, varying according to three factors:

- **Personal protection** through blocking an infectious mosquito that would otherwise feed, preventing an infectious bite from becoming an established blood-stage infection (e.g., due to prophylaxis or vaccination) or through reducing the severity of disease following a blood-stage infection
- **Impact upon onwards transmission** through preventing mosquito oviposition and emergence, reducing mosquito survivorship following emergence or in preventing mosquitoes from feeding upon infected humans.
- **Longevity and durability of effectiveness** of either personal protection, impact upon transmission or both.

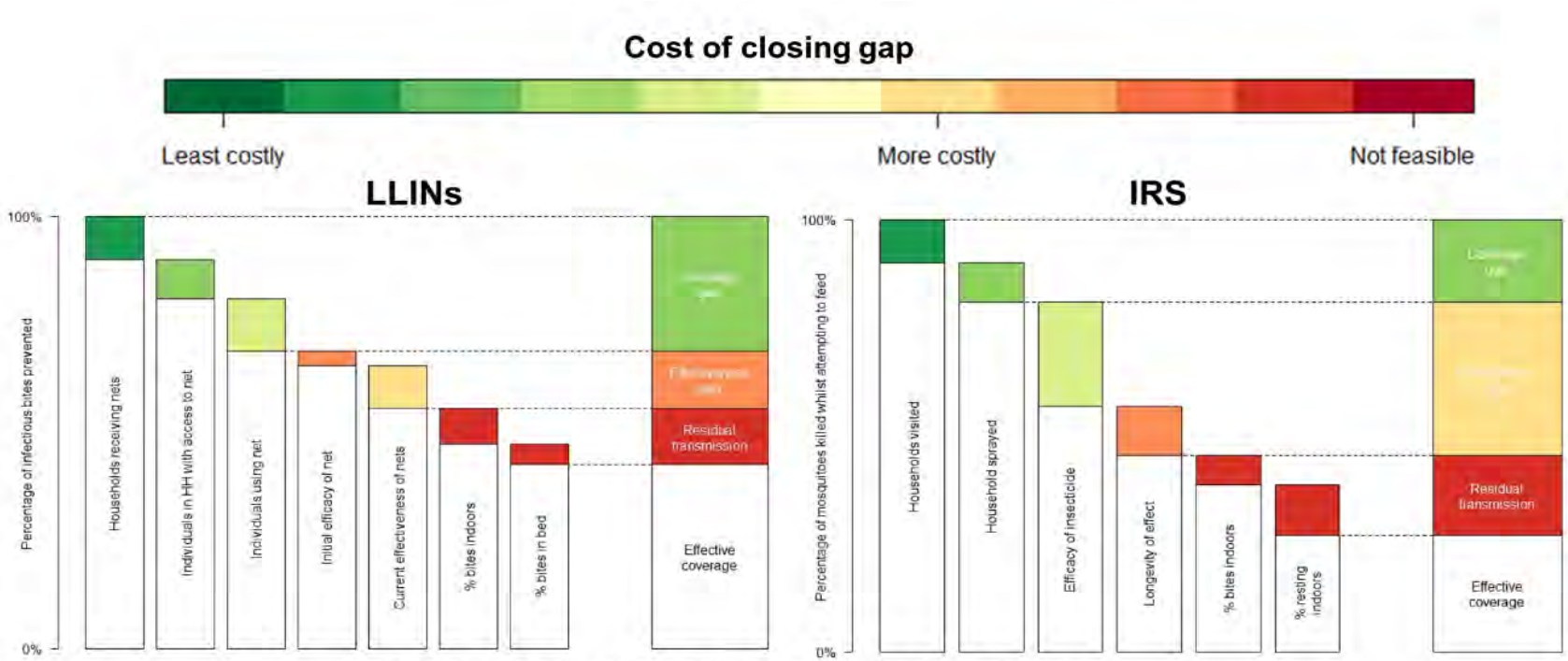
These are further modulated by interactions with a changing environment e.g., urbanization, housing etc

PART 2: WHO recommended malaria interventions and strategies: practical applications

The example of ITNs

WHO Recommendation	Impact endpoints	Considerations for scale up	Considerations for geographic targeting	Considerations for prioritization for impact within budget
i. WHO recommends deployment of pyrethroid-only long-lasting insecticidal nets (LLINs) for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission. ii. WHO suggests deploying pyrethroid-PBO nets instead of pyrethroid-only LLINs for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission where the principal malaria vector(s) exhibit pyrethroid resistance.	• All-cause child mortality • Incidence of *P. falciparum* malaria • Prevalence of *P. falciparum* malaria • Incidence of severe malaria disease	• Where the principal malaria vector(s) bite predominantly at night after people have retired under their nets. • Strong and sustained community acceptability • Main channel – mass campaigns • Continuous channels – ANC, EPI, schools etc must be functional throughout • Digital georeferenced planning and distribution tools used for efficient targeting	• ***Malaria endemic areas*** – classified baseline transmission of <1% *Pf*PR_{2-10} • ***Microstratification in urban areas*** – where receptivity has been modified from baseline levels, transmission is highly clustered, acceptability may be low – overall effectiveness is likely to be low. High targeted approach needed	• ***Malaria endemic areas*** – could be redefine by increasing baseline threshold for example <5% *Pf*PR_{2-10} • ***Equity considerations*** – communities that are disproportionately underserved given special consideration, but cost of reducing inequity can be higher for burden averted (i.e., equity vs efficiency) • ***Microstratification in urban areas*** – exclusion of all urban areas if average prevalence below the threshold of <5% *Pf*PR_{2-10} • ***Impact analysed within the broad mixes of interventions, and by endpoint*** – the effect size (and cost-effectiveness) of ITNs likely to vary across a country by endpoint. Impact relative to other interventions should be considered

PART 2: WHO recommended malaria interventions and strategies: practical applications



Data types to inform size and cost of closing gap

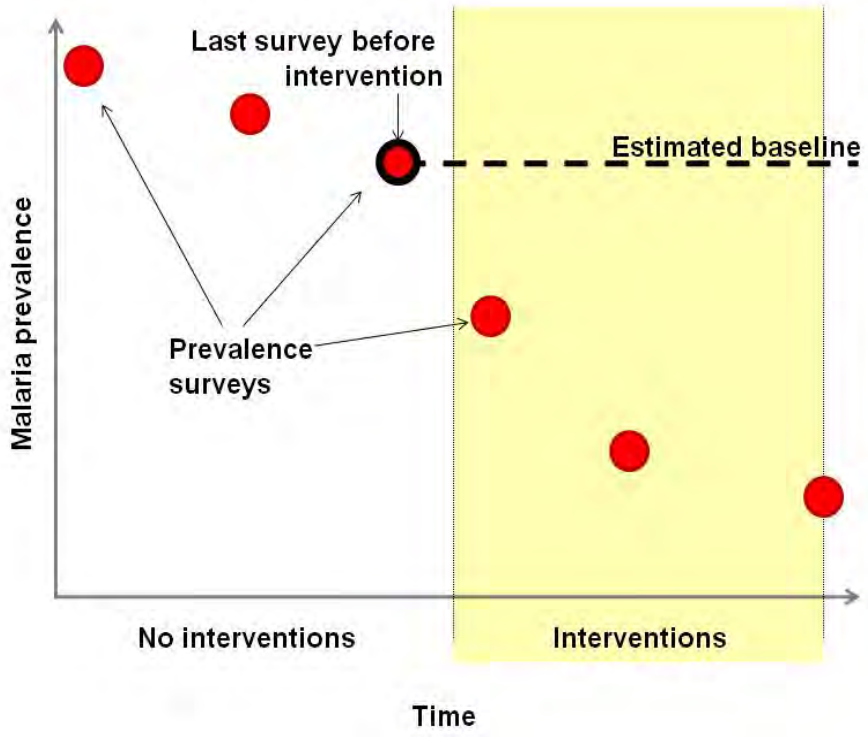
✓	✓						Census data
✓	✓			✓			Distribution data
	✓	✓					Health survey
		✓			✓	✓	Behavioral studies
	✓						Housing survey
			✓	✓			Bioassays
			✓				Costs of alternatives
					✓	✓	Entomology

✓					
✓	✓				
	✓				
	✓			✓	
			✓		
		✓	✓		
		✓	✓		
				✓	✓

Closing the gap to impact

World Health Organization

Baseline and current transmission and their determinants



A baseline in its strictest sense refers to the level of transmission where there are no interventions, including the provision of any effective treatment. In reality, there are few contexts where at least low levels of access to treatment has not been available.

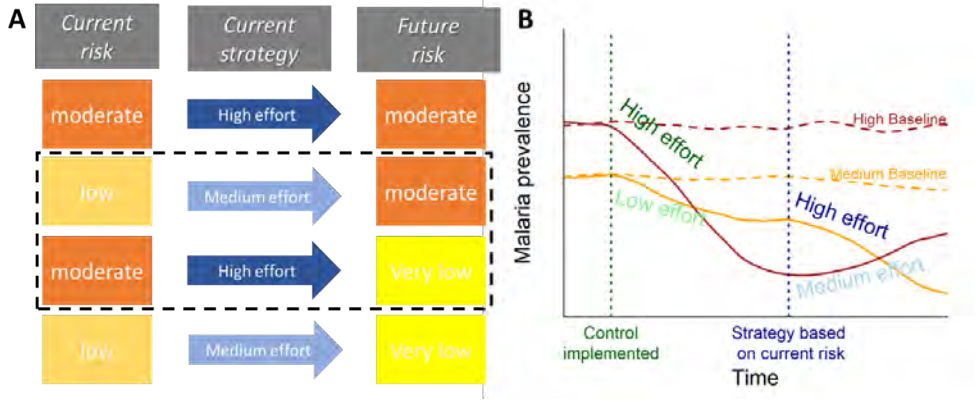
Given the possibility of changes in baseline unrelated to control measures, at least in settings where health systems are sufficiently robust that some access to effective treatment is always likely to be present, it may be most practical to use the last survey prior to the implementation of major preventative interventions (e.g. vector control or the provision of chemoprevention).

In this situation care must be made in interpreting this baseline when making strategic decisions around health system strengthening.

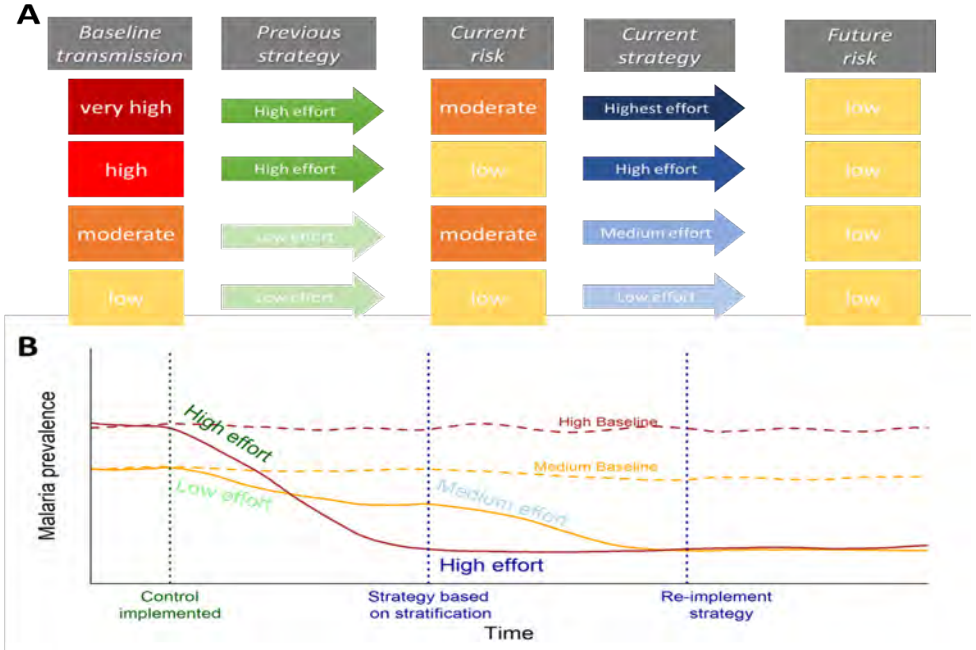
PART 3: Baseline and current transmission and their determinants

Baseline and current transmission and their determinants

Baseline transmission/risk not included



Baseline transmission/risk included



Basing a future strategy on the current level of risk while not accounting for heterogeneity in the baseline levels of transmission and the effects of previous interventions can be misleading.

In this scenario, again focusing on the two central strata within the dashed box, greater resources are dedicated to the strata with lower baseline levels of transmission and fewer to the strata with higher baseline transmission.

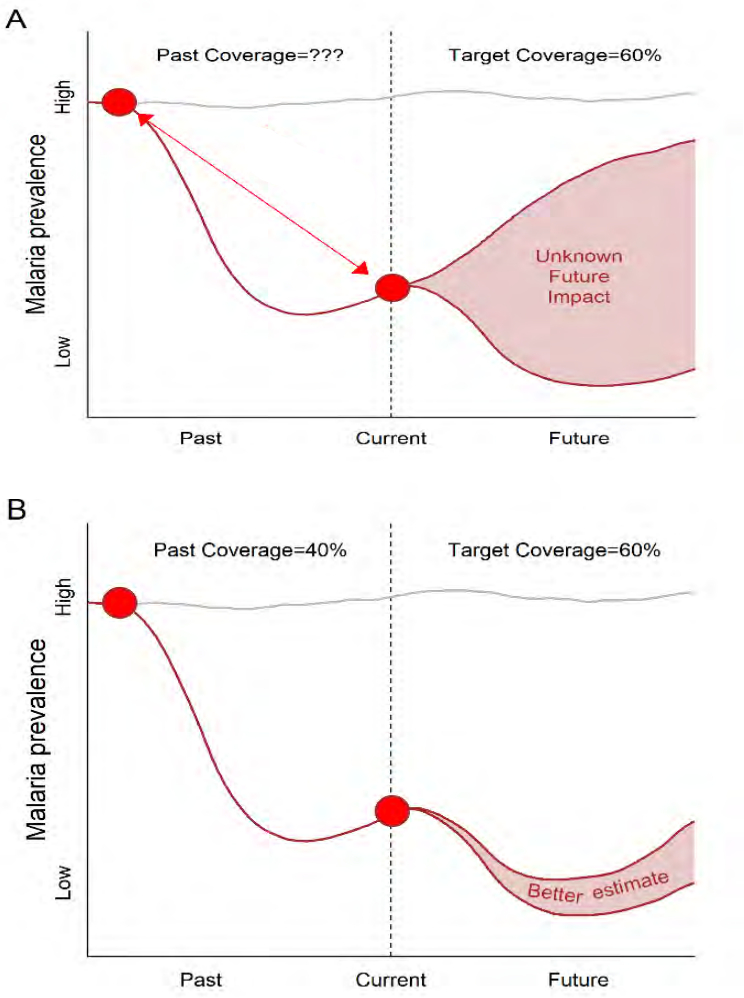
As a result, despite dedicating a higher level of overall resources (assuming strata represent approximately the same population at risk) to malaria control, this strategy is both less equitable, with fewer resources dedicated to the setting with higher baseline, and has achieved little or no incremental impact, with resurgence in the higher baseline strata cancelling out progress in the lower baseline strata.

