World Health Organization

Background documentation for Day 2

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

Wednesday, 19 April 2023			
	Session 5	**Open**	
09:00 – 10:45	Strategic Information for Response • Digital solutions • Surveillance assessment toolkit • Subnational tailoring of interventions • World malaria report Presentation	Mr Ryan Williams & Ms Mwalenga Nghipumbwa Dr Laura Anderson Dr Beatriz Galatas Dr Abdisalan Noor Strategic Information for Response	**For information**
	Session 6	**Open**	
11:15 – 12:00	Update on the technical consultation on the effectiveness of rectal artesunate and the field guide Background | Presentation	Dr Peter Olumese Diagnostics. Medicines & Resistance	**For information**
12:00 – 12:30	Update on the technical consultation on community-IPTp and the field guide Background | Presentation	Ms Silvia Schwarte Strategy & Agenda Setting	
12:30 – 13:00	Update on the WHO/TDR field guide on seasonal malaria chemoprevention Background | Presentation	Dr Peter Olumese Diagnostics. Medicines & Resistance	
	Session 7	**Open**	
14:00 – 14:30	Update on *An. stephensi* regional strategy Background | Presentation	Dr Seth Irish, Vector Control & Insecticide Resistance	**For guidance**
14:30 – 15:00	Update on HRP2 gene deletions and global response plan Presentation	Dr Andrea Bosman Malaria Director Office	**For information**
15:00 – 15:30	Update on antimalarial drug resistance in Africa Presentation	Ms Charlotte Rasmussen Diagnostics, Medicines & Resistance	
	Session 8	**Open**	
16:00 – 16:30	Closing session	Dr Daniel Ngamije Director Global Malaria Programme	**For information**

WHO/UCN/GMP/MPAG/2023.02

Strategic Information for Response Unit

Work Areas

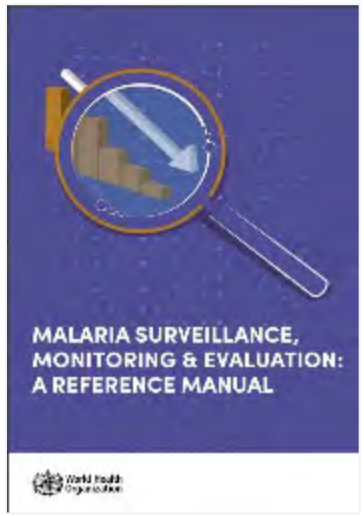
Abdisalan M Noor
Head of Unit,
Strategic Information for Response

Global **Malaria** Programme

World Health Organization

Strategic Information for Response: scope of work

Pillar 3



Guidance

GTS tracking

Tools	Routine data modules	Repository modules	Assessment toolkit
Regional support	Multi-country training	Regional repositories	
Country support	Module installations	Competency strengthening	Analysis support (SNT, MPR, NSP etc.)
Living guidance	Technical Advisory Group	Best practice documentation	Guidance updates
Data submission	WMR form	Partner contributions	
Validation	Validation algorithms	Country feedback	
Analysis & estimation	Morbidity & mortality	Interventions	Others
Visualization	WMR form dashboard	Mobile App & Website	Malaria Threat Map*

Digital Tools for Strengthening Malaria Surveillance

Data standards and innovations to improve the availability, quality, analysis and use of malaria data at country and global levels

Ryan Williams

19 April 2023, MPAG, Geneva

Global **Malaria** Programme

World Health Organization

Outline

Malaria Modules (Epi/Ento)

- Aggregate
- Case-based

National Repository

Regional Repository

What is DHIS2?

District Health Information Software

- Free, open-source software platform for **collection**, **reporting**, **analysis** and **dissemination** of data for all health programs
- Shared and integrated data warehouse
- **Aggregate, events,** and **case-based** data
- Developed by the University of Oslo
  - Network of Health Information Systems Programme (HISP)
- Evolved over the years
  - Meets the needs of most HMIS
  - Gained in stability
  - Strong user support, growing community

What are the Malaria Modules ?

Meta-data packages created for the District Health Information Software (DHIS2) and therefore compatible with existing HMIS systems in many countries.

Content

- Standardized data elements, indicators and definitions
- Standard data collection forms
- Standard data validation rules
- Standardized graphs and maps
- Standard dashboards

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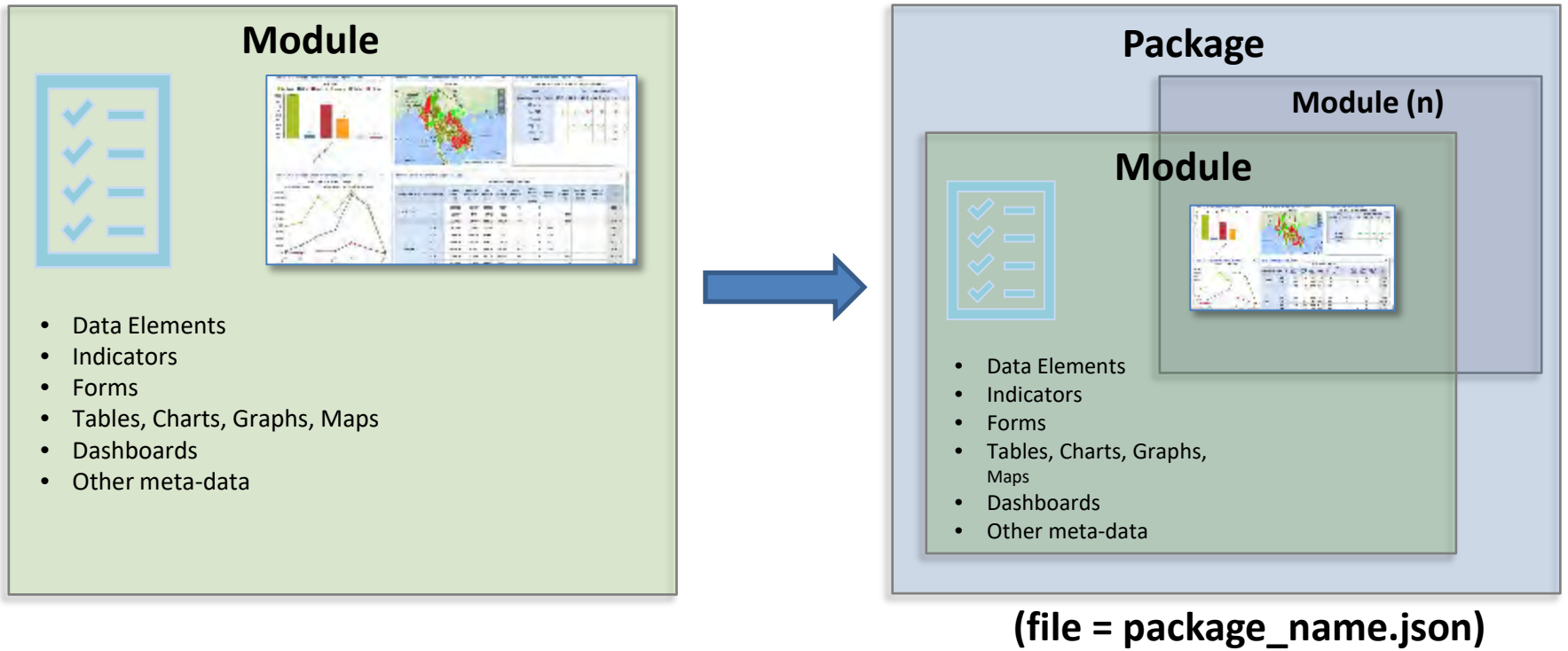
Modules -> Packages

Modules are published and delivered as **Packages**



Epidemiological Malaria Module (aggregated data)

DHIS2

Malaria Module

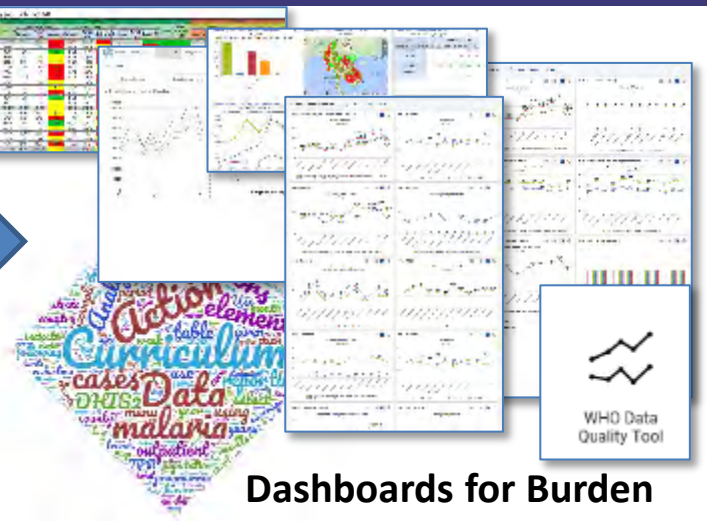
Routine HMIS

Feedback

Calculations

Analysis

Transformation



Dashboards for Burden Reduction and Elimination settings

Health Facility data

Data is aggregated and summarized at Health Facility level on a monthly or weekly basis

Often entered electronically at district for **Burden Reduction** and **Elimination** scenarios

Organisation units master listing

- Health Facilities
  - Long/lat
- Districts/Provinces
  - Geo-coded
  - Shapefiles

Malaria Module
(aggregated data)

Routine data (Aggregated)
Data elements and Indicators:

- Cases and deaths
- Laboratory results
- Case and Foci investigation
- Population at risk
- Routine interventions

Stock

- LMIS
- Stock-outs

Entomological modules

What do the modules cover?

Vector control

- LLIN campaigns
- IRS campaigns
- IRS residual efficacy

Entomology

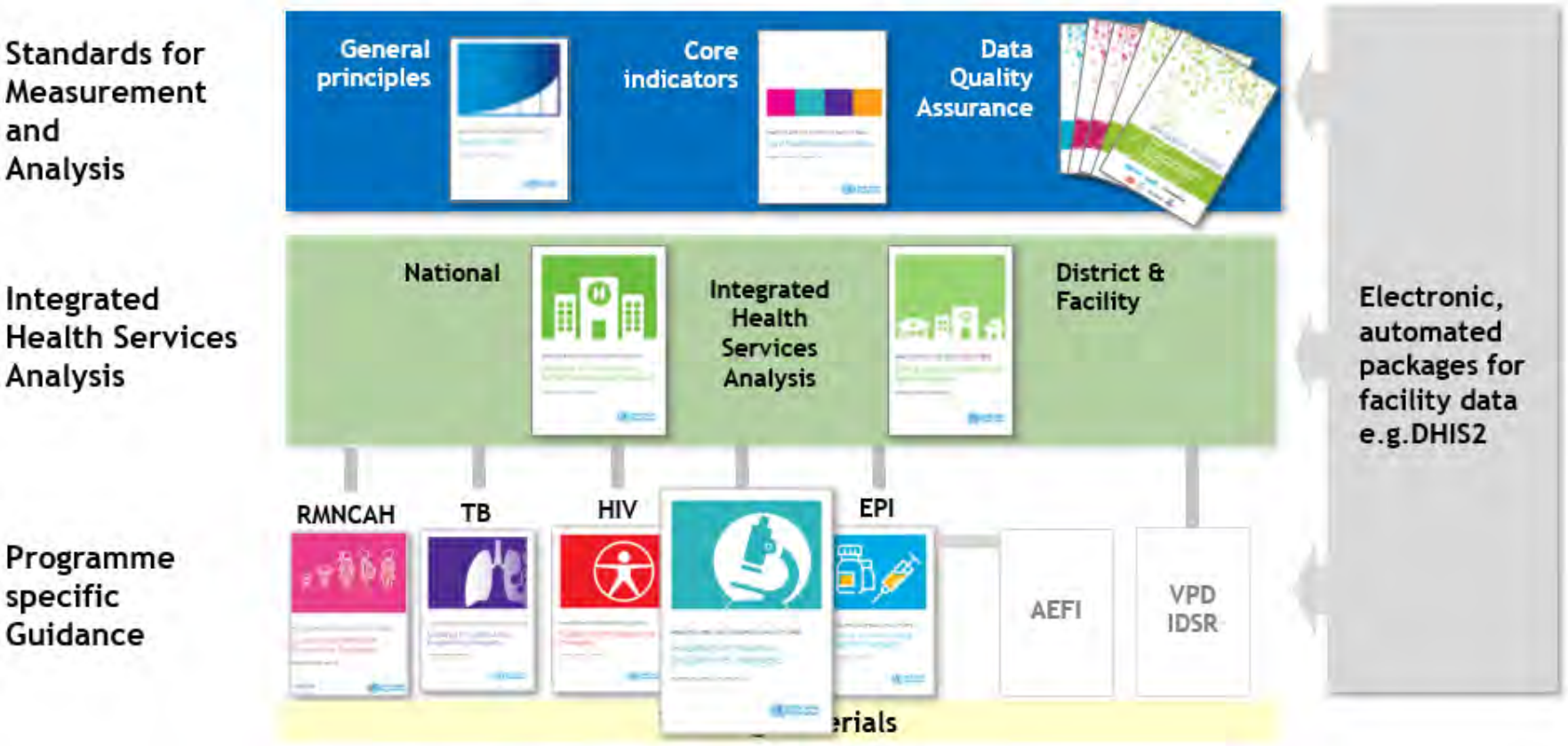
- Insecticide resistance monitoring
- Adult surveillance
- Immature stages surveillance

Module development

Continued development

- Existing Module revisions
  - Additional dashboards for EPI module
    - Data Quality
    - District/Health Facility trends
    - Elimination
  - ENTO modules
    - New modules sent to UiO (soon to be released)
    - Others in preparation
  - Updates based on country feedback
- Under development
  - SMC
  - EPI sub-national stratification
  - Test Efficacy Studies

Malaria Modules (Integrated)

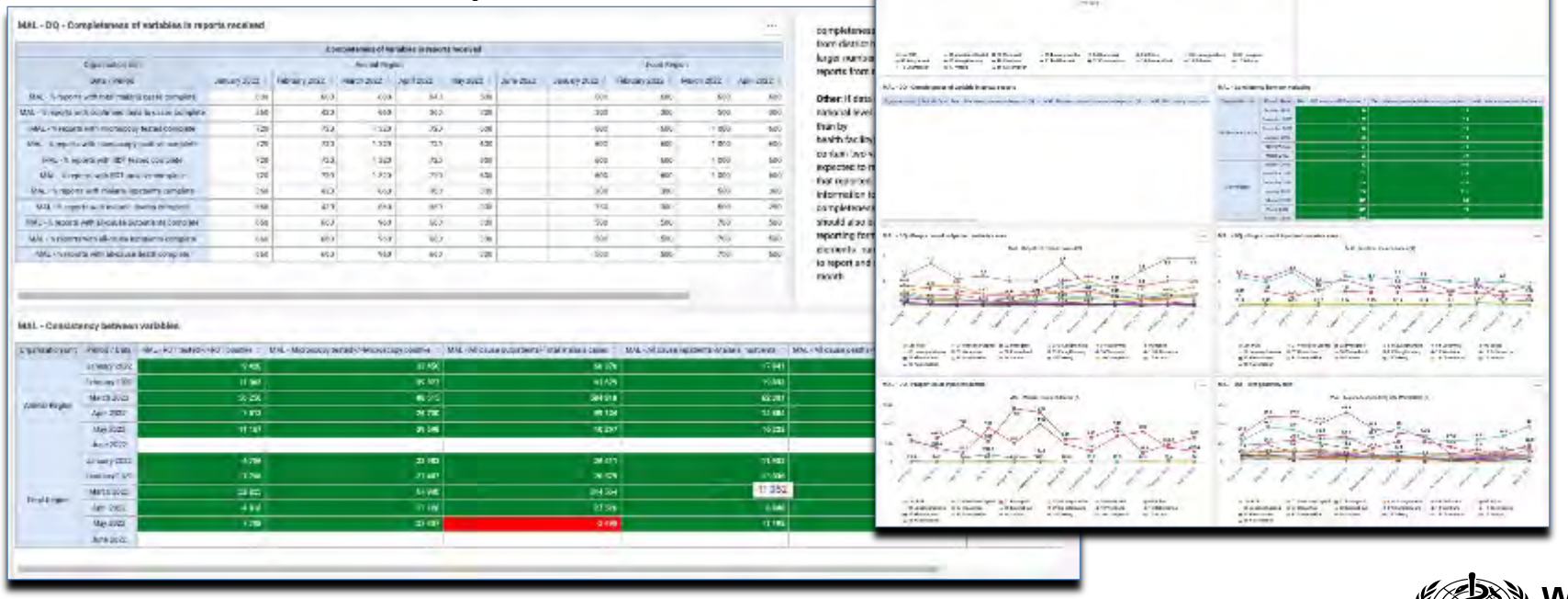


Malaria Module integrates into a broader set of WHO disease surveillance tools for the countries

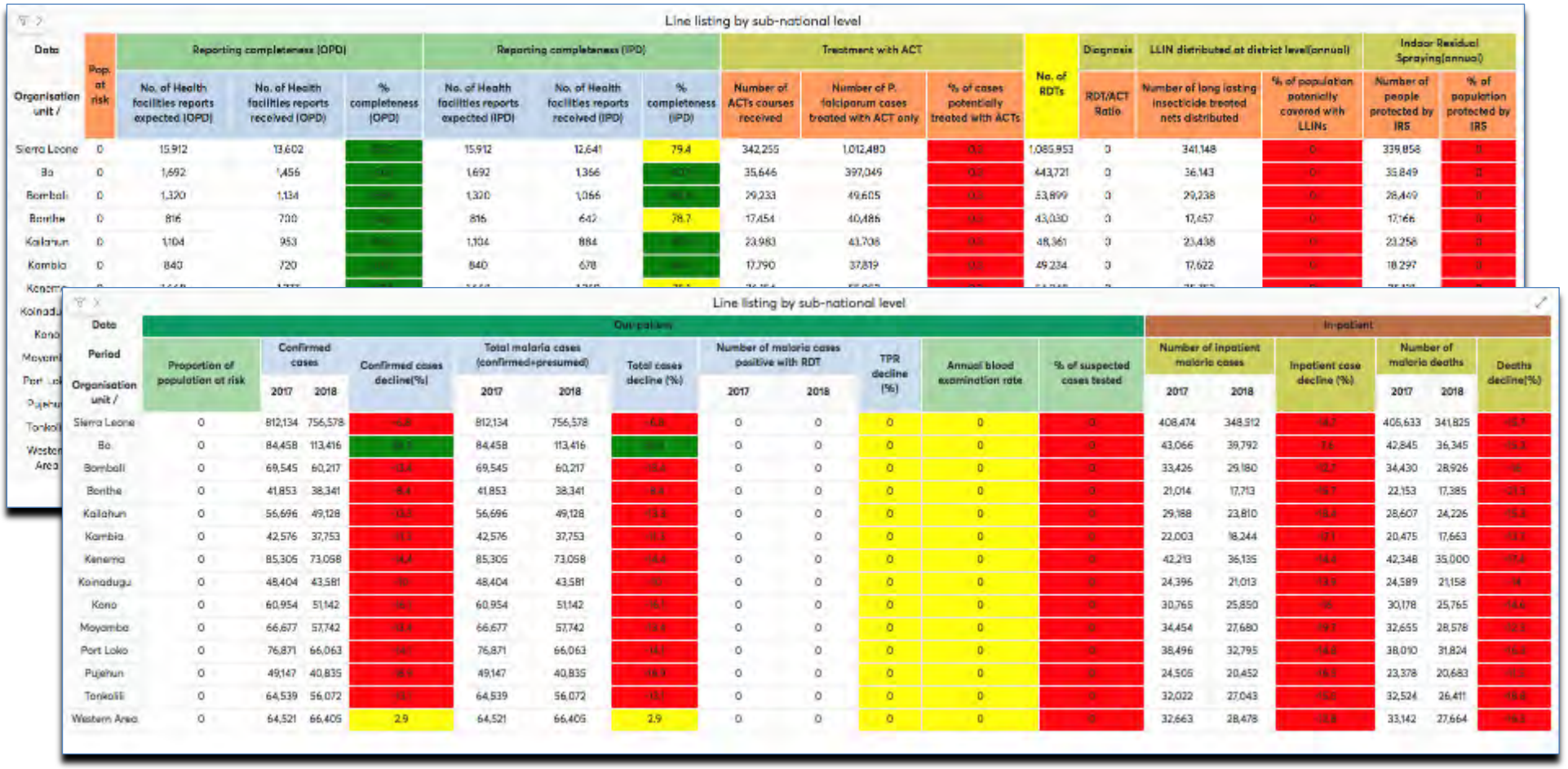
Dashboards to support data use

Data Cleaning: Data Quality dashboard

- Used to highlight discrepancies
  - Coherence data between variables
  - Coherence data over time monitoring
- Completeness of reports
- Timelines of reports