However, if future strategies adequately account for levels at which control began and what has previously been done, much more informed decisions can be made. This allows for more equitable and effective distribution of resources (**A**), ensuring gains are maintained whilst prioritising additional resources to areas that are currently most at risk, leading to sustainable reductions in transmission and burden (**B**).

World Health Organization

PART 4: Defining the optimal mix of interventions and strategies

Capturing what we did to get here: constructing the intervention/determinants layer



Detailed data around the previous scale-up of interventions and other determinants within a unit area are key to understanding the likely incremental impact of any future malaria intervention and its interaction with other determinants.

The amount an intervention reduces malaria from its baseline level is likely to differ greatly across operational units and will depend, for example, upon the magnitude of the baseline itself as well as the metric used to measure this baseline.

It will also depend upon the fraction of the population covered by an intervention, the extent to which it provides personal protection from infection or disease in those covered and the magnitude of impact of the intervention upon transmission.

As such, two places with very different baselines can have the same level of current risk due to variation in the effectiveness or coverage of interventions, and the effect of other determinants.

PART 4: Defining the optimal mix of interventions and strategies

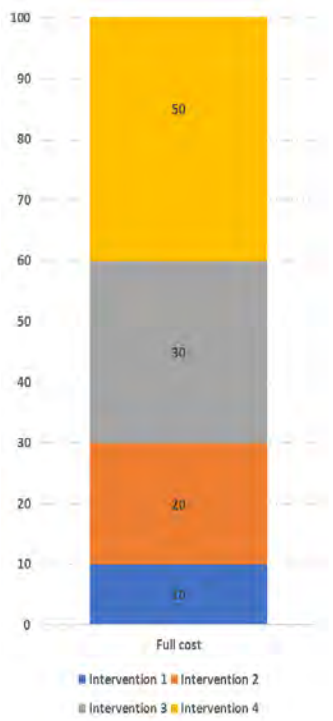
a	b	c	d	e
Where do we intervene?	**Which interventions (or strategies) should we use?**	**Which interventions can we afford and how do we prioritize?**	**How and when do we deliver interventions?**	**How do we design systems to monitor their impact?**
• Decide on operational unit • Define criteria for intervention targeting • Identify data needs (risk, determinants)	• Use layers of information to identify areas that meet criteria for a specific intervention • Repeat for all interventions • Map your intervention mixes, quantify populations in need • Project impact, refine mixes, optimize for NSP goals	• Define level of available funding • Define the 'fixed' vs 'flexible' decisions • Work within flexible decisions to prioritize investment • Choose the decisions with biggest impact (for a given endpoint) within available resources	• Discuss this during optimization and prioritization processes as it informs effectiveness and costs • Building cost-effectiveness into the modeling process may be useful • Costs vs equity considerations – more expensive to under-served	• Expect the tailoring process to be dynamic • Define future data needs • Identify appropriate M&E processes • Plan for the right M&E tools across programmatic activities • These are associated with costs and must be included in the optimization/prioritization processes
Adaptation of WHO recommendations, data assembly, stratification	*Stratification, tailored targeting, modeling*	*Re-stratification, re-tailoring, re-modeling*		

Country led stakeholder engagement to arrive at a consensus

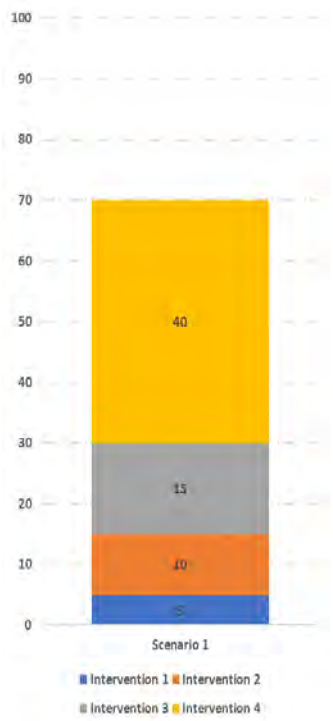
PART 4: Defining the optimal mix of interventions and strategies

Tailoring: stratification

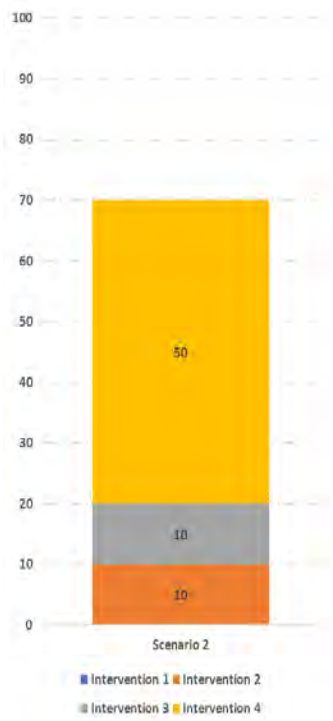
Fully funded NSP



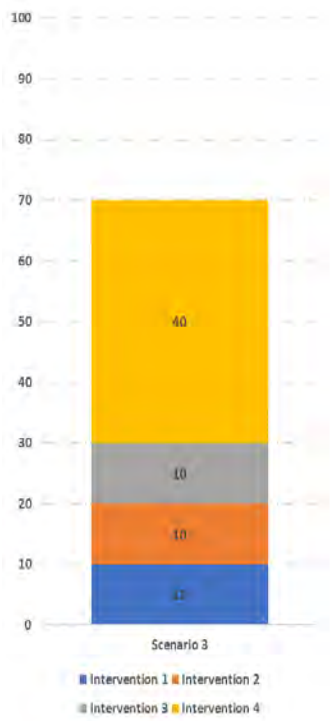
70% funded NSP



70% funded NSP



70% funded NSP



Prioritization: modelling

40% reduction in prevalence over 5 years

20% reduction in prevalence over 5 years

↓

Most cost-effective (but not most equitable)

15% reduction in prevalence over five years

↓

2nd most cost-effective (most equitable, but cost of equity initially high)

17% reduction in prevalence over five years

↓

3rd most cost-effective (not equitable)

Balancing cost-effectiveness and equity (and other value-based considerations)

Subnational tailoring of interventions: example of Ghana

Operational Unit
(district or equivalent)

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

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

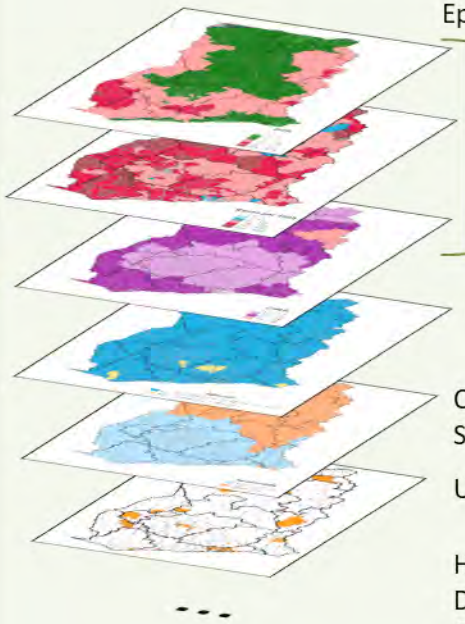
- LLIN, IRS, LSM,
- IPTp, IPTi, SMC,
- CM (Public HF, iCCM, private)

*for each intervention, WHO has:
- Recommendation
- Good practice statement
- Country adaptation
- Additional considerations for targeting

Malaria Strategic Plan development

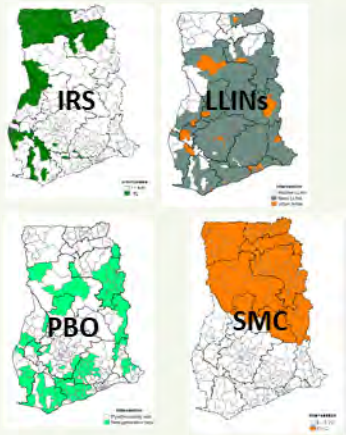
Stratification: Hierarchical ordering of one or multiple layers of information to make decisions

Indicators



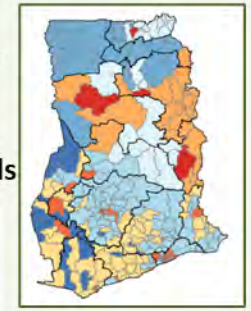
Epidemiology
Incidence
Prevalence
Mortality
Entomology
Climate & Seasonality
Urbanization
Health systems
Drug resistance
Conflict zones
Land use
etc

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

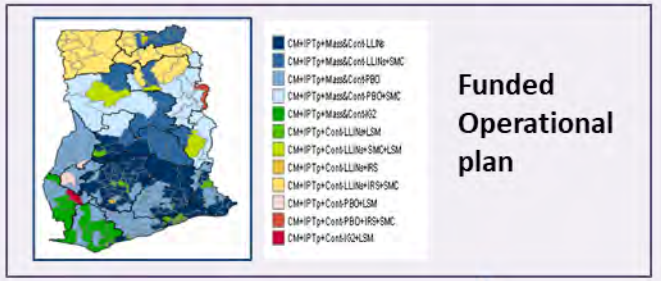


Mathematical models used to evaluate different scenarios and quantify impact of sub-nationally tailored intervention mixes

National Strategic Plan Intervention Mix Map & informed goals



Resource allocation and prioritization

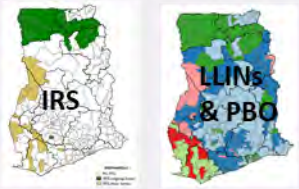


Funded Operational plan

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

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

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



Costing of national strategic plan

How much it costs

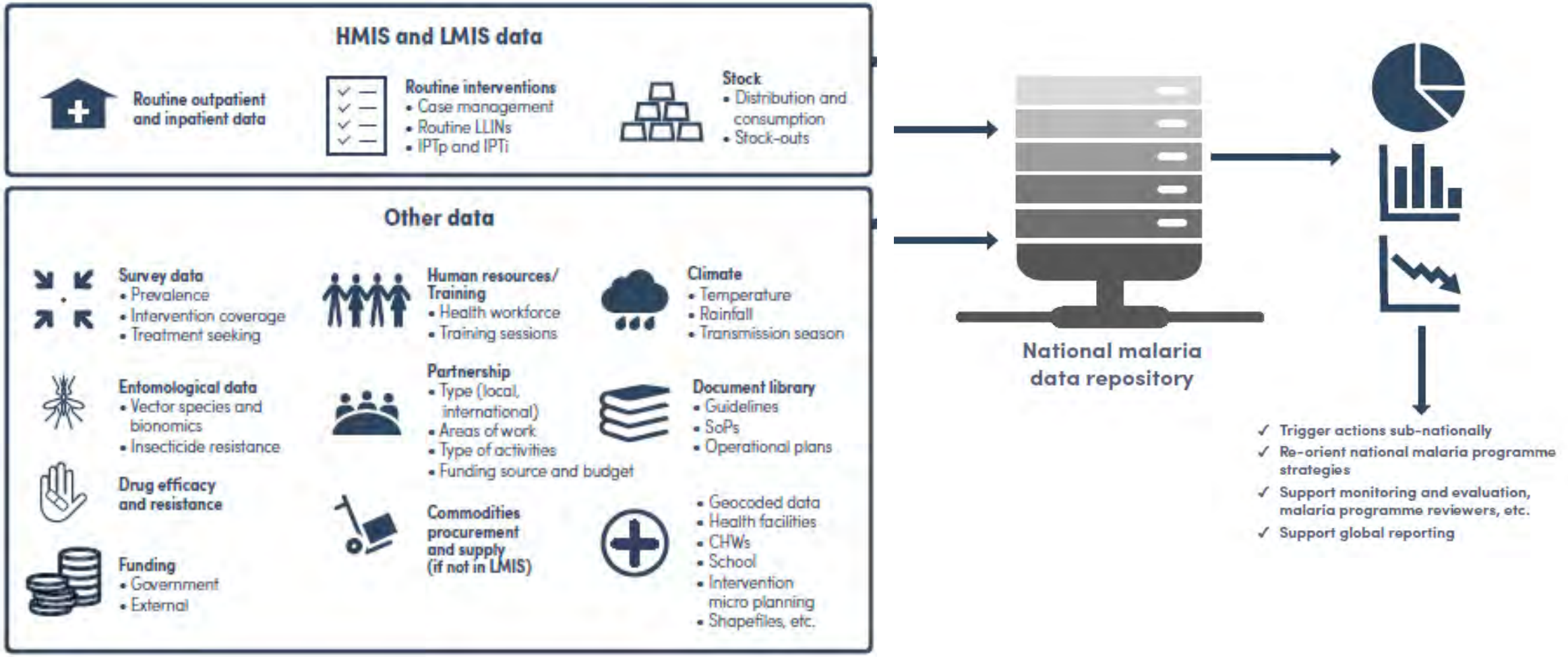
$$$

How much there is available

$

World Health Organization

PART 5: how do we measure impact?



Next steps

Develop worked examples – March 2022

Finalize draft manual and share for internal external review (including NMCPs) – April – May 2022

Final draft – May - June 2022

Dissemination (with training materials)

Acknowledgements

Imperial college

Northwestern University

Swiss Tropical Public Health Institute

Institute for Disease Modelling

PATH

Plasmodium knowlesi disease burden and transmission: implications for WHO certification of malaria elimination

Conclusions and recommendations by MECP

Li Xiaohong

Technical officer, Elimination Unit

Global **Malaria** Programme

World Health Organization

Background : WHO certification of malaria elimination and the official register

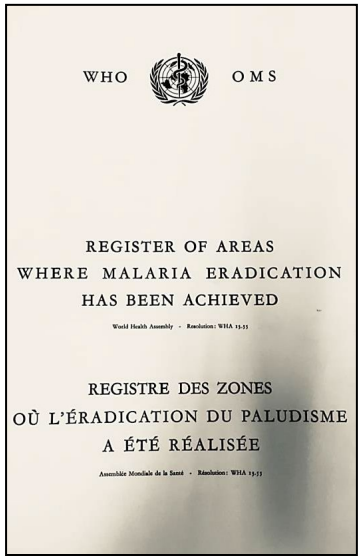
- Request WHO Director-General to establish official register listing areas where malaria eradication has been achieved, after inspection and certification by a WHO evaluation team.