District level reporting



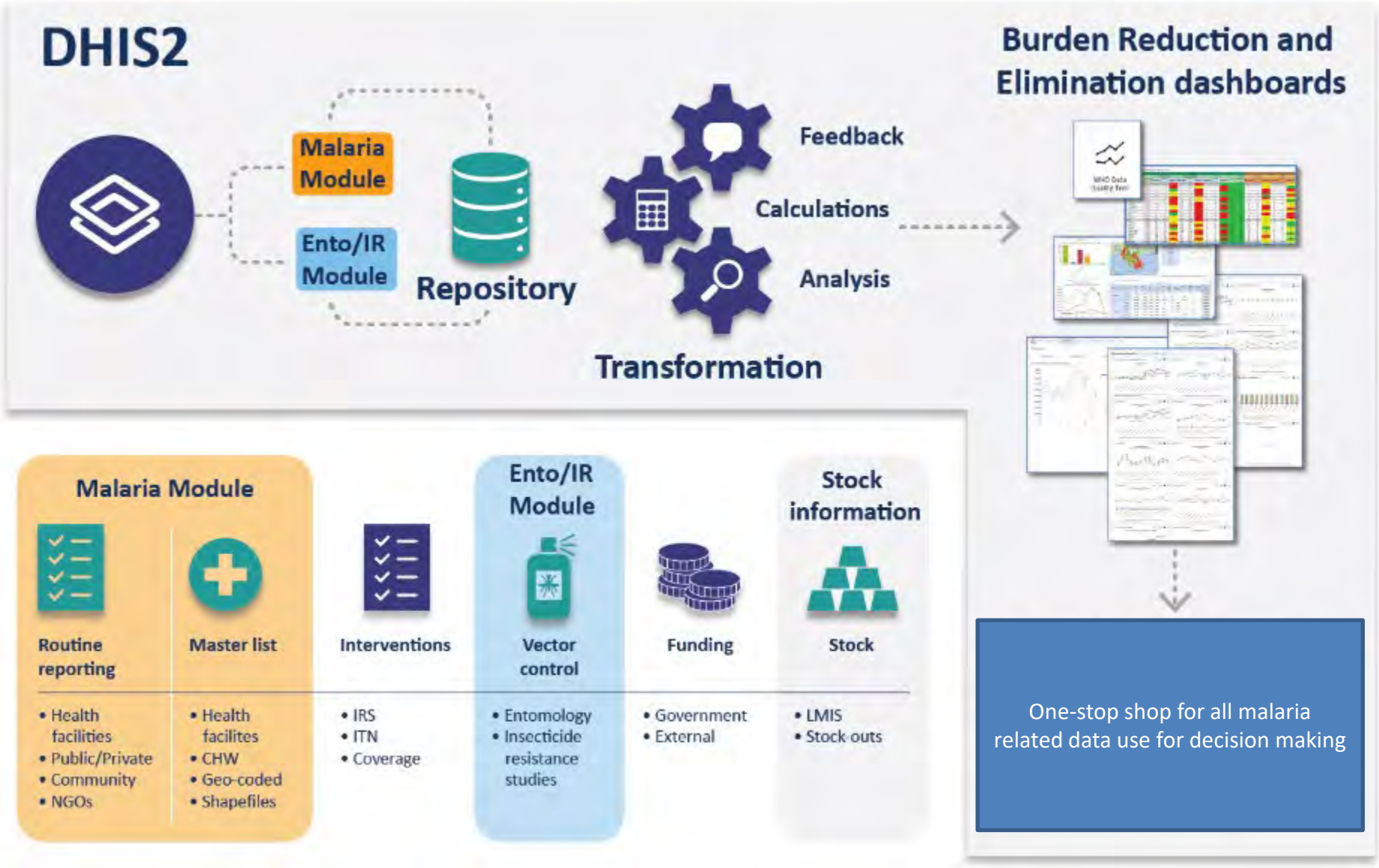
Line listing by sub-national level

Data / Organisation unit /	Pop. at risk	Reporting completeness (OPD)			Reporting completeness (IPD)			Treatment with ACT			No. of RDTs	Diagnosis	LLIN distributed at district level(annual)		Indoor Residual Spraying(annual)	
		No. of Health facilities reports expected (OPD)	No. of Health facilities reports received (OPD)	% completeness (OPD)	No. of Health facilities reports expected (IPD)	No. of Health facilities reports received (IPD)	% completeness (IPD)	Number of ACTs courses received	Number of P. falciparum cases treated with ACT only	% of cases potentially treated with ACTs		RDT/ACT Ratio	Number of long lasting insecticide treated nets distributed	% of population potentially covered with LLINs	Number of people protected by IRS	% of population protected by IRS
Sierra Leone	0	15,912	13,602		15,912	12,641	79.4	342,255	1,012,480		1,085,953	0	341,148		339,858	
Bo	0	1,692	1,456		1,692	1,356		35,646	397,049		443,721	0	36,143		35,849	
Bombali	0	1,320	1,134		1,320	1,066		29,233	49,605		53,899	0	29,238		28,449	
Bonthe	0	816	700		816	642	78.7	17,454	40,486		43,030	0	17,457		17,166	
Kailahun	0	1,104	953		1,104	884		23,983	43,708		48,361	0	23,438		23,258	
Kambia	0	840	720		840	678		17,790	37,819		49,234	0	17,622		18,297	
Kenema																
Koinadu																
Kono																
Moyamb																
Port Lo																
Pujehu																
Tonkoli																
Western Area																

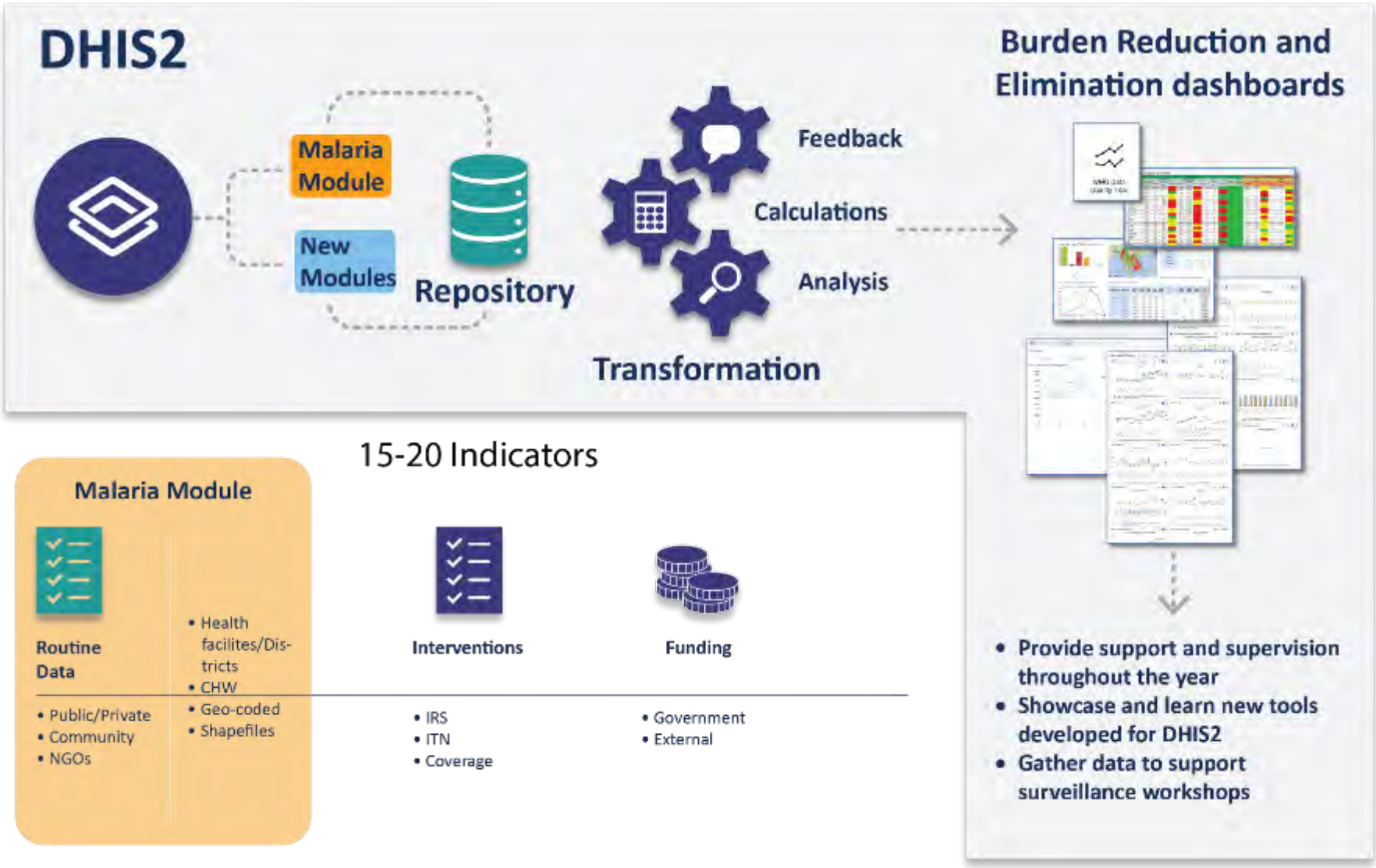
Line listing by sub-national level

Data / Period / Organisation unit /	Proportion of population at risk	Confirmed cases		Confirmed cases decline(%)	Total malaria cases (confirmed+presumed)		Total cases decline (%)	Number of malaria cases positive with RDT		TPR decline (%)	Annual blood examination rate	% of suspected cases tested	Number of inpatient malaria cases		Inpatient case decline (%)	Number of malaria deaths		Deaths decline(%)
		2017	2018		2017	2018		2017	2018				2017	2018		2017	2018	
Sierra Leone	0	812,134	756,578		812,134	756,578		0	0	0	0	0	408,474	348,512		406,633	341,825	
Bo	0	84,458	113,416		84,458	113,416		0	0	0	0	0	43,066	39,792		42,845	36,345	
Bombali	0	69,545	60,217		69,545	60,217		0	0	0	0	0	33,426	29,180		34,430	28,926	
Bonthe	0	41,853	38,341		41,853	38,341		0	0	0	0	0	21,014	17,713		22,153	17,385	
Kailahun	0	56,696	49,128		56,696	49,128		0	0	0	0	0	29,188	23,810		28,607	24,226	
Kambia	0	42,576	37,753		42,576	37,753		0	0	0	0	0	22,003	18,244		20,475	17,663	
Kenema	0	85,305	73,068		85,305	73,068		0	0	0	0	0	42,213	36,135		42,348	35,000	
Koinadugu	0	48,404	43,581		48,404	43,581		0	0	0	0	0	24,396	21,013		24,589	21,158	
Kono	0	60,954	51,142		60,954	51,142		0	0	0	0	0	30,765	25,850		30,178	25,765	
Moyamba	0	66,677	57,742		66,677	57,742		0	0	0	0	0	34,454	27,680		32,655	28,578	
Port Loko	0	76,871	66,063		76,871	66,063		0	0	0	0	0	38,496	32,795		38,010	31,824	
Pujehun	0	49,147	40,835		49,147	40,835		0	0	0	0	0	24,505	20,452		23,378	20,683	
Tonkolili	0	64,539	56,072		64,539	56,072		0	0	0	0	0	32,022	27,043		32,524	26,411	
Western Area	0	64,521	66,405	2.9	64,521	66,405	2.9	0	0	0	0	0	32,663	28,478		33,142	27,664	

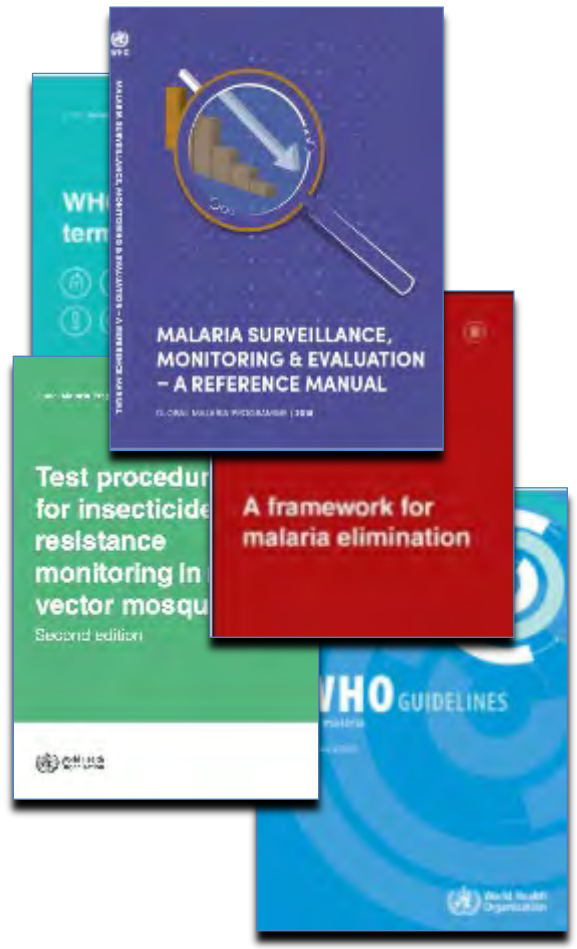
National Malaria Repository



WHO Regional Malaria Databases



Online training for our modules



Malaria

– Guidance (English)

– Guidance (French)

– Exercise book: Learner's Guide

– Exercise book: Tutor's Guide (English)

– Exercise book: Tutor's Guide (French)