  World Health Assembly 1960, WHA13.55

- Official Register
  - Purposes to set up the list: for prevention of re-establishment and for travellers
  - The first list
  - Updated list(s)

    Weekly Epidemiological Record: 1962 to now

    in WHO GMP website

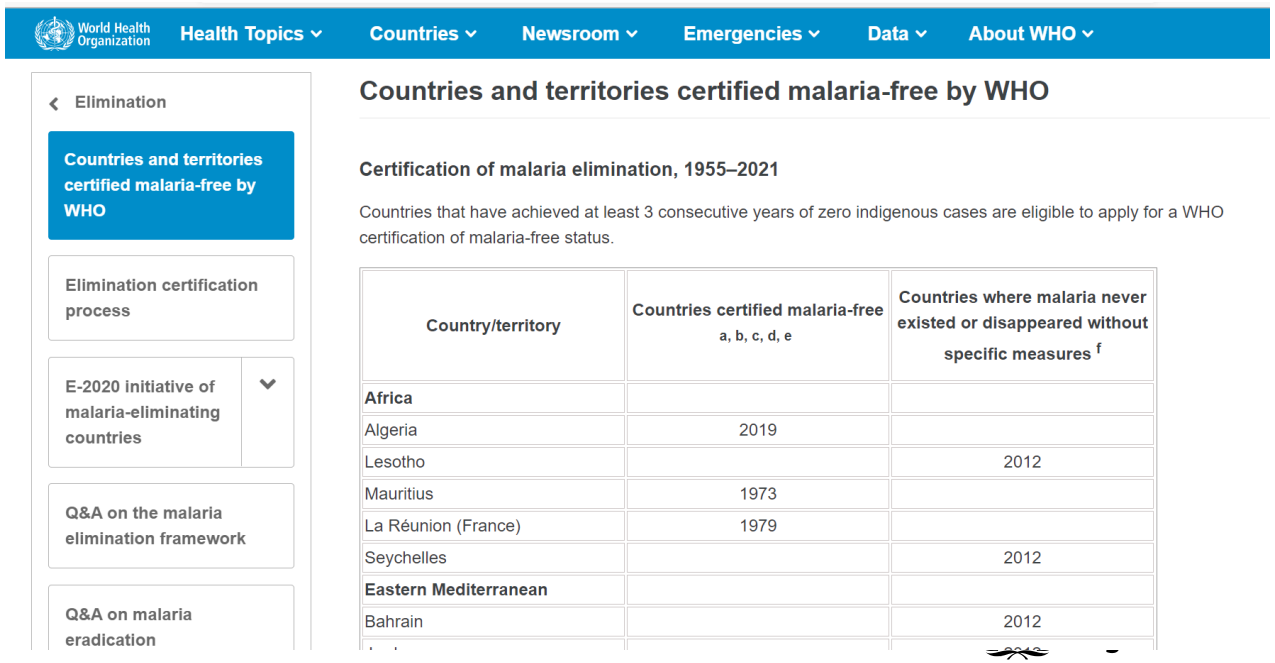

WHO OMS

REGISTER OF AREAS
WHERE MALARIA ERADICATION
HAS BEEN ACHIEVED

World Health Assembly - Resolution: WHA 13.55

REGISTRE DES ZONES
OÙ L'ÉRADICATION DU PALUDISME
A ÉTÉ RÉALISÉE

Assemblée Mondiale de la Santé - Résolution: WHA 13.55

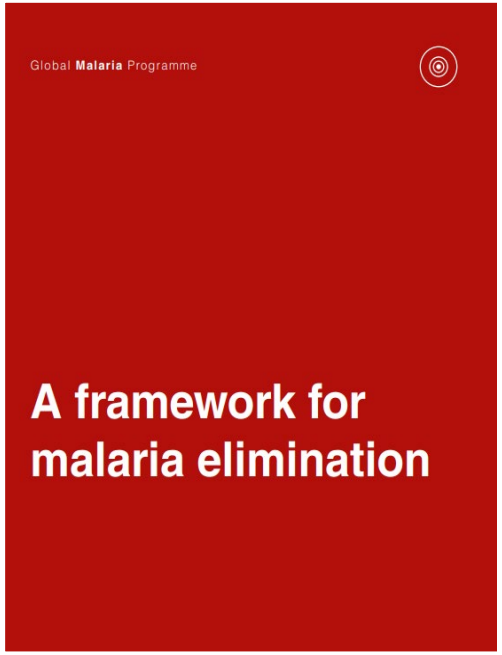


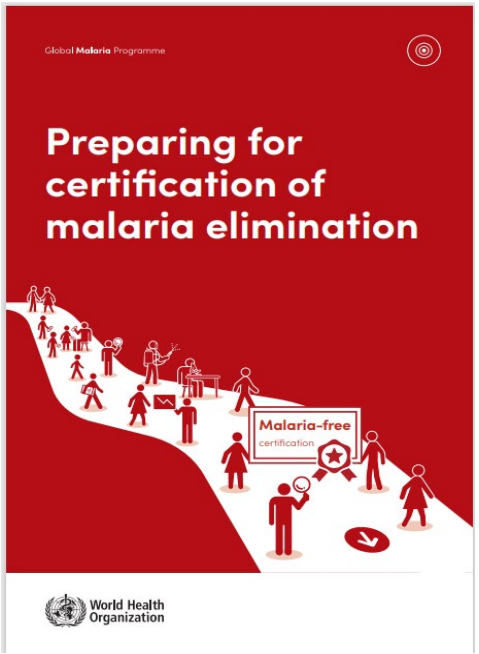
Country/territory	Countries certified malaria-free a, b, c, d, e	Countries where malaria never existed or disappeared without specific measures f
Africa		
Algeria	2019	
Lesotho		2012
Mauritius	1973	
La Réunion (France)	1979	
Seychelles		2012
Eastern Mediterranean		
Bahrain		2012

Background – certification criteria

WHO certification of malaria elimination requires proof that

- *local malaria transmission by Anopheles mosquitoes has been fully interrupted, resulting in zero incidence of indigenous cases for at least the past three consecutive years,*
- *an adequate surveillance and response system for preventing re-establishment of transmission is fully functional throughout the country*





- 40 countries and territories have been certified and entered into the official register
- Up until now, certification has been granted when countries have interrupted transmission of *P. falciparum, P. vivax, P. malariae* and *P. ovale*

11 COUNTRIES	15 COUNTRIES and 1 TERRITORY	0	7 COUNTRIES	6 COUNTRIES
1955–1969	1970–1987	1988–2006	2007–2017	2018-2021
• Bulgaria • Cyprus • Dominica • Grenada • Hungary • Jamaica • Poland • Romania • Saint Lucia • Spain • Trinidad and Tobago	• Australia • Bosnia-Herzegovina • Brunei Darussalam • Croatia • Cuba • Italy • La Réunion (France) • Mauritius • Montenegro • Netherlands • North Macedonia, • Portugal • Serbia • Singapore • Slovenia • United States of America		• Armenia • Kyrgyzstan • Maldives • Morocco • Sri Lanka • Turkmenistan • United Arab Emirates	• Algeria • Argentina • China • El Salvador • Paraguay • Uzbekistan

Review evidence and consensus

- *P. knowlesi* can infect humans and cause severe disease and death in a way that is very similar to or indistinguishable from other “human malaria parasites”.

- Human–mosquito–human transmission of *P. knowlesi* has been conclusively demonstrated in experimental human studies. *P. knowlesi* gametocytes have been identified by microscopy in natural infections in humans. There is limited evidence documenting *P. knowlesi* human–mosquito–human transmission in endemic settings. The consensus emerging from the preliminary findings of the analysis of the Malaysia data is that, while short chains of human-to-human transmission have likely occurred, most transmission is likely to be zoonotic.

- Malaysia has reported zero cases of the four main “human malaria parasites” for the past three years. However, reported data show that *P. knowlesi* has caused around 20 000 cases and 58 deaths in humans since 2015. In 2021 alone, there were 3342 cases and 13 deaths reported.

Conclusions and Recommendations (1)

- For countries where transmission of the four “human” Plasmodium species has been interrupted but *P. knowlesi* cases continue to occur, certification should depend on a careful assessment of the risks.
- When countries are reporting hundreds or thousands of *P. knowlesi* cases, certification of malaria-free status should be postponed.
- An arbitrary low threshold could be applied, e.g., 10 or fewer cases per year, below which a country can be potentially certified as having eliminated malaria, as the risk of zoonotic transmission might be considered “negligible”.

Conclusions and Recommendations (2)

- The MECP calls on WHO and partners to support countries dealing with relatively high levels of *P. knowlesi* transmission to strengthen control based on appropriate multidisciplinary approaches.
- Countries should aim to further improve the health care system and strengthen case-based surveillance in areas affected by *P. knowlesi*.
- While field epidemiology remains relevant and important, genomic epidemiology is likely to play a role in surveillance and may eventually help to clarify issues related to transmission pathways, as well as the most effective forms of control.

Conclusions and Recommendations (3)

- All countries' efforts to achieve malaria elimination should be encouraged, even if the burden is due to zoonotically transmitted malaria.

- The MECP proposes the establishment of a joint working group involving WHO and the ministries of health of affected countries to better define the problem and develop more effective strategies to control the transmission of *P. knowlesi*.

Meeting participants

MECP members

Prof Brian Greenwood (Chair)

Dr Anatoly Kondrashin (co-Chair)

Prof Fred Binka

Dr Keith Carter

Ms Cecilia T.Hugo

Dr Payre L. Josh

Prof Reza Majdzadeh

Prof Rossitza Ivanova Mintcheva

Prof Daouda Ndiaye

Dr Allan Schapira (through correspondence)

WHO Secretariat

Global Malaria Programme

Dr Pedro Alonso

Dr Abdislan Noor

Dr Kim Lindblade

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Regional Office for Europe (EURO)

Dr Elkhan GASIMOV

Regional Office for South-East Asia (SEARO)

Dr Risintha Premaratne

Regional Office for Western Pacific (WPRO)

Dr James Kelly

Regional Office for the Americas (AM/PAHO)

Dr Blanca ESCRIBANO

Observers

Prof Chris Drakeley

Dr Kim Fornace

For MPAG's decision

Does MPAG agree on the following text?

For countries where transmission of the four "human" Plasmodium species has been interrupted but *P. knowlesi* cases continue to occur, certification should depend on a careful assessment of the risk. When countries are reporting hundreds or thousands of *P. knowlesi* cases, certification of malaria-free status should be postponed. An arbitrary low threshold could be applied, e.g., 10 or fewer cases per year, below which a country can be potentially certified as having eliminated malaria, as the risk of zoonotic transmission might be considered "negligible".

Malaria Policy Advisory Group Meeting
23—24 March 2022, Geneva, Switzerland
Background document for Session 2

Technical consultation to review the classification of glucose-6-phosphate dehydrogenase (G6PD)

25 & 27 January 2022, virtual meeting

Summary

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked genetic condition affecting an estimated 500 million people worldwide. It is a cause of neonatal jaundice, acute haemolytic anaemia, and chronic non-spherocytic haemolytic anaemia (CNSHA). The acute haemolysis can be triggered by eating fava beans ("favism"), exposure to several medicines, and infection. The occurrence of acute haemolytic anaemia after exposure to the 8-aminoquinolines tafenoquine and primaquine is an important concern, as these are the only available medicines that are effective against the hypnozoite stage of *Plasmodium vivax* and so they are needed for the elimination of this malaria parasite.

The first classification of G6PD-deficient variants was made in 1966 and updated by a World Health Organization (WHO) Working Group in 1985. This classification is still in use today. Since 1985, the full cDNA sequence of the G6PD enzyme has been published, enabling the full genetic characterization of variants. In the last 36 years, over 230 genetic variants have been identified. Many studies have reported a considerable overlap between Class II and Class III variants in terms of the severity of haemolysis and neonatal jaundice, raising questions about the value of having separate classes.

The WHO Global Malaria Programme convened a panel of temporary advisors in January 2022 to review the current classification and recommend changes where needed. WHO commissioned a literature review to examine the variability of G6PD activity for variants currently classified in Classes II and III, and also invited the presentation of an interim analysis of an individual patient meta-analysis investigating the variability of G6PD activity among genetic variants.

The literature review covered 59 studies published between 1966 and 2021. Data on 2255 hemizygous males with G6PD deficiency were included. The review identified 17 variants with 117 sets of genotypic/phenotypic information. Samples from 22 countries showed significant variability of residual enzyme activity for most genetic variants. Some variants showed activity values that were consistently >10% of normal (e.g. Orissa, Kalyan-Kerala), whereas others were consistently <10% (e.g. Coimbra, Union); however, most variants had values spanning the 10% threshold between Classes II and III. Some variants had relatively low variability between studies (e.g. Mediterranean), whereas others had high variability (e.g. A-$^{(202)}$). No variant in the study (except for Kalyan-Kerala) had a weighted mean activity value that was >30% of normal, but five variants had an activity range that crossed the 30% threshold. For Kalyan-Kerala, 55% of hemizygous males had activity that was >30% of normal, and for the other four variants (A-$^{(202)}$, Mahidol, Orissa, Seattle), 12–25% of individuals had activity that was >30%.

The interim analysis of the individual patient meta-analysis included studies from 2009 to 2021. It included 20 variants and phenotypic/genotypic data from 1118 individuals, including 336 hemizygous males. Of the data-rich variants, two showed limited variability in terms of enzyme activity (Mahidol:

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median 10.2%, range 0–32.5%; Viangchan: median 7.1%, range 0–17.5%). However, the A-$^{(202)}$ variant showed high variability (median 31.5%, range 1.7–154.1%), with 20% of individuals at >80% activity.

There was general consensus among the panellists that the variation in enzyme activity values for the same variant may reflect both technical and biological factors. The participants noted the shortage of reliable data (especially for some variants) and the need for more research on phenotypic/genotypic associations, using standardized methodologies and procedures across multiple populations to generate more reliable data on individual variants.

The panel concluded that:

- the variability of activity for most genetic variants across the arbitrary threshold of 10% that distinguishes between Class II and Class III variants presents a strong argument to abandon this separation in any future classification;
- Class I should be retained, as CNSHA is a rare chronic condition that is well characterized with specific clinical manifestations associated with G6PD deficiency;
- Class V was based on a single case reported in the literature but not confirmed by further studies and, therefore, does not need to be retained;
- because of the variability of activity for any single variant, the new classification needs to include a range around the reported median enzyme activity.

Details of the discussions and conclusions of the panel advisors are included in the main body of this report. The proposed revised classification and future research from the consultation are summarized in the box on the next page.

Revised classification

In future, G6PD variants should be classified based on the median residual enzyme activity expressed as a percentage of normal activity as follows:

WHO classification of G6PD variants in homozygous and hemizygous individuals		
Class	**Median of G6PD Activity**	**Haemolysis**
A	<20%	Chronic (CNSHA)
B	<45%	Acute, triggered
C	60–150%	No haemolysis
U	Any	Uncertain clinical significance

It should be emphasized that this system is for classifying genetic variants of G6PD and should not be used to classify individual patients with G6PD deficiency.

Currently, no variants have been identified in homozygous deficient females or hemizygous deficient males that have median G6PD enzyme activity falling between 45% and 60%. Therefore, a gap has been left between Classes B and C. If new variants are found with median G6PD enzyme activity in this range, these should be included in the "U" class and studied until solid evidence is found that they induce acute haemolytic anaemia (= Class B) or do not pose a haemolytic risk (= Class C). Based on new evidence, the thresholds may then need to be revisited.

Future research

WHO should consider developing standard criteria to characterize the genotypes and phenotypes of G6PD variants. This will also help to improve comparability across studies and inform the classification of new and existing variants. Any new variant should be assigned a tentative percent activity value only if this has been measured at steady state using a validated quantitative reference test in at least three samples from unrelated males. Other items to be considered include the number of individuals required to examine the distribution of G6PD activity, number of laboratory replica measurements, criteria to define normal reference values, genetic relationships among cases, methodologies for measuring G6PD activity, phenotypic screening and variant identification, and criteria for including or excluding subjects with concurrent infection or haemolysis. Many variants have now been identified at the molecular level for which important functional properties are unknown. It is desirable to measure at least K_m^{G6P} and thermostability for these and any new variants.

Future research should also aim at addressing important gaps in knowledge, namely the risk of severe haemolysis associated with known and potential triggers in already described variants and the identification of other biological factors that might influence haemolytic response (e.g. enzyme activity in reticulocytes).

Abbreviations

AHA	acute haemolytic anaemia
AMM	adjusted male median
CNSHA	chronic non-spherocytic haemolytic anaemia
G6PD	glucose-6-phosphate dehydrogenase
MPAG	Malaria Policy Advisory Group
NNJ	neonatal jaundice
PCR	polymerase chain reaction
WHO	World Health Organization

Background

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

G6PD deficiency is an X-linked genetic condition affecting an estimated 500 million people worldwide. Most people affected live out their lives with no knowledge of their status, no symptoms and no complications. However, G6PD deficiency can lead to three clinical manifestations: neonatal jaundice (NNJ), acute haemolytic anaemia (AHA) and chronic non-spherocytic haemolytic anaemia (CNSHA).

In particular, AHA can be triggered by three possible causes, all linked to oxidative damage in red blood cells due to the reduced activity of the G6PD enzyme: eating fava beans ("favism"), drugs (such as 8-aminoquinolines like primaquine or tafenoquine), and infection.

The X-linked gene encoding G6PD is highly polymorphic, with over 230 variants identified at the molecular level *(1)*, many of which are polymorphic in different populations. The phenotypic expression in heterozygous females is highly variable, depending on the red cell mosaicism generated by the X-inactivation patterns. Therefore, in heterozygous females, the G6PD enzyme activity can vary between normal and that of a G6PD hemizygous male.

G6PD deficiency is more common in malaria-endemic countries. There is evidence that the heterozygous state (females) confers protection from severe infection by *Plasmodium falciparum* and possibly *P. vivax*. All G6PD-deficient variants entail haemolytic risk, but the range of severity of haemolysis differs for each variant.

Current World Health Organization (WHO) classification and guidance

The first international WHO meeting on G6PD was convened in December 1966, when just 20 G6PD variants had been described according to their biochemical characteristics, such as percent activity (measured by gold standard spectrophotometric assay), electrophoretic mobility (K_m) value, activity on substrate analogues, pH optimum, and thermostability *(2)*. This meeting proposed that an indication be given for each variant in terms of the enzyme activity in males. This led to a proposed classification published by Yoshida et al. *(3)*. WHO convened a Working Group on G6PD in 1985, which made some minor modifications to the Yoshida classification *(4)*. This modified classification remains in use today.

G6PD classification	Level of residual enzyme activity (% of normal)
Class I (Severe enzyme deficiency with CNSHA)	<10% with CNSHA
Class II (Severe)	<10%
Class III (Moderate to mild)	10–60%
Class IV (Very mild or no enzyme deficiency)	60–150%
Class V (Increased enzyme activity)	more than twice normal

Recent developments

Since the publication of the WHO classification in 1985, the full G6PD cDNA sequence has been published *(5).* This has enabled the identification of variants by their genotype, rather than relying on the biochemically measured level of G6PD activity. In the last 36 years, over 230 variants have been identified at the molecular level *(1)*.

Since 1985, and even before, several drugs have been shown to cause haemolytic anaemia in G6PD-deficient patients. The most notable have been antimalarials including chlorproguanil-dapsone, primaquine and tafenoquine. These drugs have been shown to trigger potentially life-threatening haemolysis in patients with Class II and Class III variants. From a public health point-of-view, the risk of haemolytic anaemia with the 8-aminoquinolines (primaquine and tafenoquine) is of particular concern, as these are the only drugs currently available that are active against the hypnozoite stage of *P. vivax* and so they are needed for the elimination of this malaria parasite.

Many studies have reported that there is considerable overlap between Class II and Class III variants in terms of the severity of haemolysis and NNJ, raising questions about the value of having separate classes.

The cut-off point between Class III and Class IV has also been questioned in relation to the threshold for "normal" G6PD activity, which was originally set at >60%. This has subsequently been set at >70% for clinical trials with tafenoquine *(6)*. A 2014 WHO consultation on point-of-care G6PD tests *(7)* recommended a threshold of G6PD activity >80% in heterozygous females and >30% in hemizygous males in order to minimize the haemolytic risks related to primaquine anti-relapse therapy *(8)*.

Given the time since the G6PD classification was established and the developments in the interim, the WHO Genomics Initiative identified the revision of the current classification scheme as a priority. It recommended that the WHO Global Malaria Programme convene a Technical Consultation to review and propose a revision of the classification in light of all the information and data currently available. This was endorsed by the WHO Malaria Policy Advisory Group (MPAG; formerly the Malaria Policy Advisory Committee [MPAC]) in October 2019.

Objectives

1. Review the results of literature searches commissioned by the WHO Global Malaria Programme and academic institutions in order to assess the variability of enzyme activity for the main G6PD genetic variants of public health interest.

On the basis of these study findings:

2. Review the distribution of G6PD activity in relation to the threshold of enzyme activity adopted to define severe G6PD deficiency.

3. Review the distribution of G6PD activity in subjects with a deficiency in relation to detection levels for current qualitative and semiquantitative point-of-care G6PD tests.

The results of this Technical Consultation are expected to be relevant to work on establishing policy and product specifications for point-of-care G6PD tests, and for the use of 8-aminoquinolines for the radical cure of *P. vivax*.

Process

1. The WHO Global Malaria Programme commissioned a literature review to gather information on the mean and variability of G6PD activity for variants currently classified in Classes II and III *(9)*, and also invited a presentation of the interim analysis of a systematic review and meta-analysis investigating the variability of G6PD activity among genetic variants *(10)*.

2. A panel of WHO temporary advisors (acting in their personal capacity) was convened remotely for two half-day virtual sessions on 25 and 27 January 2022 (see Annex 1, list of pre-reads; Annex 2, list of participants; and Annex 3, agenda of the meeting).

3. The panel of advisors reviewed the results of the two literature reviews and the implications for the classification of G6PD variants. At the end of the meeting, they held a closed session[1] during which they agreed on the conclusions of the meeting.

4. The report of the meeting was prepared by Ian Boulton (rapporteur) and shared with all participants for comment. Their inputs were then taken into account in preparing the final report for presentation to MPAG.

Report of the Technical Consultation

Issues with current WHO classification

The panel of advisors identified several problems with the existing classification:

1. The intended use of the classification of variants published in 1986 was to group genetic variants according to the mean or median levels of G6PD biochemical activity. However, this classification has been used to assign patients to the different levels of severity of G6PD deficiency based on measured enzyme activity.

2. It has become clear that there is significant overlap in the clinical manifestations of several G6PD variants in Classes II and III.

Literature review findings

Nannelli et al. *(9)*

The literature review screened 2200 unique articles by title and abstract, and identified 393 full-text records for assessment. Applying strict eligibility criteria[2], the review identified 59 studies published from 1966 to 2021 that used biochemical criteria, DNA analyses, or both. Data were gathered from 2255 hemizygous males with G6PD deficiency. Based on the available data, 17 variants and 117 sets of genotypic/phenotypic associations were included in the analysis. The variants included were:

[1] Dr Mary Relling and Professor Benedikt Ley did not attend the closed session.

[2] The study included data that could be extracted on all of the following: a) the G6PD variant was clearly identified by biochemical and/or molecular analysis; b) data were available for males ; c) G6PD activity was expressed in absolute units or as a percentage of normal G6PD values obtained in the same laboratory; d) an appropriate quantitative method was used to measure G6PD activity; e) variant activity was reported for at least three individuals (except for variants with less than three eligible studies with at least three individuals, for which articles with fewer than three individuals were also included in the analysis); and f) measurement of G6PD activity was made in steady state (not in the haemolytic or post-haemolytic period).

A-(202), A-(968), Aures, Cairo, Canton, Chatham, Coimbra, Cosenza, Kaiping, Kalyan-Kerala, Mahidol, Mediterranean, Orissa, Seattle, Union, Vanua Lava and Viangchan.

The geographical distribution of samples included is shown in Table 1.

Table 1. Geographical distribution of samples identified in Nannelli et al. *(9)*

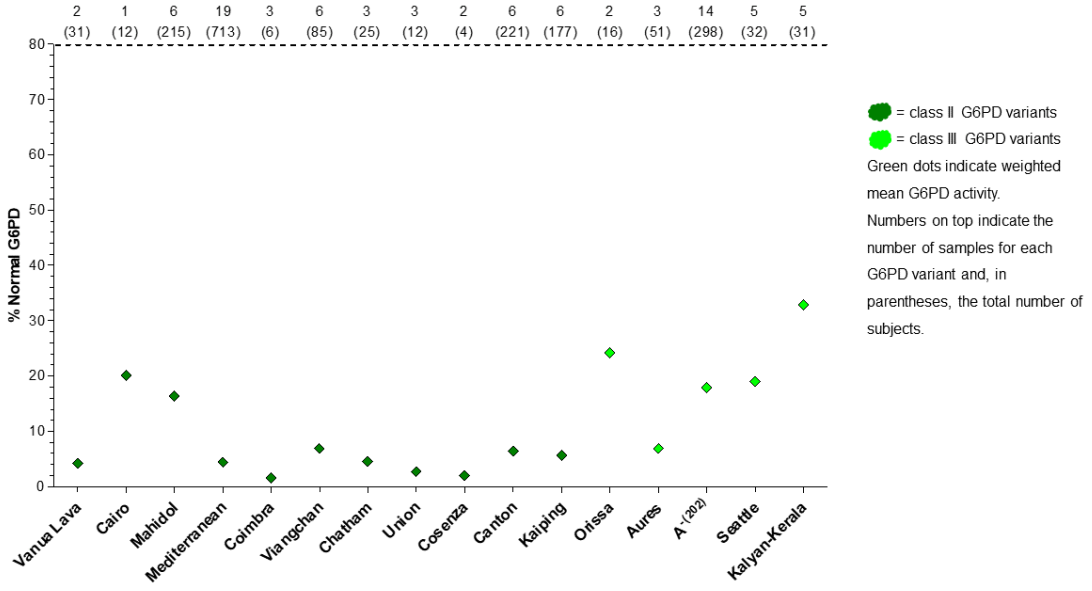
Geographical origin	Orissa	Aures	A-(202)	Vanua Lava	Cairo	Mahidol	Mediterranean	Coimbra	Seattle	Viangchan	Kalyan-Kerala	A-(968)	Chatham	Union	Cosenza	Canton	Kaiping	Total samples	(%)
Algeria			3				1		1									6	(5.1)
Bangladesh	1					1					1							3	(2.6)
Brazil			1															1	(0.9)
Cambodia										1								1	(0.9)
China										1				1		3	10	15	(12.8)
France							1											1	(0.9)
Greece							1		1									2	(1.7)
India	2						1				4							7	(6.0)
Indonesia				2				1		2			1					6	(5.1)
Iraq							3						2					5	(4.3)
Italy			2				17	1	8					1	2			31	(26.5)
Mozambique			1															1	(0.9)
Myanmar						1												1	(0.9)
Nigeria			3															3	(2.6)
Occupied Palestinian territory, including east Jerusalem			1		1		1											3	(2.6)
Portugal			1					1	1			1						4	(3.4)
Saudi Arabia		1	1				2											4	(3.4)
Sudan			1															1	(0.9)
Thailand		2				2				2					2	2	2	12	(10.3)
Thai-Myanmar						2										1		3	(2.6)
Tunisia			1				1											2	(1.7)
USA			4				1											5	(4.3)
Total	3	4	19	2	1	6	29	3	11	6	5	1	3	2	4	6	12	117	(100)

The subjects included in the review were recruited from 22 countries. The majority of the data were related to four variants (A-(202), Mediterranean, Seattle and Kaiping) and were from three countries (China, Italy and Thailand).

Analysis of the distribution of mean/median G6PD activity reported in each study showed that the Orissa and Kalyan-Kerala variants consistently have activity values above 10% of normal (the current threshold between Class II and Class III variants). Coimbra, Chatham, Union and Cosenza variants have values consistently below 10%. However, all the other variants (A-(202), Canton, Kaiping, Mahidol, Mediterranean, Seattle, Viangchan) have mean/median values that span the 10% threshold. For some variants (e.g. Mediterranean), the results are quite tightly grouped, but for others (e.g. A-(202)), there is a much greater degree of variability. Data from studies that identified variants based on biochemical criteria alone aligned well with data from studies using DNA-based identification.

The weighted mean activity for 16 variants is shown in Fig. 1. The A-$^{(968)}$ variant was excluded, as there was only one value available.

Fig. 1. Weighted mean G6PD activity for variants identified in Nannelli et al. *(9)*



With the exception of the Kalyan-Kerala variant, the weighted average activity for all other variants is below 30%. The Cairo and Mahidol variants (Class II) have a weighted average activity above 10%, and the Aures variant (Class III) falls below 10%.

Sample variability was estimated by pooling data from all samples available for each variant and including information about the variability observed in each sample.

Analysis of the estimated overall variability showed that, for 12 variants, values for a significant number of samples span the 10% cut-off. This is observed for the following variants: A-$^{(202)}$, Aures, Canton, Chatham, Kaiping. Kalyan-Kerala, Mahidol, Mediterranean, Orissa, Seattle, Vanua Lava and Viangchan. For five variants, values overlap the 30% cut-off. In particular, for the Kalyan-Kerala variant, an estimated 55% of samples have activity values above the 30% cut-off. Considering the spread around the median (assuming a normal distribution of results), four variants (A-, Mahidol, Orissa and Seattle) have an estimated 12–25% of males with G6PD activity above 30%. The authors concluded that, with the exception of the Kalyan-Kerala variant, all variants falling into Classes II and III have a median enzyme activity below 30% of normal.

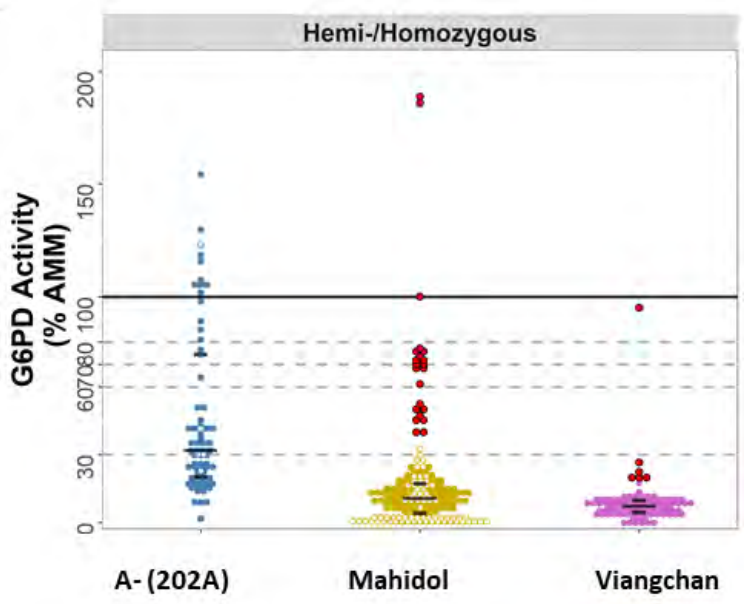
The variability among samples may be due to methodological as well as biological factors. The methods used in the studies conducted over a 55-year period were not always well described and documented in the publications. Results may have been influenced by variability in spectrophotometric methods, procedures for specimen storage and transport, blood sample preparation, reaction mixture and temperature control in assay procedures, use of single or replicate tests, and the way white cells were or were not removed. However, these concerns were not considered great enough to significantly distort the overall results.