– Configuration package

Guidance material

Curriculum

Online training

Malaria Modules

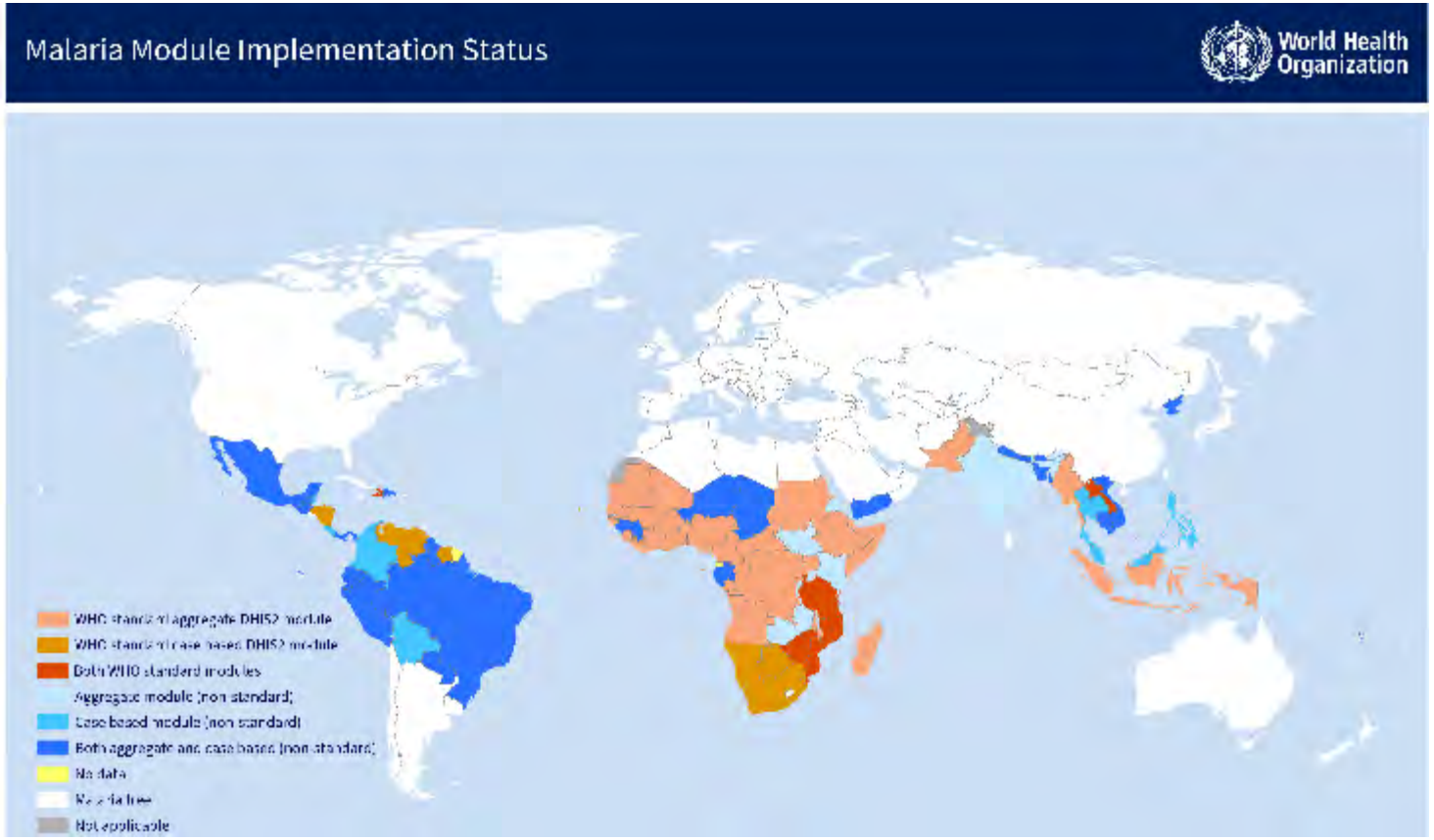
Malaria Modules : Based on WHO recommendations and publications:

- Used to harmonize data collection across countries, disseminate guidance recommendations

Developed In consultation with partners

- **Support** from partners in rolling out the modules (UiO, Global Fund, PMI, BMGF, CHAI,…)

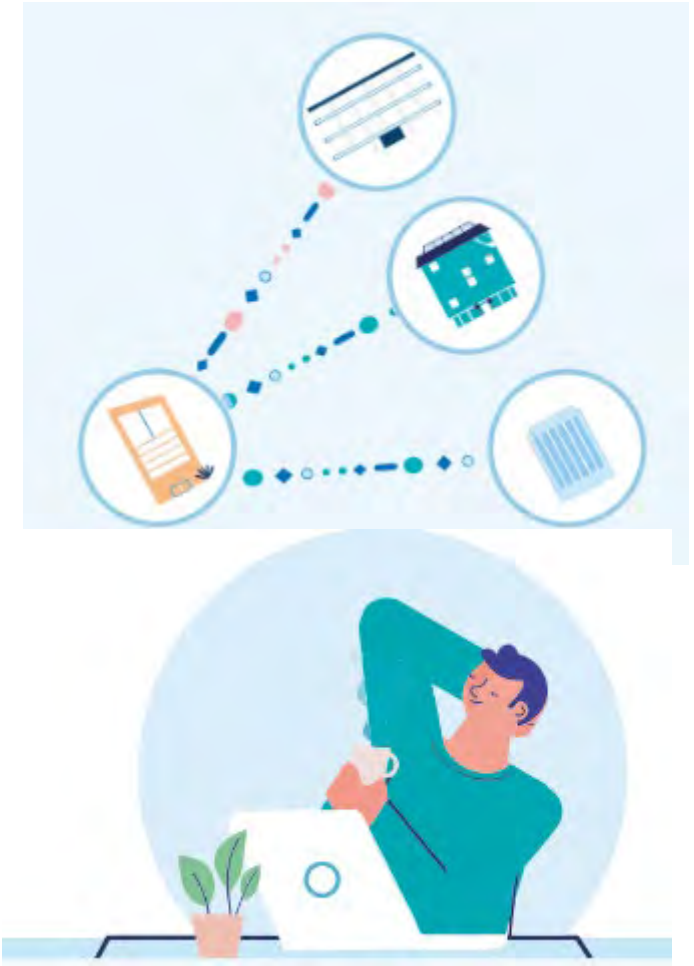
Adopted by over 40 countries



Reduce the burden of reporting

From mainly manual reporting

To automatize reporting



Digital Tools for Strengthening Malaria Surveillance

Malaria case-based surveillance module

Mwalenga Nghipumbwa

19 April 2023, MPAG, Geneva

Global **Malaria** Programme

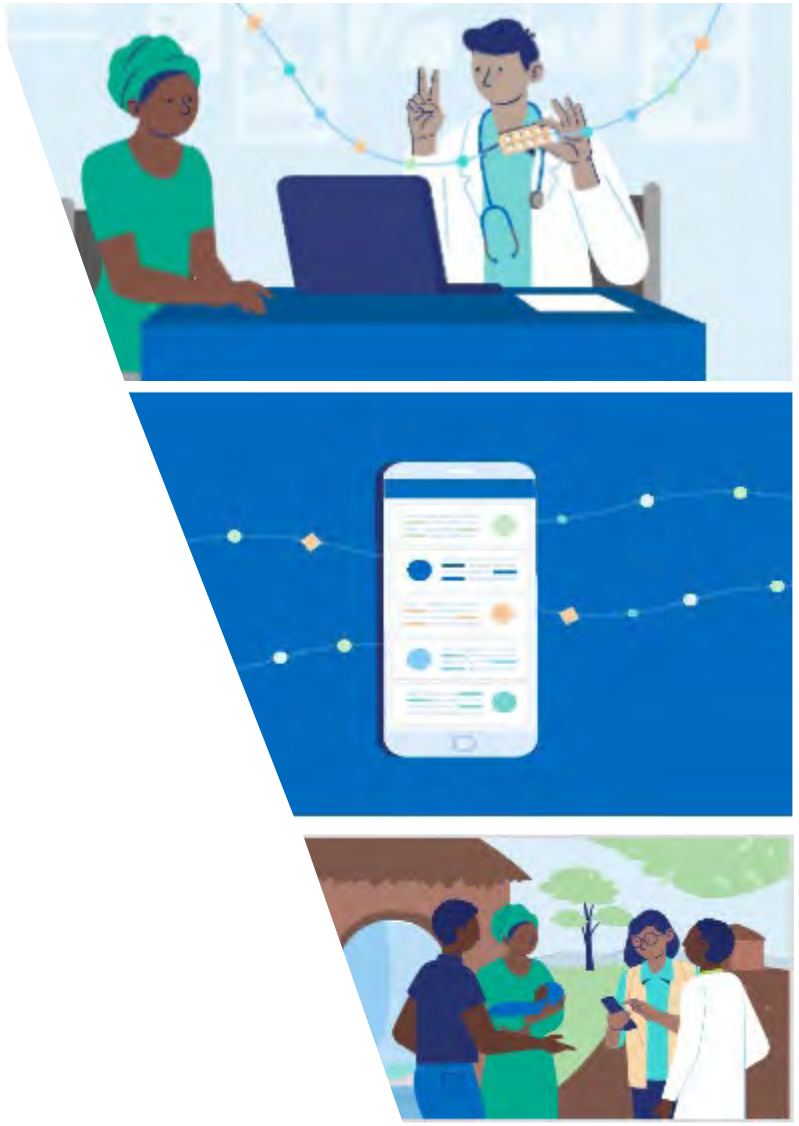
World Health Organization

Malaria elimination module

Objective: Develop effective digital tools to make complete, timely, and accurate data reporting easier and to improve decision-making processes.

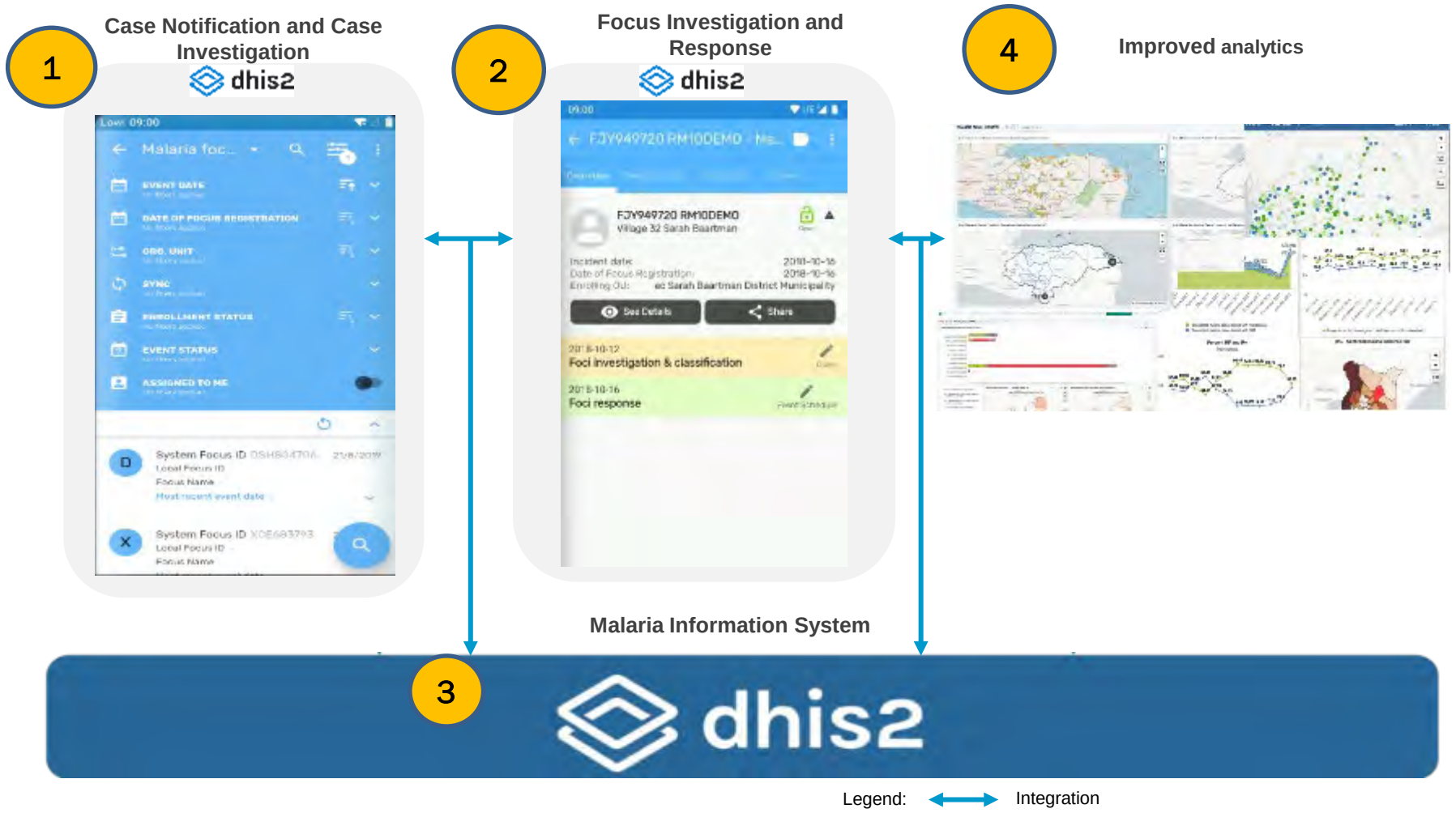
<u>Content</u>

- Standardized data elements, indicators and definitions
- Standard data collection forms
- Standard data validation rules
- Standardized graphs and maps
- Standard dashboards



Case-based module and Focus module

The digital tools can be used together or independently based on the country digital ecosystem and operational readiness.