Pfeffer et al. *(10)*

This is an *interim* analysis of a larger meta-analysis to assess the range of G6PD activity for known G6PD genotypes.[3] A literature review screened 838 unique articles by title and abstract, and identified 153 full-text records for assessment. A set of strict eligibility criteria were applied to generate a preliminary dataset for the purposes of this review. This yielded 13 datasets published since 2005 using one of three common spectrophotometry assay kits for individual patient data analysis. All studies were conducted between 2009 and 2021, and variants were identified by DNA analysis. The database contained phenotypic/genotypic data from 1118 G6PD-deficient individuals, of which 336 were hemizygous males, for 20 different variants (three data-rich [n≥30] and 17 data-poor). Data were generated in eight countries, the majority being from South-East Asia (77%), followed by Africa (14%) and the United States of America (8%). Some of the datasets used were also included in Nannelli et al.'s *(9)* literature review.

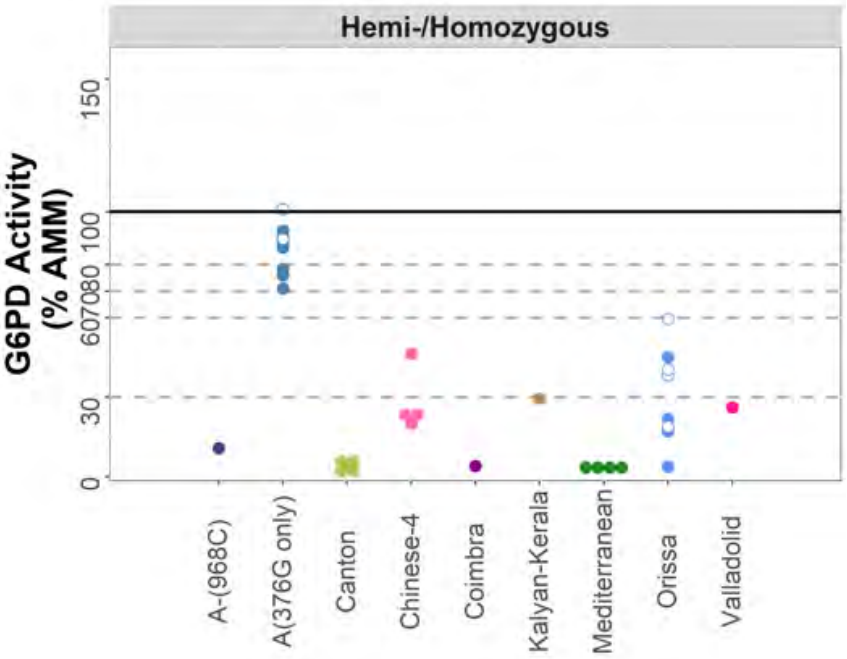
The G6PD activity values for data-rich variants (A-$^{(202)}$, Mahidol, and Viangchan) among male hemizygous and female homozygous individuals are shown in Fig. 2. To mitigate the influence of extreme measurements, outliers were defined for all data-rich variants and excluded from analyses. The data on homozygous/hemizygous individuals show a much wider variation for the A-$^{(202)}$ variant (median = 31.5%, range 1.7–154.1%) than for the other two variants, Mahidol (median = 10.2%, range 0–32.5%) and Viangchan (median = 7.1%, range 0–17.5%). Fig. 3 shows the data for the data-poor variants among male hemizygous and female homozygous individuals.

Fig. 2. G6PD activity levels for data-rich variants among male hemizygous and female homozygous individuals, Pfeffer et al. *(10)*



[3] The full analysis is expected to be completed by March 2022.

Fig. 3. G6PD activity levels for data-poor variants among male hemizygous and female homozygous individuals, Pfeffer et al. *(10)*



Note. G6PD activity (% AMM) as measured by spectrophotometry among 93 individuals confirmed by PCR or sequencing to carry a genetic variant other than A-, Mahidol, Viangchan. Individuals <1 year of age or positive for malaria were excluded. Horizontal lines indicate diagnostic thresholds: 100% (black), 80%, 70%, 60% and 30% (grey, dashed) G6PD activity. Homozygotes are indicated using hollow points.

For the data-rich variants, observations were binned according to the commonly used diagnostic thresholds for G6PD deficiency: severe (<30%) or intermediate (<60%, <70% or <80%). These results are shown in Table 2.

Table 2. Number and percentage of individuals falling into the various diagnostic categories for data-rich variants, Pfeffer et al. *(10)*

Variant	n	Studies (n)	Number (%) included using diagnostic thresholds				
			<30%	<60%	<70%	<80%	≥80%
A-(202A)							
Hemi-/Homozygous	72	5	33 (45.8)	55 (76.4)	56 (77.8)	58 (80.6)	14 (19.4)
Mahidol							
Hemi-/Homozygous	201	5	200 (99.5)	201 (100)	201 (100)	201 (100)	0 (0)
Viangchan							
Hemi-/Homozygous	90	3	90 (100)	90 (100)	90 (100)	90 (100)	0 (0)

Virtually all Mahidol and Viangchan variants fall below the 30% threshold in hemizygous and homozygous individuals. However, in almost 20% of cases, the A-$^{(202)}$ variants show >80% of normal activity in homozygous/hemizygous individuals.

Some of the variation has been attributed to imprecise assay techniques. Furthermore, a limitation of the survey is that, in 10 out of 13 studies, participants were only genotyped if they met pre-defined G6PD activity thresholds used in phenotypic screening tests. Therefore, the results may have been skewed towards the lower end of the activity spectrum. However, the authors argued that the overall variability observed was too great to be explained solely by confounding factors.

Discussion on the literature reviews

The panel appreciated the amount and quality of work reflected in these two reviews. The inclusion of both individual and sample-level data was particularly appreciated.

The two reports covered largely overlapping sets of variants. For most variants, there was generally good agreement between results, except for the A-$^{(202)}$ variant. The higher median value derived by Pfeffer et al. *(10)* for G6PD A- might be attributable to the inclusion of subjects with higher G6PD activity due to unidentified methodological or biological factors.

These reviews showed that rich datasets are available for six G6PD variants: A-$^{(202)}$, Canton, Kaiping, Mahidol, Mediterranean and Viangchan. The reviews demonstrated that there is still a shortage of reliable published data on the activity of different variants, and there is a need for more widespread genotyping of variants from populations in different geographical areas.

It was noted that the variation in phenotypic screening before genetic identification of G6PD variants was not always documented in publications. In Nannelli et al. *(9)*, 33 out of 117 sets had G6PD phenotypic screening, while in Pfeffer et al. *(10)*, 10 out of 13 studies had G6PD phenotypic screening; however, the panel did not think that this invalidated the overall findings from the two reviews.

The literature reviews revealed differences in the methods used to obtain the published results and the quality or reproducibility of the spectrophotometry methods. It was noted, however, that the individual patient data analysis by Pfeffer et al. *(10)* showed considerable variability for the A-$^{(202)}$ variant and several “outliers” for the Mahidol and Viangchan variants, despite 75% of the spectrophotometry data being from the same Trinity Biotech spectrophotometry assay.

The measurement of G6PD activity in blood samples could be affected by the time taken and temperature during transportation of the samples to the laboratories in less-than-ideal storage conditions, as well as by the specific technique used to remove the white blood cells to prepare the blood samples. These important details were rarely provided in the publications.

There was general consensus that variation in enzyme activity values for the same variant may reflect both technical and biological factors. The panel supported work on developing more standardized research methods to study G6PD genotypic/phenotypic association in order to increase the availability of reliable data on individual variants.

Nannelli et al.’s *(9)* review of the published literature assumed that enzyme activity measurements of male hemizygous individuals were normally distributed (based on the limited individual data available), but this should be confirmed by analysing additional individual data using standardized approaches.

It would be highly desirable to assign median enzyme activity values to each variant as part of characterizing them within a classification system, but it was felt that this is not yet possible for many variants.

In future, it would be ideal for G6PD surveys to include the variant's genotype, phenotypic presentation, and clinical risk in different populations and geographical areas. This will be more feasible as genetic methods become more widely available and less expensive. Studies based on G6PD phenotypic screening should also genotype a sample of participants considered to be normal in order to identify possible genetic variants undetected by the screening assays (that can only discriminate between <30% and >30%). This will enable detection of individuals who carry a G6PD mutation but present with less severe enzyme activity deficiency.

Discussion on revision of the G6PD classification

The panel recommended that any revision of the classification system be as clear and simple as possible. It should be practical and relevant for clinical use, including in challenging field conditions where access to genotyping may not be easy or the volume of patients makes routine genotyping impractical.

There was concern that the current G6PD classification *(4)* has been often used as a way to classify patients based on enzyme activity, rather than a way to classify individual variants and their intrinsic potential haemolytic risk to patients. This needs to be made very clear in any update to the current classification.

The panel agreed that, in view of the significant overlap in the distribution of activity among variants allocated to Class II and Class III, the distinction based on the 10% threshold is no longer useful. The panel agreed that these two classes could be merged into one, with no distinction between "severe" and "moderate to mild" deficiency.

Class I variants manifest with severe G6PD deficiency and CNSHA, which is a rare congenital condition. Therefore, it was agreed that this class should be retained. There has been only one example of a Class V variant (activity >150%) – G6PD Hektoen – and there has been no other since. It was agreed that there was no practical purpose in retaining Class V.

The classification of variants based on mean or median residual enzyme activity serves a clear purpose in identifying variants that may cause haemolysis. However, the panel also discussed the fact that there is limited data on haemolytic response in many variants and that the same variant may cause different levels of haemolysis in different patients. A variant such as Kalyan-Kerala, which is the second most common variant in India, has a median enzyme activity of 32.2%. While this may mean that there is enough G6PD activity to prevent serious haemolytic episodes in some male hemizygous patients, there could be serious haemolysis in other subjects. In practice, any classification should include a range around the median G6PD activity to reflect this variability.

While some studies have used thresholds of 70% enzyme activity as exclusion criteria in drug development studies, it was felt that it would be too disruptive to other work to raise the threshold for normal hemizygous males above 30% of normal activity in a revised classification of variants. There was also no clear consensus about whether 70% or 80% would be a more appropriate value for a threshold of G6PD enzyme activity in female heterozygous individuals.

Conclusions from the consultation

Revised classification

In future, G6PD variants should be classified based on the median residual enzyme activity in male hemizygous individuals for each variant expressed as percentage of normal activity as follows:

WHO classification of G6PD variants in homozygous and hemizygous individuals		
Class	**Median of G6PD Activity**	**Haemolysis**
A	<20%	Chronic (CNSHA)
B	<45%	Acute, triggered
C	60–150%	No haemolysis
U	Any	Uncertain clinical significance

It should be made clear in all publications that this system is strictly for classifying genetic variants of G6PD and applies primarily to hemi/homozygous individuals carrying a particular mutation. It should not be used to classify individual patients.

The above G6PD classification scheme is binary, and each genetic variant is defined as deficient or normal under this classification. Class B indicates G6PD deficiency without CNSHA. Class U, regarded as of ”uncertain clinical significance”, will serve as a temporary classification for newly discovered G6PD variants until the residual activity can be reliably measured in at least three samples from unrelated males in a steady state and the clinical significance is assessed.

By reviewing/using the combined data from the reviews by Nannelli et al. *(9)* and Pfeffer et al. *(10)*, each variant can be tentatively assigned a percent activity value. These values will be subject to review as new data become available. The percent activity value should be calculated from the median value of genotypically normal male individuals, not from the AMM, considering the overlap of most variants across the 10% threshold.

Currently, no variants have been identified that have median G6PD enzyme activity values in male hemizygous and/or female homozygous individuals falling between 45% and 60%. Therefore, a gap has been left between Classes B and C. If new variants are found with median G6PD enzyme activity between 45% and 60%, these should be included in the “U” class and studied until solid evidence is found that they induce AHA in male hemizygous and/or female homozygous individuals (= Class B) or pose no haemolytic risk (= Class C). The thresholds will then need to be revisited as new evidence becomes available.

Future research

WHO should consider developing standard criteria to characterize the genotypes and phenotypes of G6PD variants. This will also help to improve comparability across studies and to inform the classification of new and existing variants, particularly those of uncertain clinical significance. Any new variant should be assigned a tentative percent activity value only if it has been measured at a steady state using a validated quantitative reference test in at least three samples from unrelated males. Other items to be considered include the number of individuals required to examine the distribution of G6PD activity, number of laboratory replica measurements, criteria to define normal reference

values, genetic relationships among cases, methodologies for measuring G6PD activity, phenotypic screening and variant identification, and criteria for including or excluding subjects with concurrent infection or haemolysis. Many variants have now been identified at the molecular level for which important functional properties are unknown. It is desirable to measure at least K_m^{G6P} and thermostability for these and any new variants.

Future research should also address important gaps in knowledge on the risk of severe haemolysis associated with known and potential triggers in already described variants and the identification of other biological factors that might influence haemolytic response (e.g. enzyme activity in reticulocytes).

References

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8. WHO Guidelines for malaria. Geneva: World Health Organization; 2022 (https://app.magicapp.org/#/guideline/6108).

9. Nannelli C, Dugué P-A, Bosman A, Luzzatto L. Updating the WHO classification of G6PD variants. Unpublished 2021.

10. Pfeffer DA, Satyagraha AW, Sadewa A, Price RN, Ley B. Interim analysis of variability in G6PD activity with genetic variant: a systematic review and meta-analysis. Unpublished 2021.

Annex 1. List of pre-reads

Nannelli C, Dugué P-A, Bosman A, Luzzatto L. Updating the WHO classification of G6PD variants. Unpublished 2021.

Pfeffer DA, Satyagraha AW, Sadewa A, Price RN, Ley B. Interim analysis of variability in G6PD activity with genetic variant: a systematic review and meta-analysis. Unpublished 2021.

Luzzatto L, Ally M, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Blood. 2020;136(11):1225–40. doi:10.1182/blood.2019000944.

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WHO Working Group. Glucose-6-phosphate dehydrogenase deficiency. Bull World Health Organ. 1989;67:601–11

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Annex 3. Agenda

25 January 2022		
	Session 1	
14:00 – 14:10	Welcome by the Director, Global Malaria Programme Introductions	P Alonso
14:10 – 14:15	Declarations of Interest	A Bosman
14:15 – 14:20	Objectives of the meeting	A Bosman
14:20 – 15:00	Literature search of G6PD activity in males with prevalent G6PD genetic variants Discussion	C Nannelli & P A Dugué
15:00 – 15:25	Interim analysis of variability of G6PD activity with genetic variant: a systematic review and meta-analysis Discussion	D A Pfeffer & B Ley
15:25 – 15:35	*Break*	
15:35 – 16:20	Perspectives on use of current classification of G6PD genetic variants Discussion	G Bancone W Jiang A Minucci J T Prchal M Sirdah O Sodeinde W Wanachiwanawin
16:20 – 17:00	Reflections on updating the classification of G6PD deficiency Discussion	L Luzzatto

27 January 2022		
	Session 2	
14:00 – 14:15	Recap of Day 1 discussions	I C Boulton
14:10 – 15:00	Requirements and process for changing the classification of Classes II and III, including knowledge gaps	*Discussants:* J T Prchal W Wanachiwanawin
15:00 – 15:35	Requirements and process for changing thresholds of Classes I, IV and V, including knowledge gaps	*Discussants:* G Bancone O Sodeinde
15:35 – 16:00	Considerations on 30% detection threshold for G6PD deficiency, including knowledge gaps	*Discussant:* L. Luzzatto
16:00 – 16:10	*Break*	
16:10 – 16:45	Discussion and main points of agreement	T Vulliamy
16:45 – 16:50	Next steps	A Bosman
16:45 – 17:00	Closing remarks	P Alonso

WHO Technical Consultation to review the classification of Glucose-6-Phosphate Dehydrogenase (G6PD)

Virtual Meeting via ZOOM, 25 and 27 January 2022

Global **Malaria** Programme

World Health Organization

Normative context of the G6PD WHO Consultation

- The WHO Genomics Initiative, hosted by the WHO Department of Service Delivery and Safety, has identified the revision of the WHO G6PD classification scheme as a priority and has recommended that WHO Global Malaria Programme (GMP) convenes a technical consultation to this effect.
- The Malaria Policy and Advisory Committee of WHO in October 2019 ° endorsed the need to convene the proposed Technical Consultation and proposed an additional objective:
  - to investigate what assessment of G6PD activity should be required prior to administration of primaquine or tafenoquine, and whether G6PD testing needs to be repeated before administering each course of treatment with those drugs.

° https://www.who.int/publications-detail-redirect/WHO-CDS-GMP-2019.12

Current classification of G6PD, known as the "WHO Classification"

I. Activity <10% of normal, severe enzyme deficiency with CNSHA (chronic non-spherocytic haemolytic anaemia)
II. Activity <10% of normal, severe enzyme deficiency
III. Activity 10–60% of normal, moderate to mild enzyme deficiency, intermittent acute haemolysis
IV. Very mild or no enzyme deficiency (60–150% of normal)
V. Increased enzyme activity (more than twice normal)

The WHO Working Group on G6PD deficiency convened in 1985 listed 310 G6PD variants according to the above classification

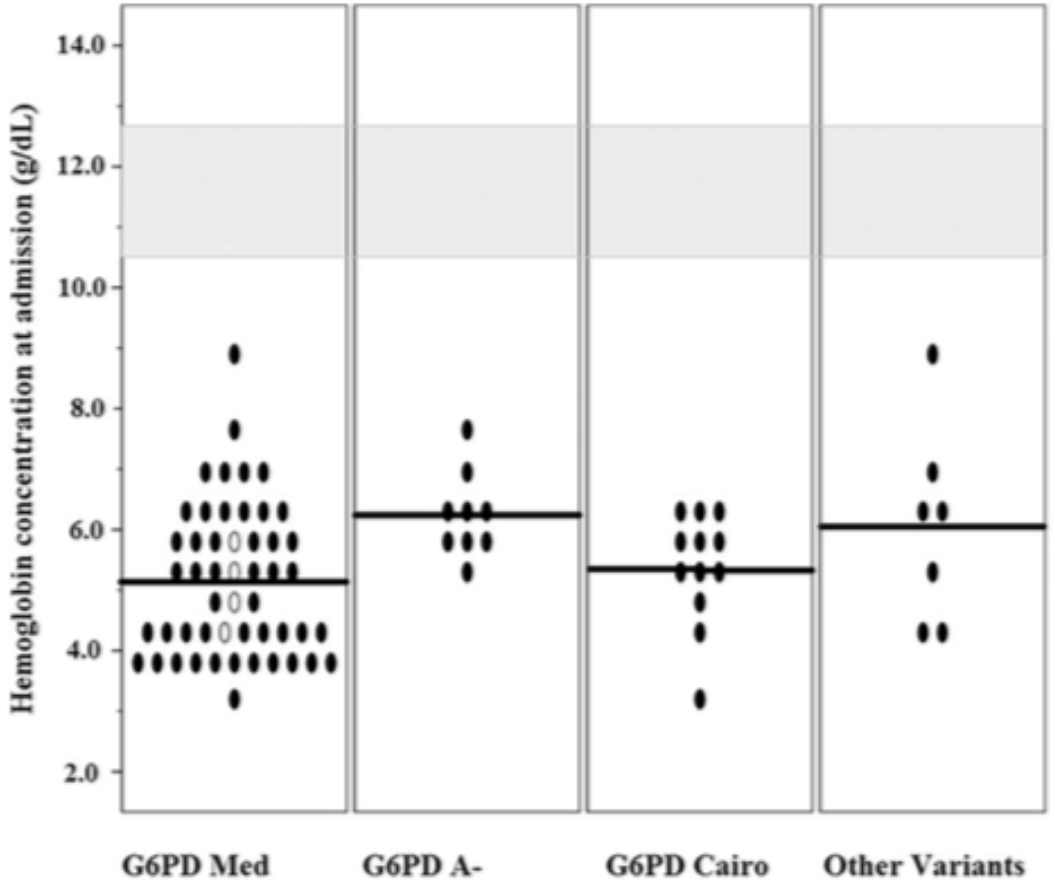
Issues with the current G6PD classification

- Since 1986, when the full G6PD cDNA sequence was published, new genetic variants have been reported, and individual mutations underlying several known G6PD variants were identified.
- Several of the most prevalent G6PD variants classified as class II and class III appear to have the same clinical manifestations, especially severe acute hemolytic anemia,
- The threshold for “normal” G6PD activity, has been set at >70% for clinical trials with tafenoquine and at >80% by a WHO consultation on point-of-care G6PD tests to guide primaquine treatment in female heterozygotes.
- Regarding class V, no single additional case of G6PD Hektoen, or of any variant with activity >150% has ever been reported.
- Regarding class I, variants associated with CNSHA may have, in the steady state, G6PD activity >10%.

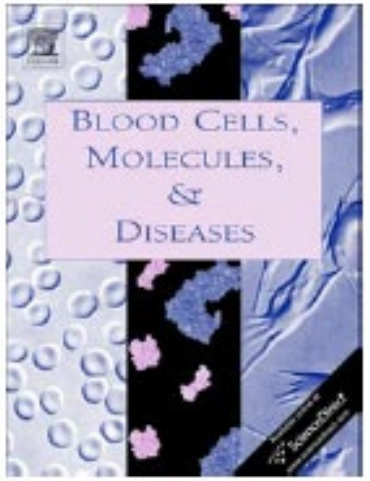
Urine collection of a 5-year-old boy with G6PD deficiency on D4, D5 and D6 (from left to right) after the 4th daily dose of primaquine 15mg.

At admission to the emergency ward of Wad Medani Pediatric Hospital (Sudan), the child had Hb = 2 g/dL corrected to 8 g/dL after blood transfusion

Severity of acute favism in children with different G6PD variants within the same population



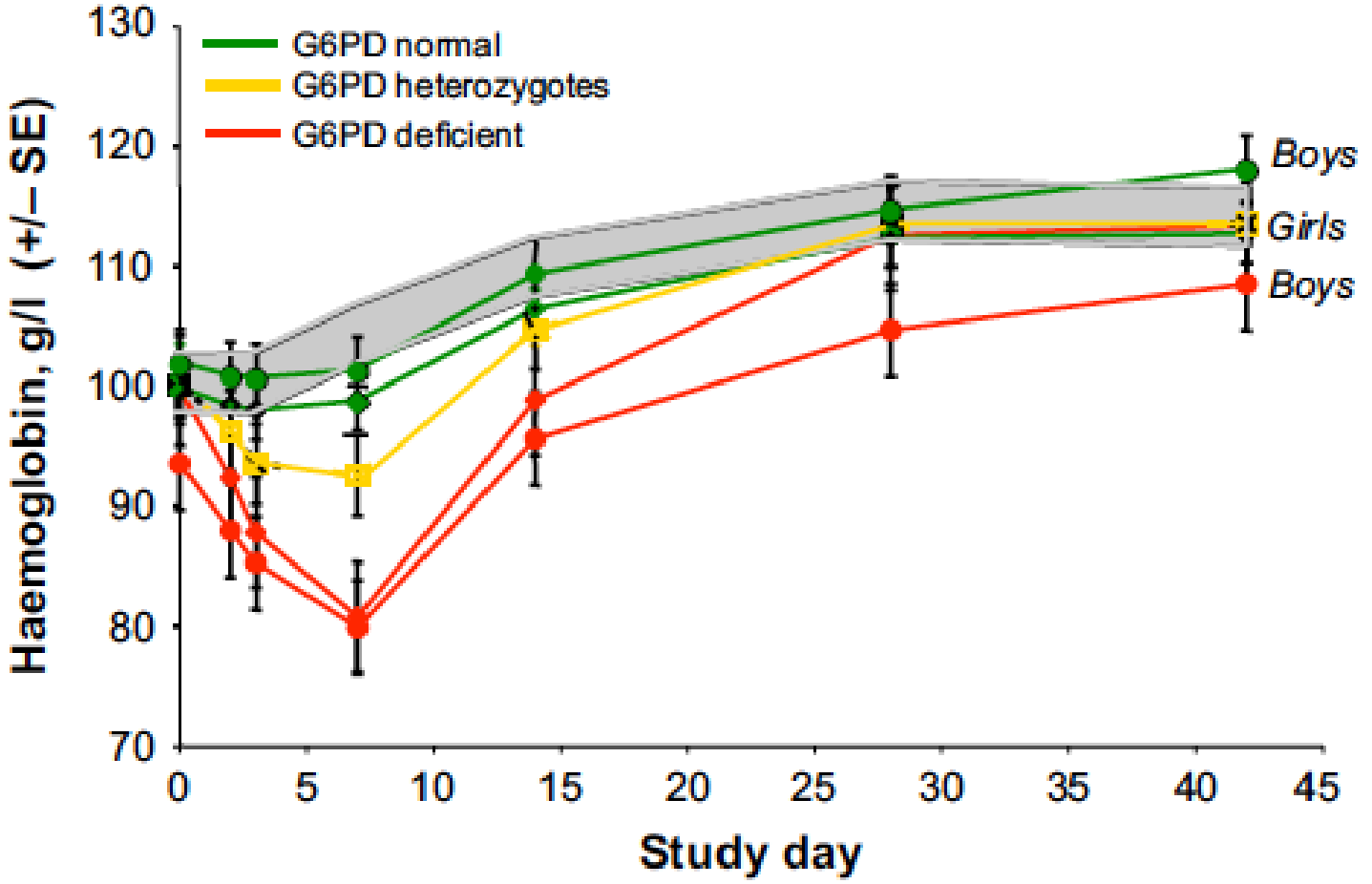
- ● Males hemizygous
- o Females heterozygous

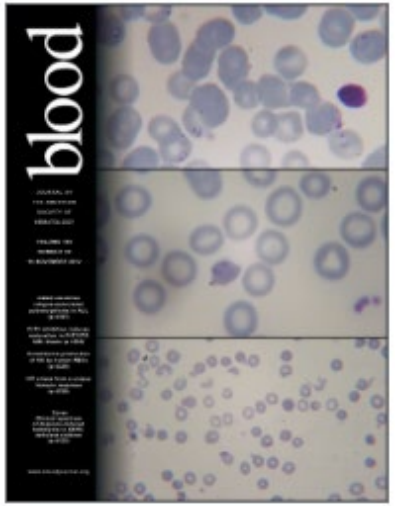


from Reading *et al*, *Blood Cells, Molecules and Diseases (2016),* **60**:58-64
doi: 10.1016/j.bcmd.2016.07.001

Courtesy of Prof L. Luzzatto

ACUTE HAEMOLYTIC ANAEMIA IN CHILDREN WITH MALARIA RECEIVING CHLORPROGUANIL-DAPSONE (LapDap™)





Modified from Pamba *et al*, *Blood* 2012,**120**:4123-4133
doi: 10.1182/blood-2012-03-416032)

Courtesy of Prof L. Luzzatto

Objectives of WHO Consultation on G6PD classification

1. To review results of literature searches commissioned by WHO GMP and academic institutions to assess the variability of enzyme activity of the main G6PD genetic variants of public health interest

On the basis of the study findings:

2. To review the distribution of G6PD activity of prevalent genetic variants in relation to thresholds adopted to define severe G6PD deficiency.

3. To review the distribution of G6PD activity in subjects with deficiency in relation to detection levels of qualitative and semiquantitative point-of-care G6PD tests.

4. To discuss and deliberate on whether the current classification of G6PD variants that cause G6PD deficiency deserves to be revised

Literature reviews for the WHO Consultation on G6PD classification

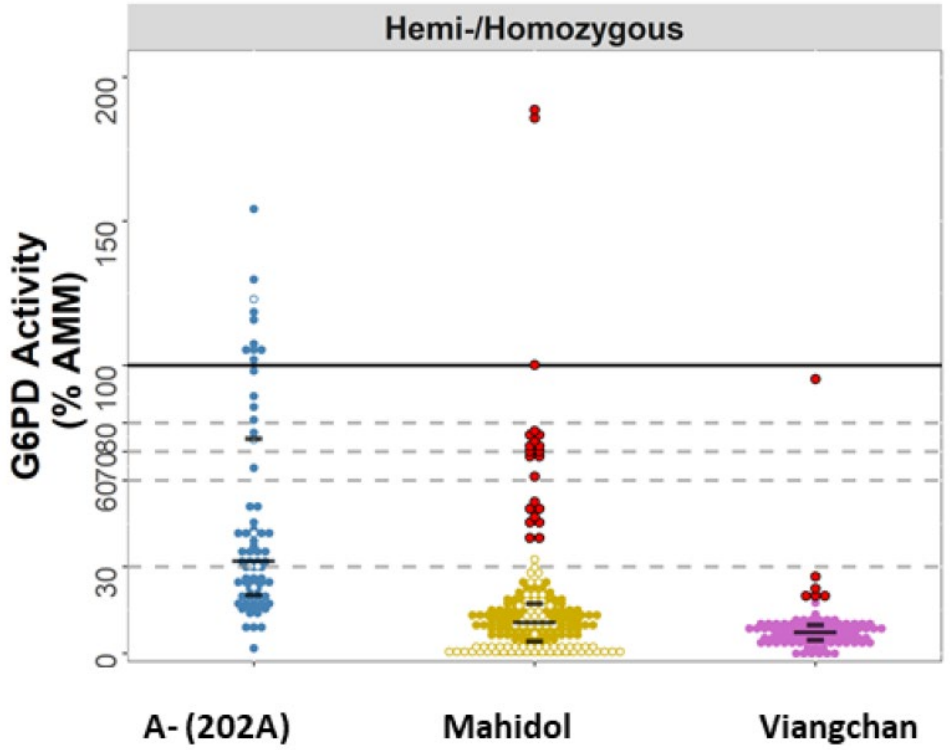
Nannelli et al.

- The literature review screened 2200 unique articles by title and abstract and identified 393 full-text records for assessment. Applying strict eligibility criteria , the review identified 59 studies published from 1966 to 2021 that used biochemical criteria, DNA analyses, or both. Data gathered for 2255 hemizygous males with G6PD deficiency with the following data:
  - a) G6PD variant identification; b) hemizygous males; c) G6PD activity as percentage of normal males in the same laboratory; d) appropriate quantitative G6PD measurement; e) at least three individuals (w exception); and f) measurement in steady state (not hemolytic or post-hemolytic).
  - Excluded newborns, malaria patients, relatives and inappropriate use of normal values for G6PD activity
- Sample-based analysis of 117 sets of genotypic/phenotypic associations for 17 variants

Pfeffer et al.

- This is an interim analysis of a larger meta-analysis to assess the range of G6PD activity for known G6PD genotypes. A literature review screened 838 unique articles by title and abstract and identified 153 full-text records for assessment. Applying strict eligibility criteria 13 datasets were included, published since 2005 using one of three common spectrophotometry assay kits for individual patient data analysis. All studies were conducted between 2009 and 2021, and variants were identified by DNA analysis.
- Individual based phenotypic/genotypic data from 1118 G6PD-deficient individuals, of which 336 were hemizygous males, for 20 different variants (three data-rich [n≥30] and 17 data-poor).