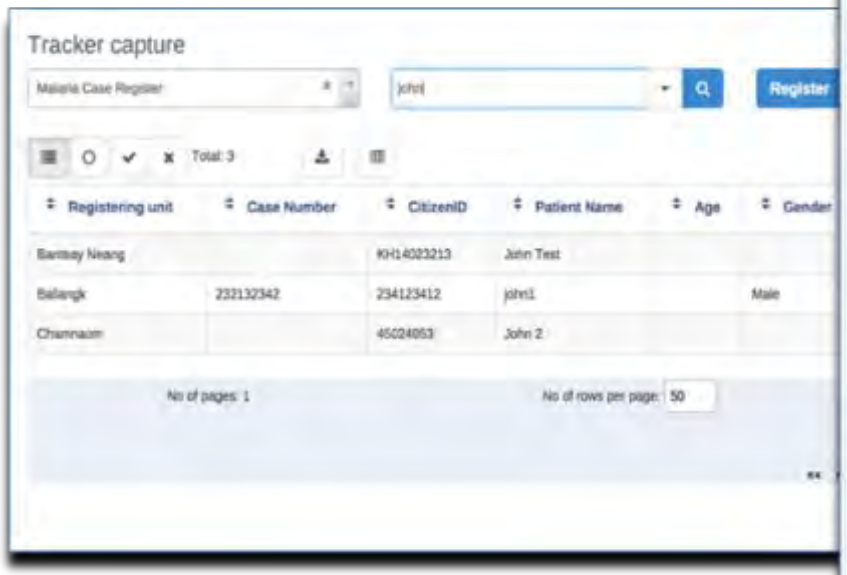
What is in the elimination module

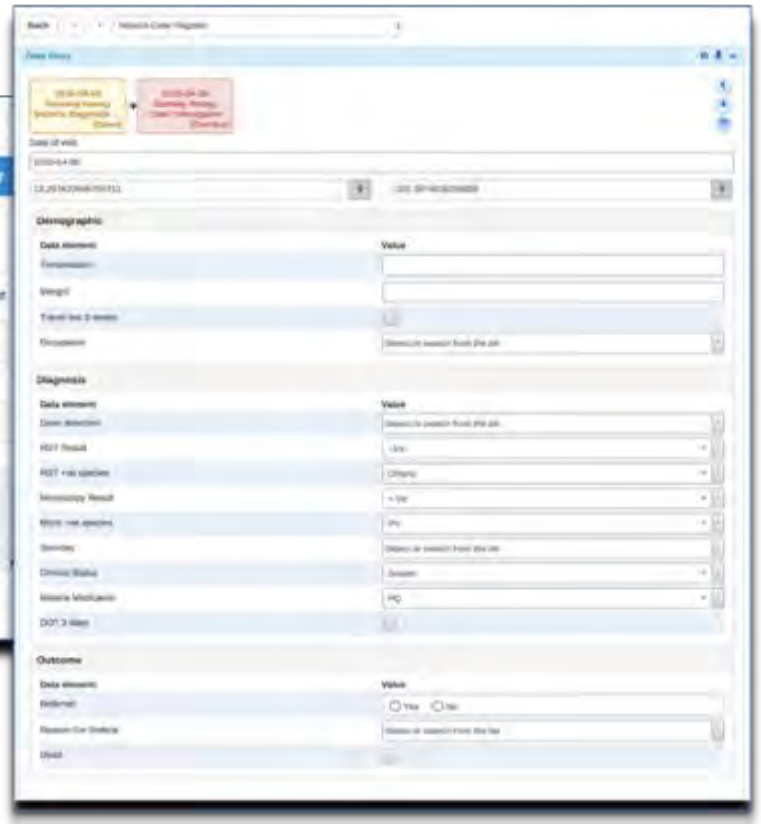
Patient registration **(patient Id)**

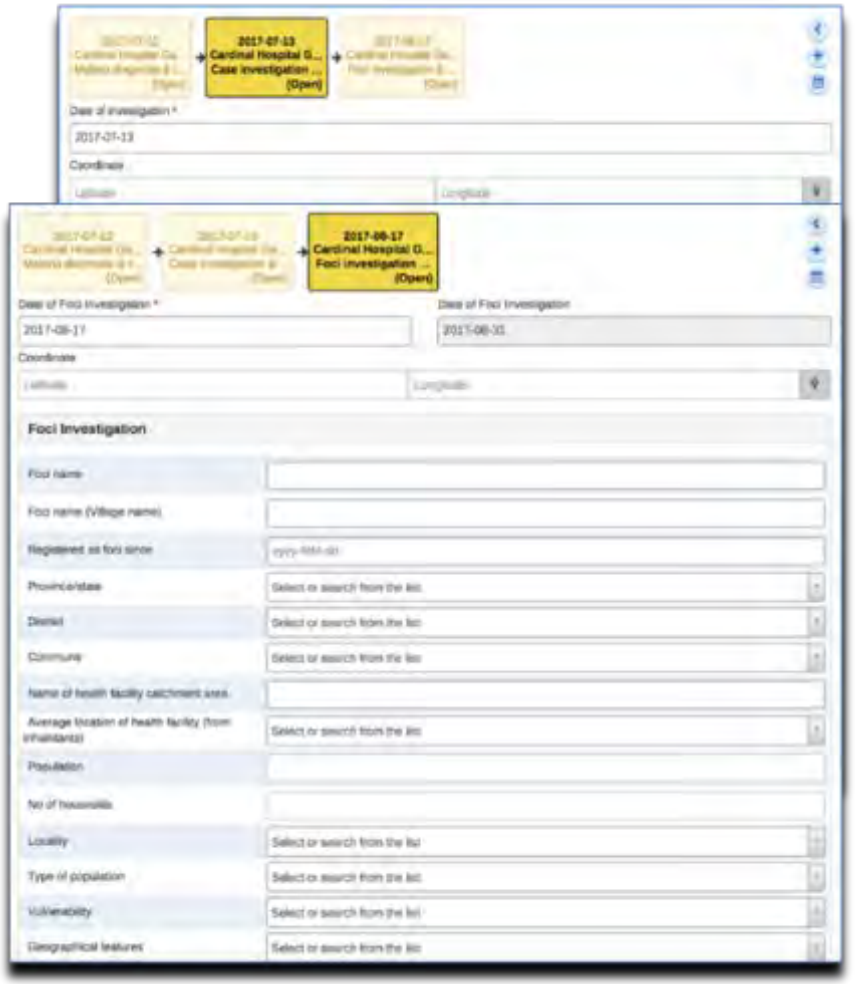
Diagnosis, confirmation and Treatment

Case investigation

Foci investigation







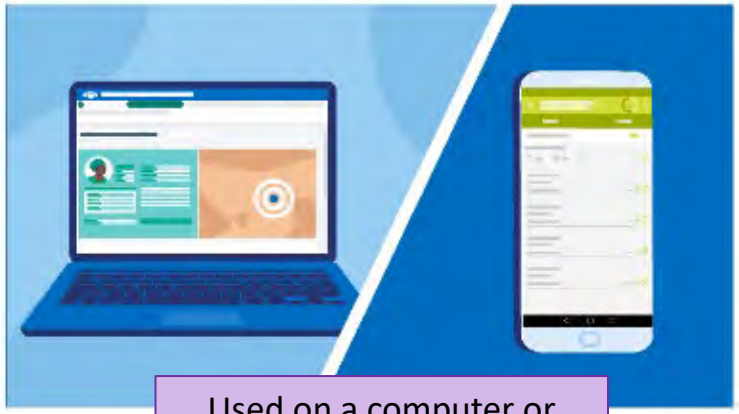
Global **Malaria** Programme

Elimination modules

These modules make it easy for health workers and field investigators to:

- enter data on new malaria cases
- follow up cases at household level and
- register and monitor foci
- record case data and investigation data during their surveillance activities
- improved data visualization for interpretation through dashboards

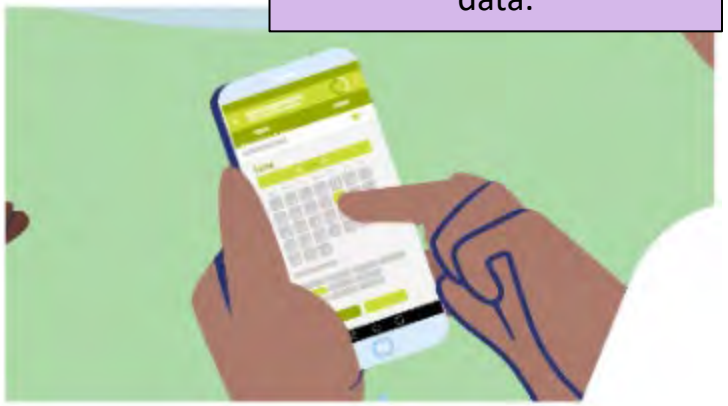
Benefits



Used on a computer or using an android device.

Online and offline data capture capabilities.

Updating of information and uploading of historical data.

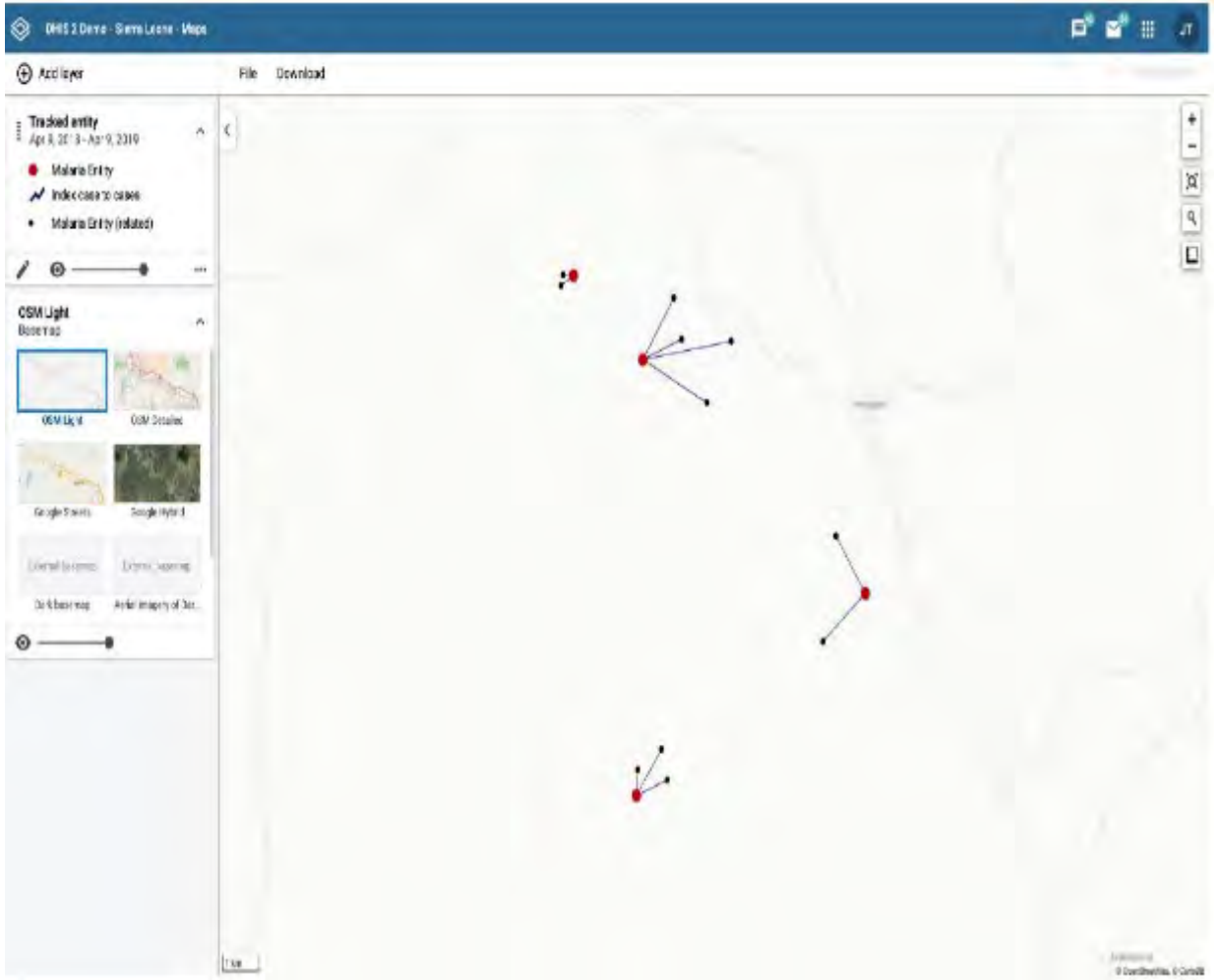


Real-time data collection.