IPD interim analysis: G6PD activity for data-rich variants



Pfeffer *et al.*

red points: outliers
filled points: male hemizygous
hollow points: female homozygotes

Variant	n	Studies (n)	Number (%) included using diagnostic thresholds				
			<30%	<60%	<70%	<80%	≥80%
A-(202A)							
Hemi-/Homozygous	72	5	33 (45.8)	55 (76.4)	56 (77.8)	58 (80.6)	14 (19.4)
Mahidol							
Hemi-/Homozygous	201	5	200 (99.5)	201 (100)	201 (100)	201 (100)	0 (0)
Viangchan							
Hemi-/Homozygous	90	3	90 (100)	90 (100)	90 (100)	90 (100)	0 (0)

Key Conclusions

- Overall good agreement between the two literature reviews, using individual and sample level data, except for A- variant
- Classification is designed for average enzymatic activity of genetic variants but has been misused to classify individual patients
- Class II & Class III classification could be merged, and Class V removed
- Significant inter and intra-variant variability in G6PD enzyme values may reflect both technical and biological factors.
- Need for more evidence on phenotypic/genotypic associations for many G6PD variants and additional geographical locations

Draft recommendations

Revised Classification - G6PD variants should be classified based on the median residual enzymatic activity expressed as percentage of normal activity

WHO Classification of G6PD variants in homozygous and hemizygous individuals		
Class	**Median of G6PD activity**	**Haemolysis**
A	<20%	Chronic (CNSHA)
B	<45%	Acute, triggered
C	60-150%	No haemolysis
U	Any	Uncertain clinical significance

Draft recommendations: future research

- WHO should develop standard criteria to characterize G6PD genotypes and phenotypes to improve comparability across studies and inform the classification of variants.
- Any new variant should be assigned a % activity value only if this has been measured in at least 3 samples from unrelated males.
- Other parameters to be considered include
  - **number of individuals required to examine the distribution of G6PD activity,**
  - **number of laboratory replica measurements,**
  - **criteria to define normal reference values,**
  - **genetic relationships among cases,**
  - **methodology used for measuring G6PD activity,**
  - **methods for phenotypic screening and variant identification, and**
  - **criteria of inclusion of subjects with concurrent infection or haemolysis.**
- Future research should aim at addressing important knowledge gaps, namely the risk of triggers of severe haemolysis in already described variants and identification of other factors that might influence haemolytic response (*e.g.* enzyme activity in reticulocytes).

WHO Guidelines for malaria

Malaria Policy Advisory Group meeting

23 March 2022

Dr Pedro Alonso, Dr Jan Kolaczinski, Dr Kim Lindblade,

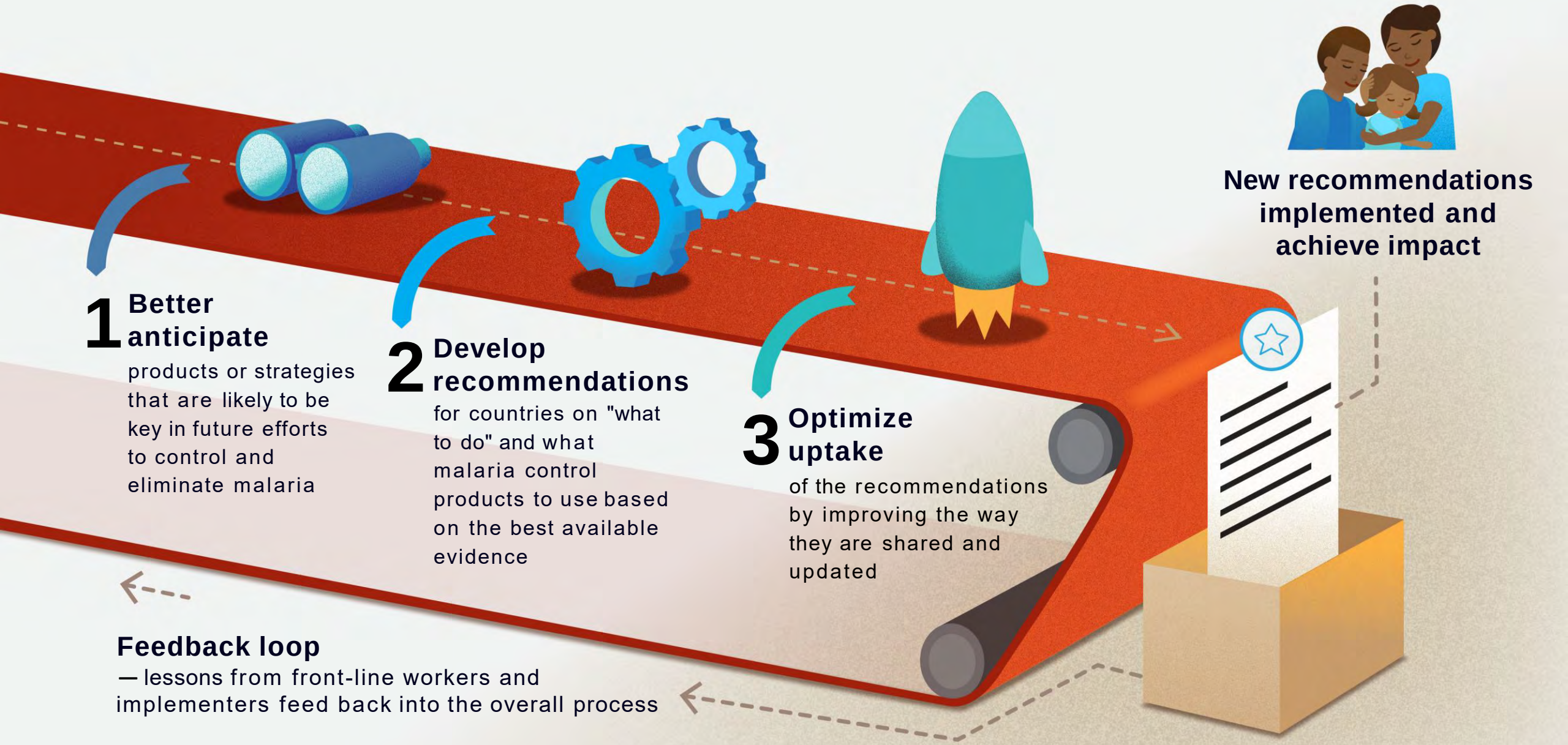
Dr David Schellenberg, Dr Peter Olumese,

Dr Jane Cunningham and Ms Saira Stewart

Global **Malaria** Programme

World Health Organization

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

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.

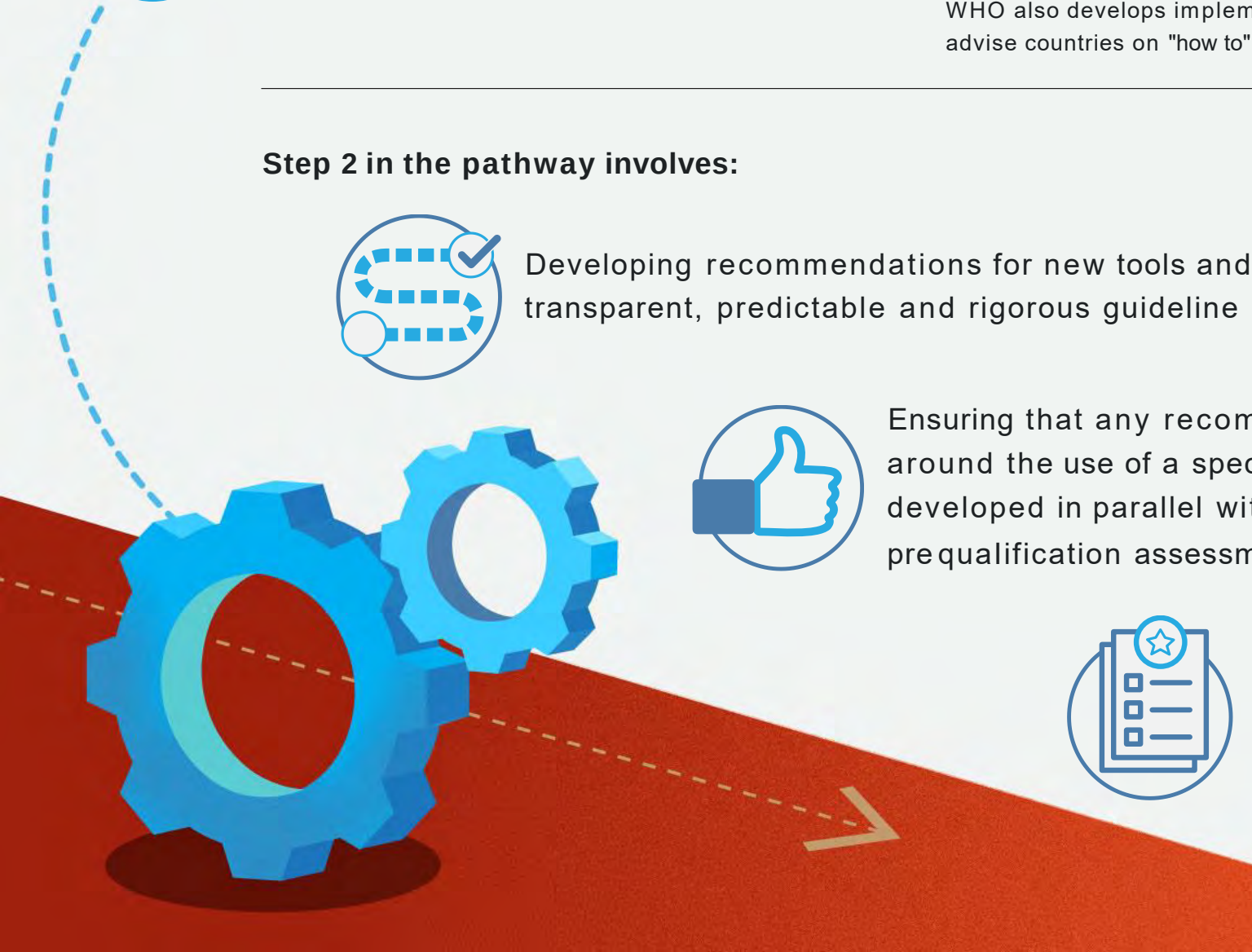
Step 2 in the pathway involves:

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

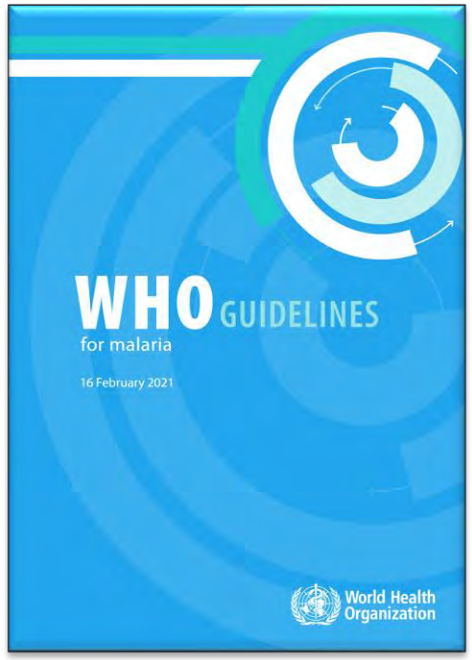
Ensuring that any recommendation around the use of a specific product is developed in parallel with its prequalification assessment

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



Develop recommendations



- WHO Guidelines for Malaria
  - 4 Guidelines Development Groups – Vector control, Elimination, Chemoprevention & Treatment
  - 1 Planning proposal in development – Diagnosis
- Published in February 2021; 1st update July 2021; 2nd update February 2022
- French version published; Arabic and Spanish to be launched soon
- Mobile app available for download (WMR, Threats Map and Guidelines)

Vector Control

Vector control updates and timeline – 2nd set

Guidelines Development Group meeting June 2021, planned for publication March 2022

- **Pyrethroid-PBO nets** – **update of conditional recommendation for, moderate certainty evidence**
  - Two trials now complete, systematic review updated and published
  - Studies conducted in 'high' resistance areas
  - Considerations of higher unit cost compared to pyrethroid-only nets

- **Co-deploying IRS and ITNs** -**no change to current conditional recommendation against, moderate certainty evidence**
  - Systematic review updated with inclusion of other insecticides, other nets
  - However, unclear if addition of IRS is filling a coverage gap rather than adding extra benefit on top of nets
  - Large costs associated with delivering both

- **Vector control in humanitarian emergencies** – **new strong recommendation for ITNs, high-certainty evidence**
  new conditional recommendation for IRS, very-low certainty evidence
  - New systematic review including review of ITNs, IRS, ITC, repellents, ITPs, treated cattle (under peer review)
  - Limited evidence available (single studies identified per intervention) except for ITNs and IRS
  - Considerations of logistical issues

- **Cost and cost-effectiveness** of vector control interventions – systematic review considered in evidence-to-decision tables

Pyrethroid-PBO net recommendation – updated 2022

WHO suggests deploying pyrethroid-PBO nets instead of pyrethroid-only LLINs for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission where the principal malaria vector(s) exhibit pyrethroid resistance

Conditional recommendation, moderate-certainty evidence

In deciding whether pyrethroid-PBO nets may be appropriate in their context, malaria programmes should:

- consider the deployment of pyrethroid-PBO nets in areas where resistance to pyrethroids in local vectors has been detected;
- determine whether resources are adequate to cover the extra cost of pyrethroid-PBO nets, while ensuring that coverage of populations at risk of malaria is not affected;
- note that WHO recommends that ITNs prequalified by WHO be selected for deployment.

Vector control updates and timeline – 3rd set

Guideline Development Group meeting planned for Q4 2022

- **Topical repellents** – update of systematic review to include studies that may estimate personal protection effects

- **Residual surface treatments** (including full indoor, selective indoor, and outdoor treatments) – to update IRS systematic review and review outdoor treatments. To include new insecticides, new application methods

- **New nets**
  - Interceptor® G2 : alphacypermethrin & chlorfenapyr (BASF)
  - Royal Guard ®: alphacypermethrin & pyriproxyfen (DCT)

  Trial data to be shared with WHO in Q3 2022. VCAG assessement of public health value in Q4 2022. Potential recommendation available in public domain (MAGICapp) Q1/2 2023.

Elimination

Key Questions for Malaria Elimination Guidelines

ACCELERATOR STRATEGIES

- Mass drug administration (MDA) – *P. falciparum* in very low/low vs. moderate to high; *P. vivax*
- Mass (screen) test and treat (MTaT)
- Mass relapse prevention

TARGETED STRATEGIES

- Targeted drug administration
- Targeted test and treat
- Test and treat at points of entry (routine vs. organized groups)

REACTIVE STRATEGIES

- Reactive drug administration
- Reactive test and treat (reactive case detection)
- Reactive indoor residual spraying

Elimination recommendations

- Guidelines Development Group meetings in August, November and December 2021
- Systematic reviews searched thousands of records but found few studies
  - Review teams also included contextual factors
  - Disaggregation of impact by gender or age is not routinely done but should be encouraged
- Overall very low to low certainty of evidence
  - Some questions without any relevant studies, although there are studies underway
  - Except for MDA, almost no opportunity to look at potential effect modifiers, including species
- GDG judged chemoprevention strategies more favourably than test and treat strategies
  - Few studies in areas with *P. vivax* used a full therapeutic course of an 8-aminoquinoline
- MDA and mass relapse prevention will appear in the Chemoprevention section of the Consolidated guidelines, along with MDA for burden reduction
- Reframing: “Interventions for the final phase of elimination and prevention of re-establishment”
- Recommendations submitted to GRC in February
  - Minor revisions required by GRC

Malaria elimination orientation curriculum

- Currently under executive review and to be disseminated on OpenWHO in April 2022

- 0 - The rationale for malaria elimination
- 1 - Principles and goals of malaria elimination
- 2 - Malaria parasite biology, immunology and epidemiology in areas approaching elimination
- 3 - Malaria case management in areas approaching elimination
- 4 - Vector biology, vector control and entomological surveillance in areas approaching elimination
- 5 - Surveillance and response in areas approaching elimination
- 6 - Chemoprevention to accelerate malaria elimination
- 7 - Community engagement for malaria elimination
- 8 -Multi-sectoral collaboration and political commitment for malaria elimination
- 9 - Prevention of re-establishment of malaria transmission
- 10 - Stratification to tailor intervention mixes in areas approaching elimination
- 11 -Management and planning of an elimination programme
- 12 - Innovation and research for malaria elimination
- 13 - Certification of malaria elimination

Chemoprevention

Abbreviated PICO questions for Chemoprevention GDG

1. Should children living in settings with **perennial malaria transmission** be given anti-malarial medicines as chemoprevention?

2. Should children living in settings with **seasonal malaria transmission** be given anti-malarial medicines as chemoprevention?

4. Is **mass drug administration** (MDA) a safe and effective approach to reduce the burden of malaria in moderate and high transmission settings?
   - During emergencies or periods of health service disruption, should people living in malaria-endemic settings be given anti-malarial medicines for chemoprevention?

5. Should women be given anti-malarial medicines as chemoprevention during **pregnancy**?
6. Should **school-age children** living in settings with malaria transmission be given anti-malarial medicines as chemoprevention to reduce disease burden?
7. Should children hospitalized with severe anaemia in malaria-endemic settings be given anti-malarial medicines as **chemoprevention post-discharge**?
8. In areas of moderate to high malaria transmission, should residents known to be at increased risk of clinical malaria, severe malaria, death, or other adverse effects of *P falciparum* infection, be given anti-malarial medicines as chemoprevention?

Chemoprevention guideline timeline

GDG **evidence review** and **formulation of recommendations**

PMC

SMC & MDA for burden reduction

External review feedback incorporated, guidelines edited and finalized

WHO Guideline Review Committee

Submission 19jan22

Resubmission 16mar22

Publication of revised guidelines as pdf and in MAGICapp

July 2021 | Oct 2021 | Oct – Dec '21 | Dec '21 | Feb '22 | Mar '22 | Apr '22

Systematic review on **IPTi**

Systematic reviews on **SMC & MDA** for burden reduction

Full narrative drafting and approval by GDG

WHO Guideline Review Committee Submission 13apr22

External review feedback incorporated, guidelines edited and finalized

Systematic reviews

GDG **evidence review** and **formulation of recommendations**

IPTp & school children chemoprevention 15-17 February 2022

Post discharge chemoprevention 1-2 March 2022

Global **Malaria** Programme

World Health Organization

Planned changes to chemoprevention recommendations

- SMC and IPTi recommendations will no longer specify
  - Strict age groups
  - Transmission intensity thresholds
  - Numbers of SMC cycles or IPTi doses
  - Specific drugs
- Encourage use of local data to inform subnational tailoring of chemoprevention strategies
  - Ages at greatest risk of severe malaria / malaria admission
    - IPTi -> Perennial Malaria Chemoprevention (PMC)
  - Recognise that as transmission intensity decreases, disease burden decreases and value of chemoprevention strategies for burden reduction will also decrease
  - Duration of transmission season should determine the number of rounds of SMC; age-specific disease burden, feasibility and affordability of delivering PMC doses
  - Consider local data on costs, duration of protection of each treatment course*, extent of seasonal variation, mix of interventions already deployed, etc

** Use the standard Chemoprevention Efficacy Study (CPES) protocol*

Treatment

Treatment process updates and timeline

- Planning proposal approved by GRC *(December 2020)*

- 1st GDG Meeting: Finalization of PICO Questions *(4-5 May 2021)*
  - For uncomplicated Pf malaria, is AS-Pyr an effective and safe option for treatment?
  - For uncomplicated malaria during the first trimester of pregnancy, is any artemisinin -based combination therapy (ACT) as safe and efficacious as quinine-based therapies?
  - For radical cure of Pv/o malaria, can the currently recommended total dose be given safely and effectively over a shorter period than 14 days?

- Systematic reviews based on the PICO questions *(June 2021)*

Treatment process updates and timeline

- 2nd GDG meeting - formulation of recommendations *(11-12 Nov 2021)*
  - For uncomplicated Pf malaria, is AS-Pyr an effective and safe option for treatment?
  - For radical cure of Pv/o malaria, can the currently recommended total dose be given safely and effectively over a shorter period than 14 days?

- 3rd GDG meeting - formulation of recommendation *(April 2022)*
  - For uncomplicated malaria during the first trimester of pregnancy, is any artemisinin -based combination therapy (ACT) as safe and efficacious as quinine-based therapies?

- External Review of draft recommendations; finalization of recommendations and clearance through GRC *(March - June 2022)*

Diagnosis

Diagnosis updates and timeline

- Planning proposal drafted in discussions with GRC
  - Scope limited to recommendations concerning use of near patient G6PD tests
- Cochrane systematic review of diagnostic test accuracy of near-patient G6PD tests in people undergoing treatment or prophylaxis with primaquine or tafenoquine or in people susceptible to malaria
  - Protocol published January 2021
  - Analysis October 2021
- 1st GDG Meeting: Finalization of PICO Questions – May 2022
- Reviews of contextual factors and exploring linked evidence approach (LEA) – Q2 2022

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

Dissemination strategy and taskforce

Dissemination strategy: goal and target audiences

Overall goal of the strategy?

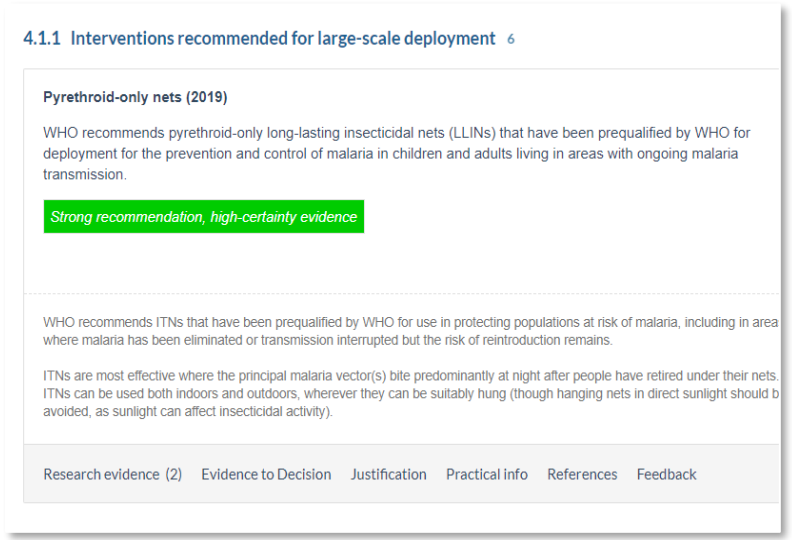
Optimizing uptake of WHO's malaria guidance in endemic countries by improving the way it is packaged and shared.

Main target audiences?

Primary: Staff working within Ministries of Health, National Malaria Programmes and implementing agencies

Other: Health providers, epidemiologists, the vector control and research communities, representatives from CSOs, funders, medical students, people at risk of malaria.

Key digital platforms (1) MAGICapp

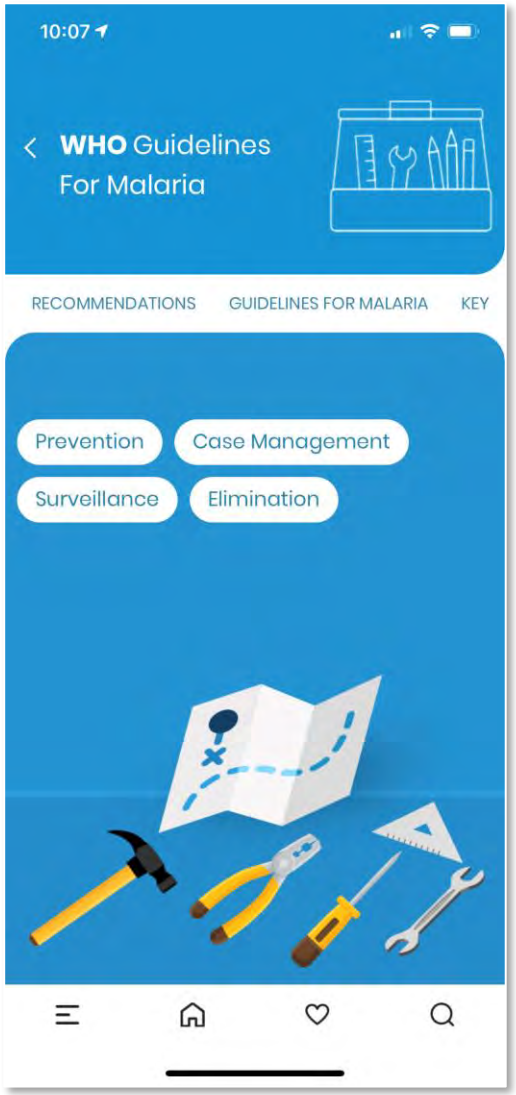


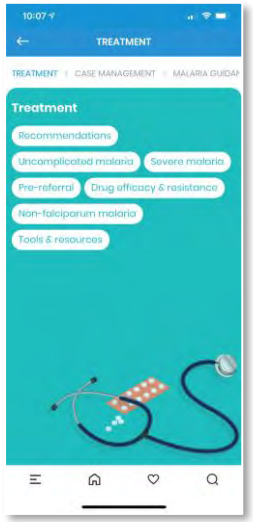
(1) MAGICapp includes:

- All official WHO malaria recommendations.
- Links to other resources, such as manuals, handbooks, and frameworks.

- **Key stats as of 22 March 2022:**
  - **More than <u>18 000 pageviews</u>** of the *WHO Guidelines for malaria on* MAGICapp (Eng, Fr)
  - More than **<u>66 000 downloads</u> (PDF)** of the English-language version of the guidelines.
  - More than **<u>10 000 downloads (PDF)</u>** of the French-language version of the guidelines.

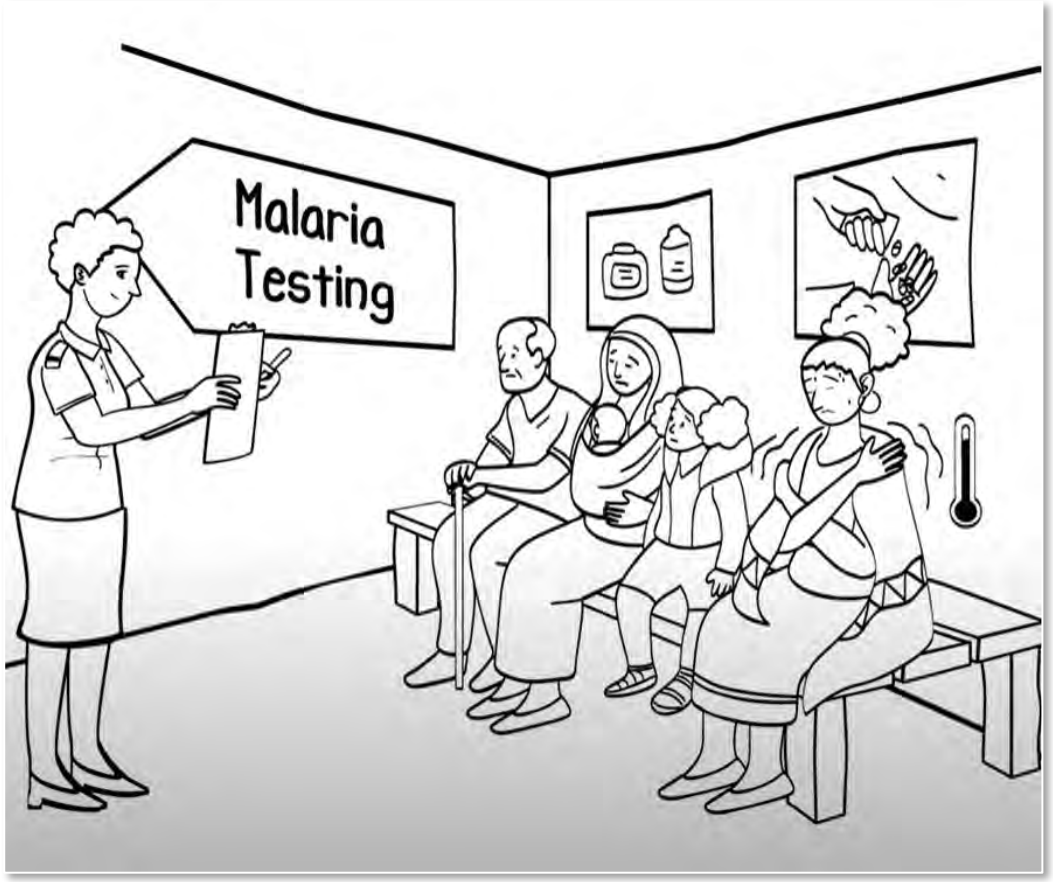
Key digital platforms (2): Mobile app





- **January 2016:** WHO launches first version of mobile app with data and key findings from the *World malaria report*
- **July 2020:** WHO releases expanded version of the app with a section focused on malaria guidance
- A **user-friendly resource** to rapidly verify data and guidance in the field
  - No internet connection needed after the app has been downloaded

Other dissemination tools: short videos (new!)



- WHO is also developing **short videos** across a range of technical areas – from surveillance and diagnostics to preventive therapies for infants.
  - first video on HRP2 gene deletions released in Dec 2021
  - chemoprevention videos to be released in April 2022, and more videos in the pipeline

WHO Malaria Dissemination Taskforce

- Established to support the optimized uptake of WHO's malaria guidance and advise on dissemination tools and platforms
- First meeting held on 8-9 Feb 2022 with participation from stakeholders based at country, regional and global levels.
- Taskforce members flagged the need for:
  - More language versions of the *WHO guidelines for malaria*
  - Simple messages and tailored products for different audiences
  - Advance notice for stakeholders about forthcoming WHO guidance
  - Expanded target groups and audiences
  - Additional dissemination products
  - Improved feedback loops at the local level

Next steps

- Short-term priorities (Q2 2022)
  - Provide Spanish and Arabic versions of the consolidated guidelines
  - Create PPT slide in multiple languages with links to dissemination platforms
  - Finalize 2 videos focused on new chemoprevention recommendations
  - “What’s on deck”: targeted communication semi-annually to key stakeholders advising on forthcoming guidance
  - Provide push notifications on the mobile app to inform users of new content
  - Update WHO mailing lists and explore partner platforms through which WHO guidance can be shared