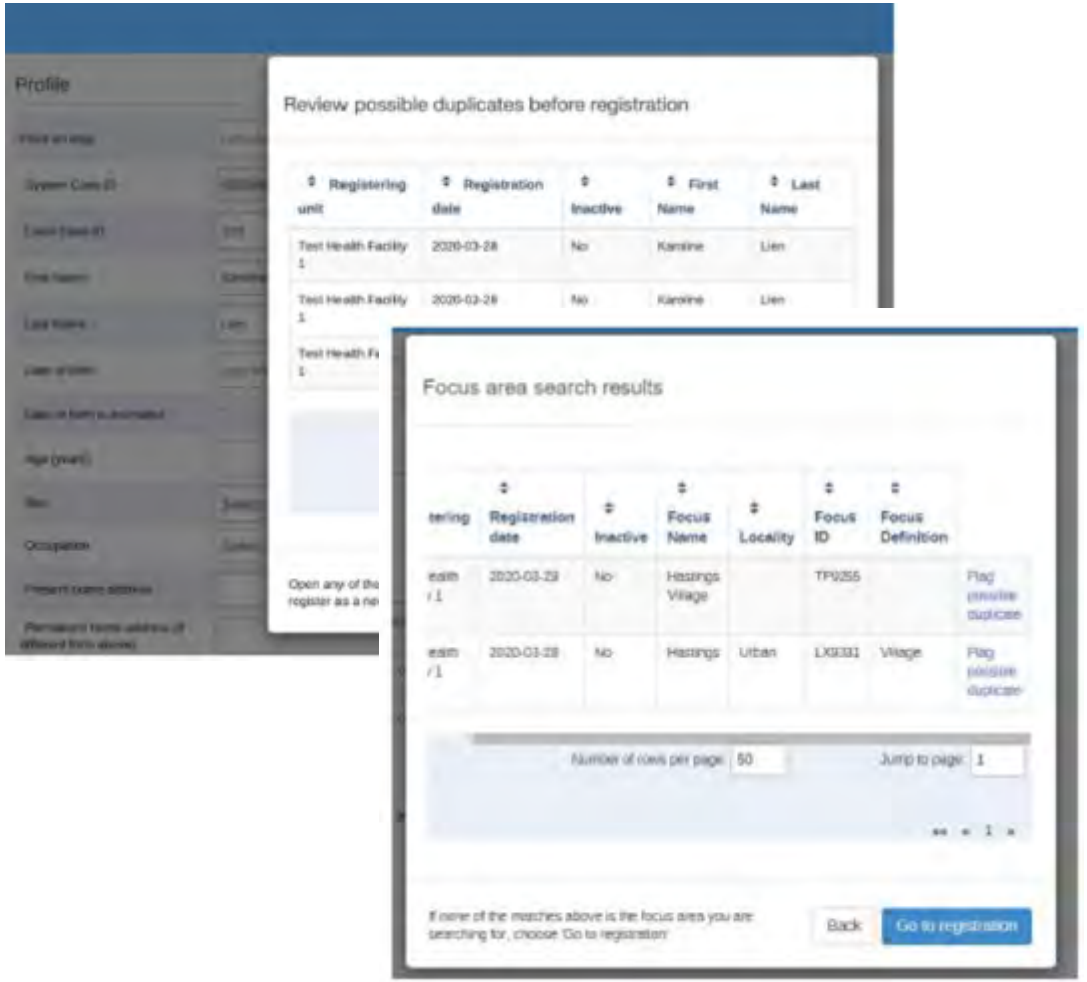
- Fully customizable.
- Integratable into existing DHIS2, saving time and minimizing maintenance costs

Key highlights & what is new

Mapping of relationships (case to case and case to foci)

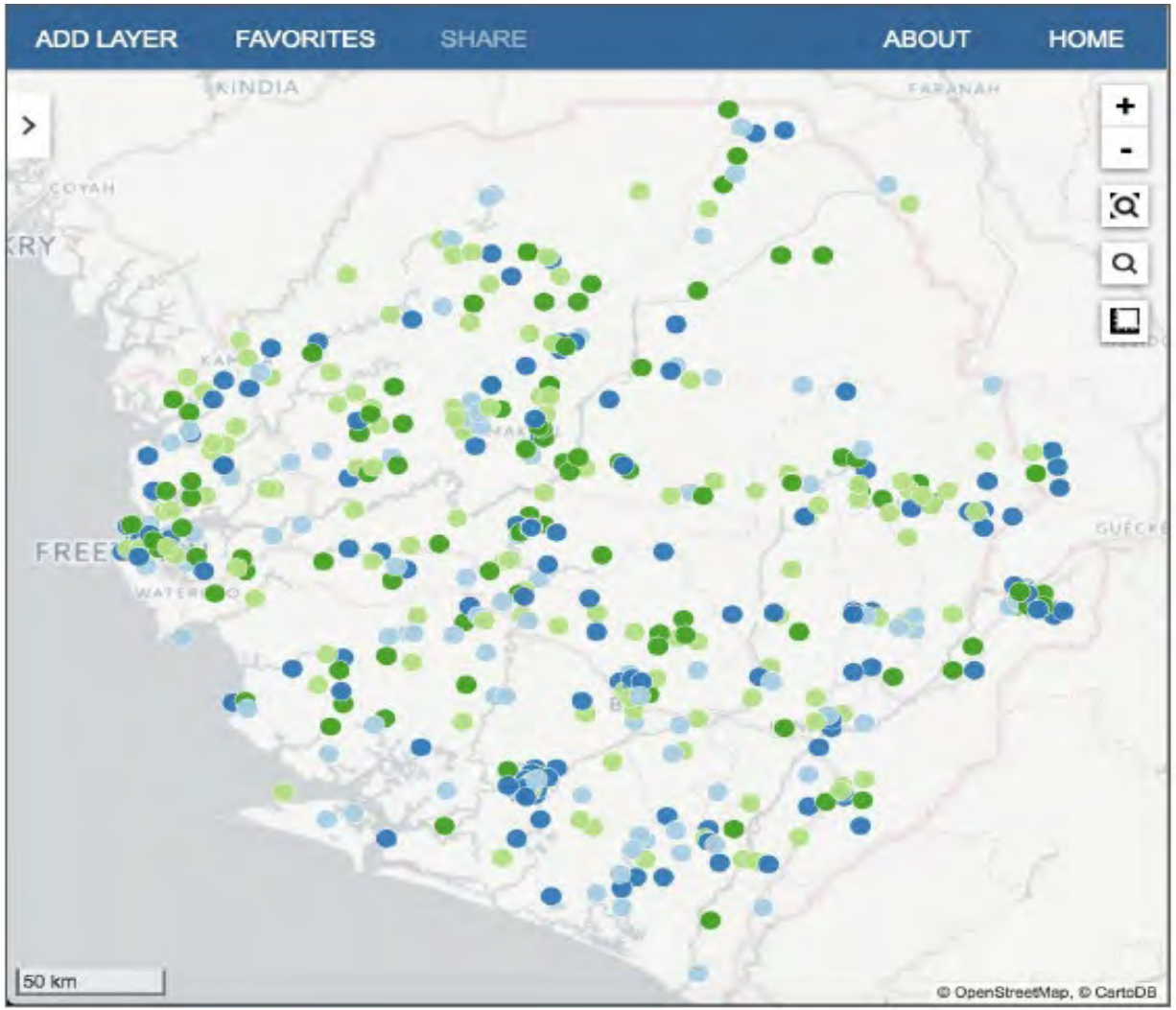


Reducing the potential for duplicates

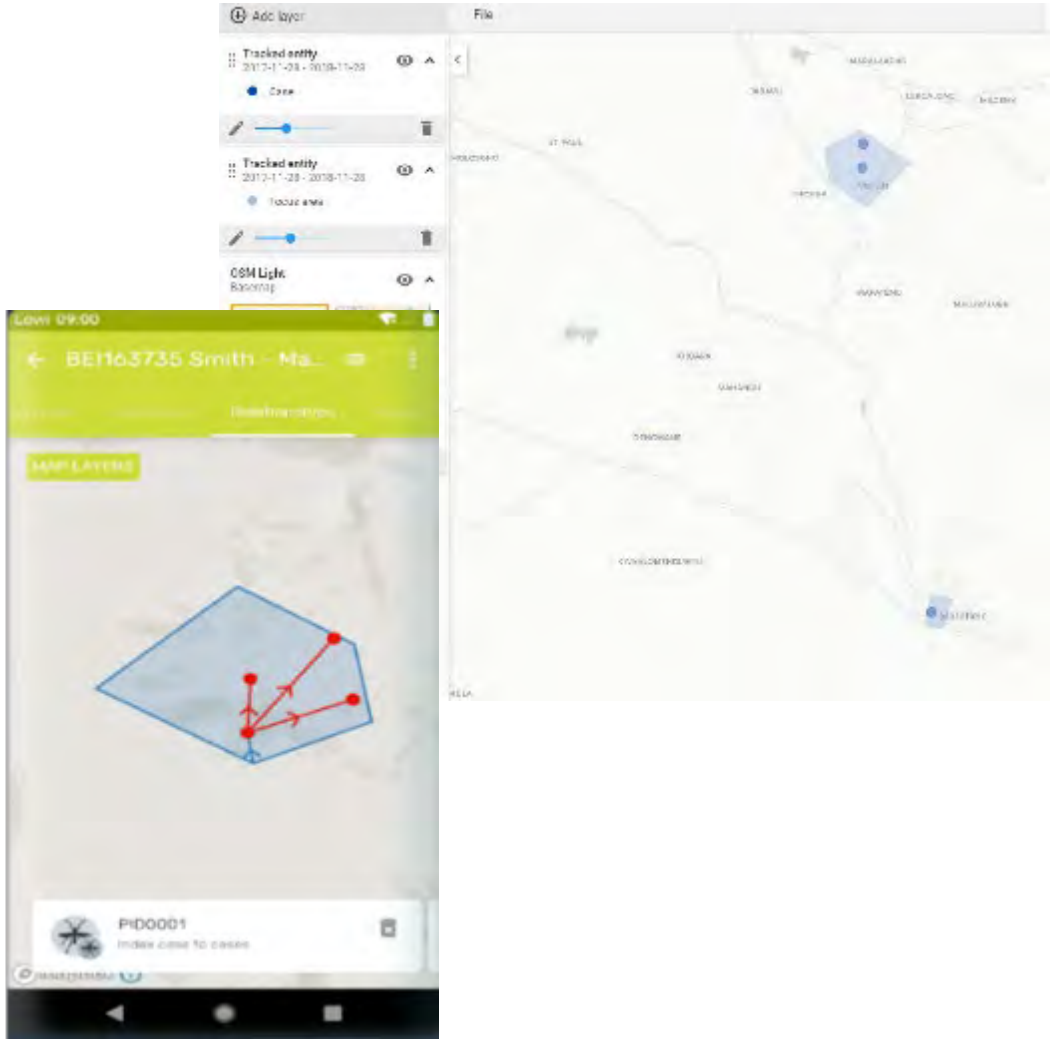


Key highlights and what is new

Geolocation of cases

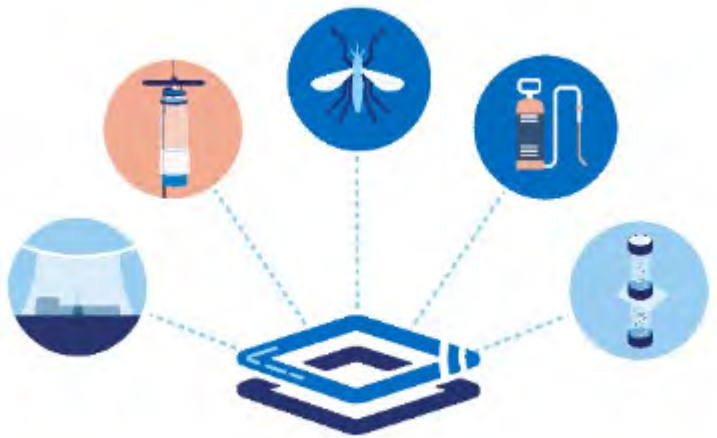


Visualization of foci in the form of polygons



Versatility

- In addition to being designed for use with the aggregate DHIS2 Packages the versatile modules allow other malaria data to be incorporated such as entomological and vector control data.

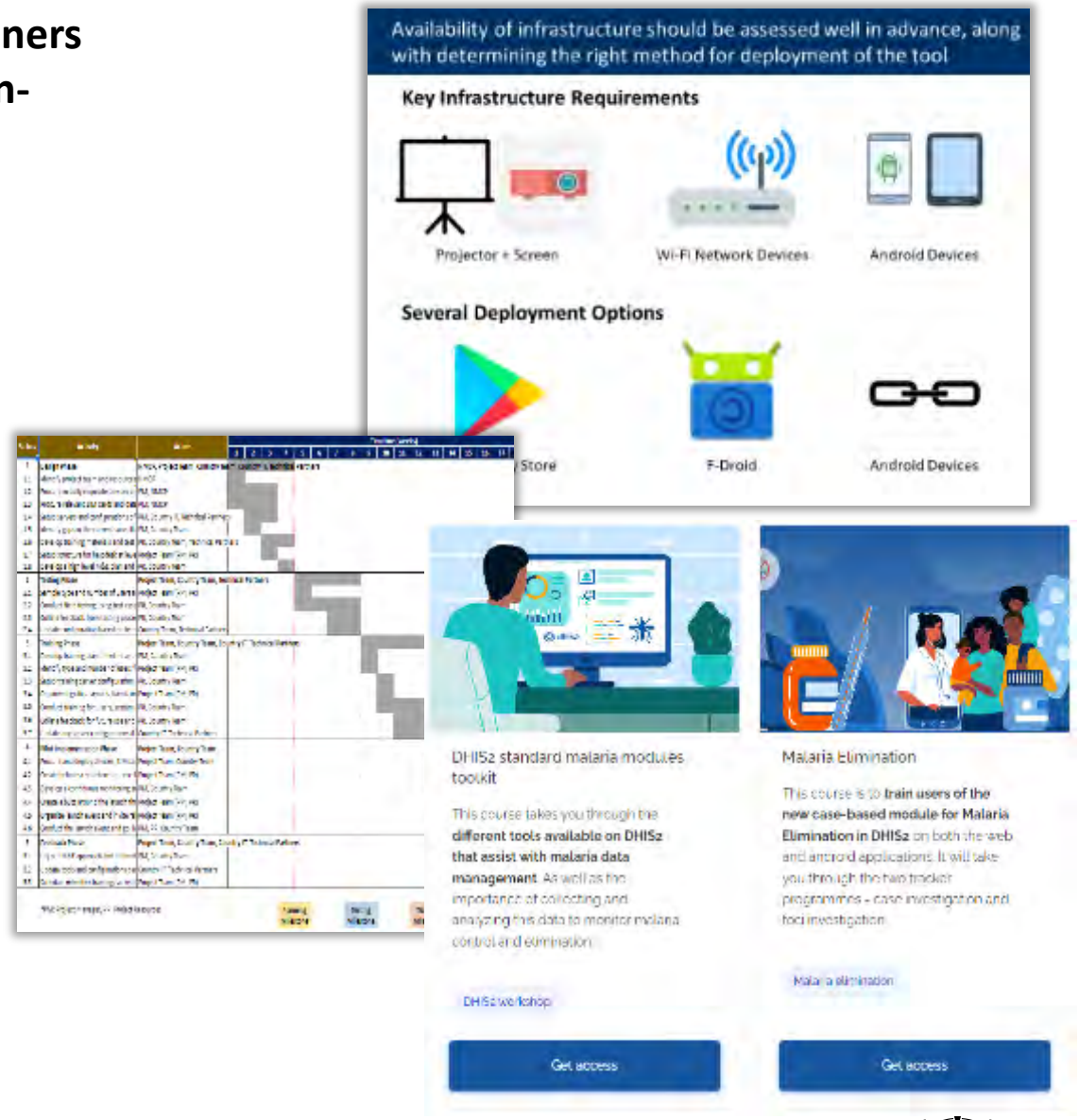


Implementation guiding material

Common Goods: products that can be used by partners across technical platforms for both malaria and non-malaria use cases

A comprehensive set of documents and tools for country implementation has been developed. These include:

- Operational readiness guide and checklist
- Customizable work-plans
- Trainings and videos (in production)



Acknowledgements

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

GOBIERNO DE LA
REPÚBLICA DE HONDURAS
SECRETARÍA DE SALUD

กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH
กรมควบคุมโรค
Department of Disease Control
สำนักโรคติดต่อนำโดยแมลง
Bureau of Vector – Borne Disease

Republic of Namibia
Ministry of Health and Social Services

CLINTON
HEALTH ACCESS
INITIATIVE

UiO : University of Oslo

Malaria surveillance assessment toolkit

Laura Anderson
Strategic Information for Response Unit
MPAG Meeting, 19th April 2023

Global **Malaria** Programme

World Health Organization

Malaria surveillance assessment toolkit

Implementation reference guide

2 August 2022 | Toolkit

Download (680 kB)

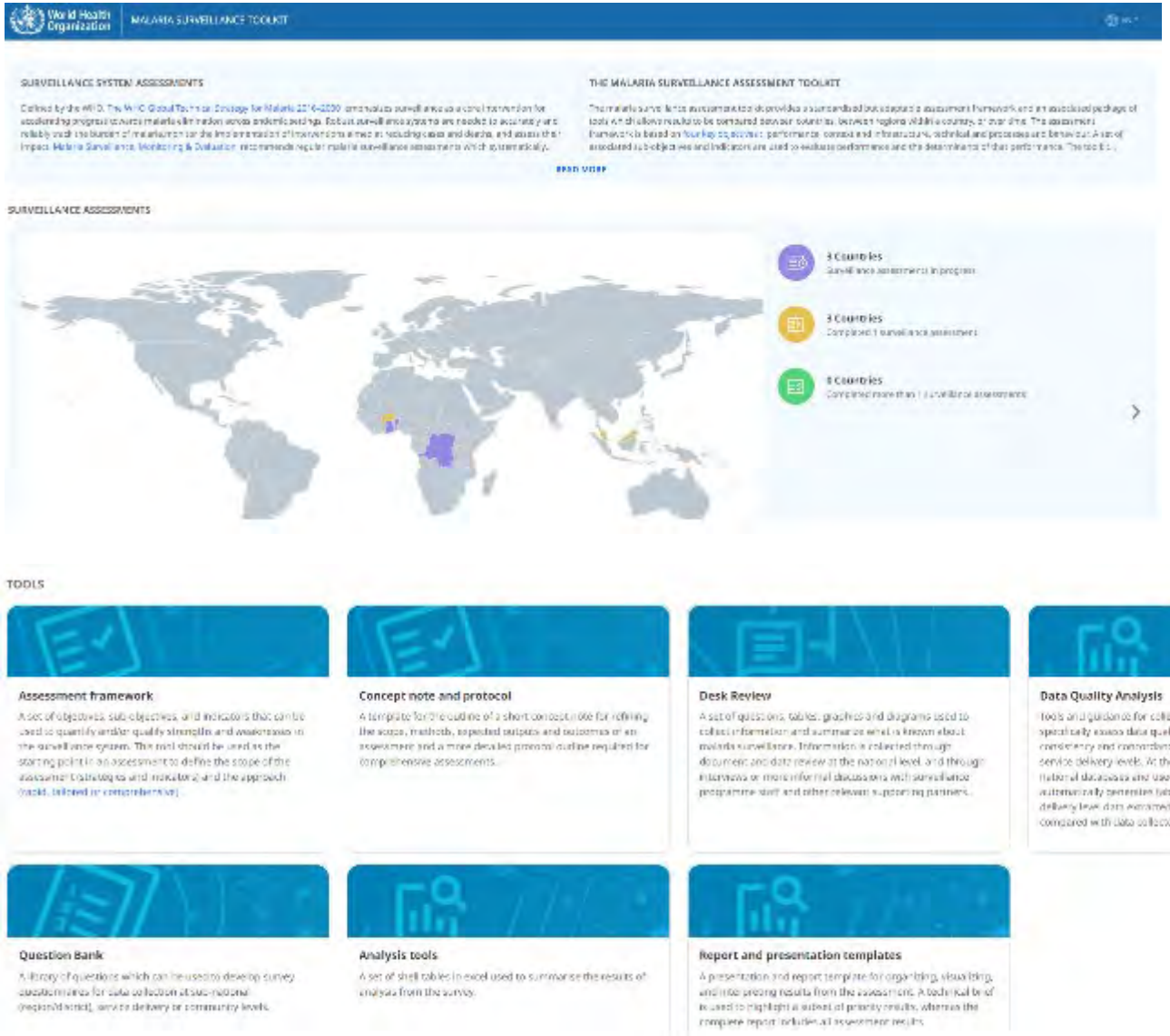
Overview

This Malaria Surveillance Assessment Toolkit implementation reference guide is a comprehensive reference document, as well as a step by-step guide. It aligns and adapts available tools into a single set of standardized tools, which can be used to conduct malaria surveillance assessments across all transmission settings. Use of these standardized tools allows comparison of results between countries and within the same country over time, enabling countries to track their progress towards surveillance system strengthening.

→ Malaria surveillance assessment toolkit

Malaria surveillance assessment toolkit (who.int)

Malaria surveillance toolkit landing page



[Welcome to Malaria Toolkit (who-malaria-uat.azurewebsites.net)]

http://who-malaria-uat.azurewebsites.net/

An overview of the toolkit and a summary of surveillance assessments

Tools can be downloaded in English and in French

What is a malaria surveillance assessment?

What	A systematic approach to measuring the performance of malaria surveillance systems, and identifying and evaluating the determinants of that performance.
Where	All malaria endemic countries should carry out a surveillance system assessment. In elimination settings recommended when there are fewer than 100 cases and in three years of reporting zero cases.
Who	Implemented by national malaria programmes and partners interested in malaria surveillance strengthening.
When	Undertaken at any time but recommended as part of key NMP planning milestones such as a Malaria Programme Review (MPR) and National Strategic Plan (NSP) development. In elimination settings prior to certification and as part of the assessment for whether a programme is in place to prevent re-establishment.
Why	To provide actionable and prioritized recommendations on how to strengthen surveillance systems for malaria control and elimination. In elimination settings; Prepare documentation and check quality of data prior to certification

Four key objectives

Desired functions of surveillance

1: Performance

Determinants of surveillance

2: Context and infrastructure

3: Process and technology

4: Behavior

Objective 1: Measure the **performance of the surveillance system**, which is defined by surveillance system coverage, data quality (completeness, timeliness and concordance and consistency) and data use

Objective 2: Describe and evaluate **contextual and infrastructural aspects** of the surveillance that may influence performance. This includes an assessment of health sectors reporting, if minimum data is captured by each surveillance strategy, detail on information systems used, available documentation and guidelines and whether guidelines are adhered to, human and financial resources and partner support, and infrastructure.

Objective 3: Describe and evaluate **process and technical aspects** of the surveillance system that may influence performance. This includes an assessment of processes, tools and personnel involved with the flow of data from recording to response.

Objective 4: Describe and evaluate **behavioral aspects** of the surveillance system that may influence performance. This includes an assessment governance structures in place and the promotion of an information culture, as well as proficiency, motivation and accountability of staff involved in malaria surveillance within a country.

The toolkit has the following characteristics

Adaptable assessment framework:

Standardized package of tools:

User can define the **assessment scope** by

1. choosing the case surveillance (burden reduction or elimination) and malaria control strategies implemented in country
2. the indicators to be included in the assessment (indicators specific to elimination)

All malaria surveillance assessments conducted using the Toolkit will include a **minimum set of priority indicators** and **generate common and consistent expected outputs.**

The content of the Toolkit

The Toolkit consists of eight tools (below) with different functions and an Implementation Reference Guide which is a step-by-step guide on how to carry out an assessment

Function	Tools
Define scope	**1. Assessment framework tool** **2. Concept note and protocol** **3. Surveillance assessment planning tool**
Collect & analyse data	**4. Desk review Tool** **5. Data Quality Assessment tools** **6. Question Bank** **7. Analysis tools**
Develop and prioritize recommendations	**8. Technical brief and Report outline**

How is an assessment implemented using the Toolkit?

The scope will determine the assessment approach, which can be summarized in to 3 potential approaches:

	Rapid	Tailored	Comprehensive
Scope	Only *priority indicators* from all four objectives for surveillance of malaria cases and deaths by transmission setting and surveillance of all other malaria control interventions and strategies implemented in country and selected for assessment	*Priority indicators + user selected optional indicators of interest* from the four objectives surveillance of malaria cases and deaths by transmission setting and surveillance of all other malaria control interventions and strategies implemented in country and selected for assessment	*All indicators* from all four objectives for case surveillance and *priority indicators* for surveillance of malaria cases and deaths by transmission setting and priority indicators for all malaria control strategies implemented in country
Methods	Primarily limited to desk review only with few essential site visits	Desk review and surveys at different levels of the health systems (i.e., national, subnational, a sample of facilities and community healthcare workers)	Desk review and surveys at different levels of the health systems (i.e., national, subnational, a sample of facilities and community healthcare workers)
Estimated resource requirement	Low; 2-4 weeks	Medium/High; a minimum of 3 months up to 12 months depending on context	High: a minimum of 3 months up to 12 months depending on context
Suggested frequency	Once every 3-5 years in line with the MPR and NSP development or if necessary, once a year as part of the annual programme review. Annual in elimination settings.	Once every 3-5 years in line with the MPR and NSP development. Annual in elimination settings depending on need and resources.	Once every 3-5 years in line with the MPR and NSP development. Annual in elimination settings depending on need and resources.

Implementation of a malaria surveillance assessment occurs in four phases

Phase 1

Assessment initiation

- **Establish a steering committee** of key stakeholders
- Define the assessment rationale, scope, objectives and methods in a **concept note and/or protocol**
- **Customize selected data collection** tools based on scope and country context

Phase 2

Data collection and review

Conduct a

- **desk review**[a] of literature and data supplemented by interviews with programme staff and key stakeholders
- **data quality assessment** of retrospective data in national databases and source documents
- **survey** of surveillance staff at all relevant levels of the health system

Phase 3

Data analysis and output development

- **Manage and clean data** from all data collection sources
- Analyze qualitative and quantitative data collected to **produce tables and figures**

Phase 4

Prioritization of recommendations and dissemination

- Produce dissemination material including **standardized technical brief and/or report**
- **Generate and prioritize recommendations** through discussion with steering committee
- **Create an action plan with stakeholders** and discuss the feasibility to address priority gaps

[a]the desk review may begin in phase 1 to inform the protocol or concept note

How does the toolkit work?

Select transmission setting

Burden reduction

Elimination

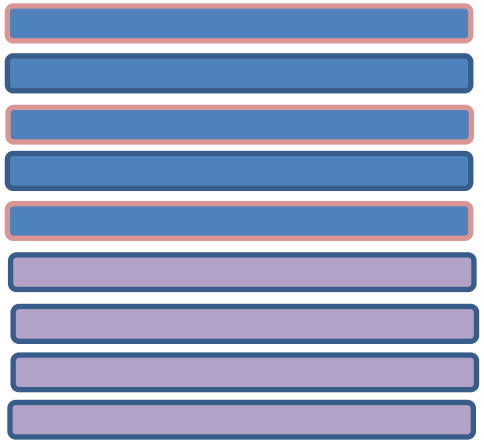
Select assessment type

Rapid

Tailored

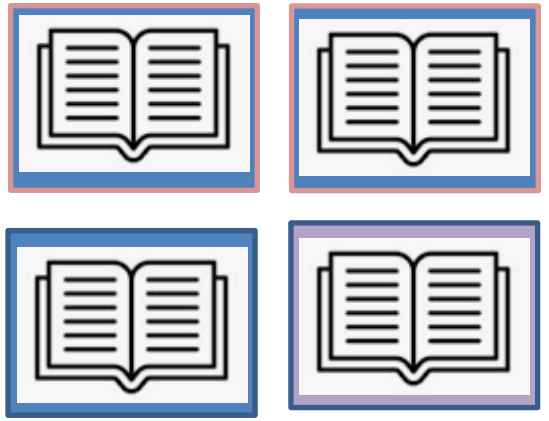
Comprehensive

Indicators selected

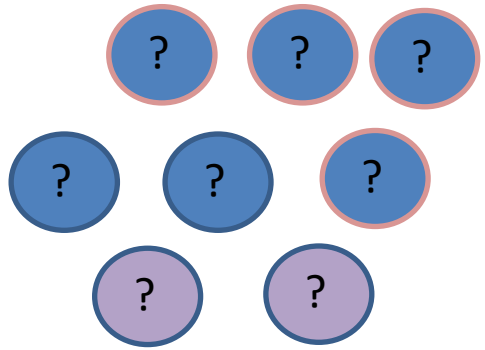


Tools filtered automatically

Desk review



Question bank



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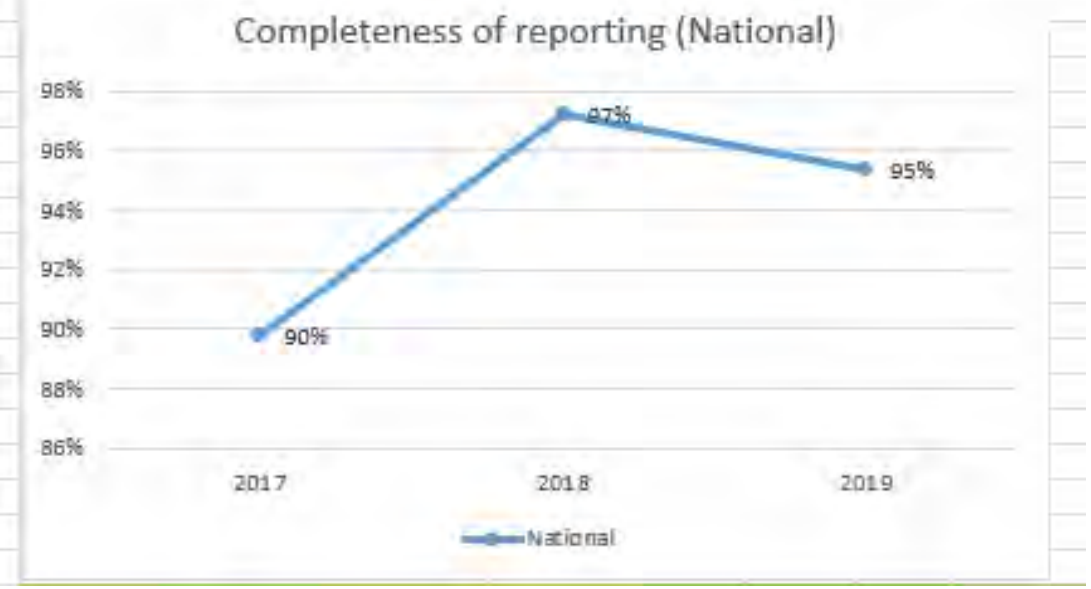
Data quality assessment desk level tools

Populate a standardized template with aggregate or case-based data extracted from the national surveillance system (minimum 3 years of data)

Country (Name)	Completeness of reporting 2017	2018	2019
National	90%	97%	95%



Tables and graphs automatically generated at all health system levels

A summary results table is automatically populated

Summary national data quality estimates	
	National level results
Completeness of reports	95%
Timeliness of reporting	86%
Completeness of core variables within reports	84%
Consistency between core variables	82%
Concordance of key variables between two reporting systems	73%
Consistency over time for core indicators	Consistent trend (Yes/No)
1. Proportion of malaria outpatients	Yes
2. Proportion of malaria inpatients	No
3. Proportion of malaria inpatient deaths	Yes
4. Test positivity rate	Yes
5. Slide positivity rate	Yes
6. RDT positivity rate	No
7. Proportion of suspects tested	Yes

DQA tools for elimination settings: Service delivery level

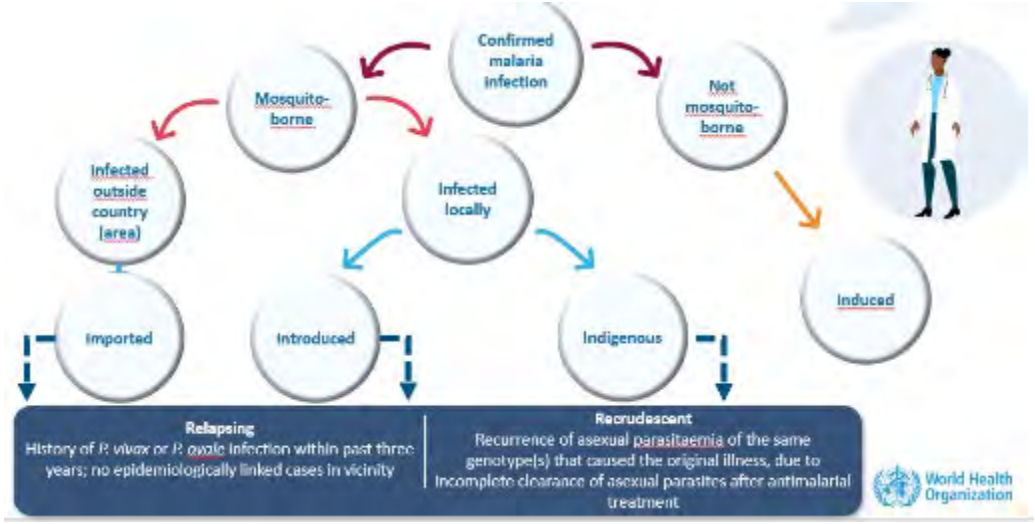
Populate a standardized template with case-based data extracted from the national surveillance system.

Patient details									Location of treatment facility			Diagnosis and Treatment									
Method of case detection	Patient ID/ System ID	Family name	First name	Date of Birth	Age	Sex	Nationality	Location of patient residence (village, suburb)	Healthy Facility	District	Province	Date of symptom onset (dd/mm/yy)	Date of diagnosis (dd/mm/yy)	Diagnosis confirmation method	Species identified	Date of treatment initiation (dd/mm/yy)	Treatment prescribed	Outcome of illness	Date of case notification (dd/mm/yy)	Recent travel within the country (Y/N Red response if YES)	Region/ district name, Town/village name of travel destination

Compare data on cases, case investigations and foci investigations from national level with data in source documents (registers and case investigation forms) at health facilities, labs and districts/provinces.

Diagnostic facility/<specify name>		Level conducting investigations			From the source document *(original registers or data forms)*													
Patient found in lab register? (y/n)	Patient case notification form found? (y/n)	Case notification form found? (y/n)	Patient case investigation form found? (y/n)	Focus investigation form found? (y/n)	Date of symptom onset (dd/mm/yy)	Date of diagnosis (dd/mm/yy)	Date of treatment (dd/mm/yy)	Documented follow-up at day 28 (or 42)?	Complete treatment documented? (y/n)	Date of case investigation (dd/mm/yy)	Date of focus investigation (dd/mm/yy)	Classification	Is classification appropriate? (y/n)	Explain why classification is or is not appropriate	Date of focus investigation (initiation) (dd/mm/yy)	Focus investigation complete? (y/n)	Elements of focus investigation	Case notification form found? (y/n)

Assess whether cases have been classified appropriately.



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Assess whether all cases have been reported to each administrative level.

Table 2	Data source*			
Number of cases in 2017-2019, by parasite species	National	State/Region	District	Facility
P. falciparum				
P. vivax				
P. malariae & others				
Mixed (P. falciparum and P. vivax)				
P. knowlesi				

* *Cases here are represented by numbers*

World Health Organization

Dashboards

Country

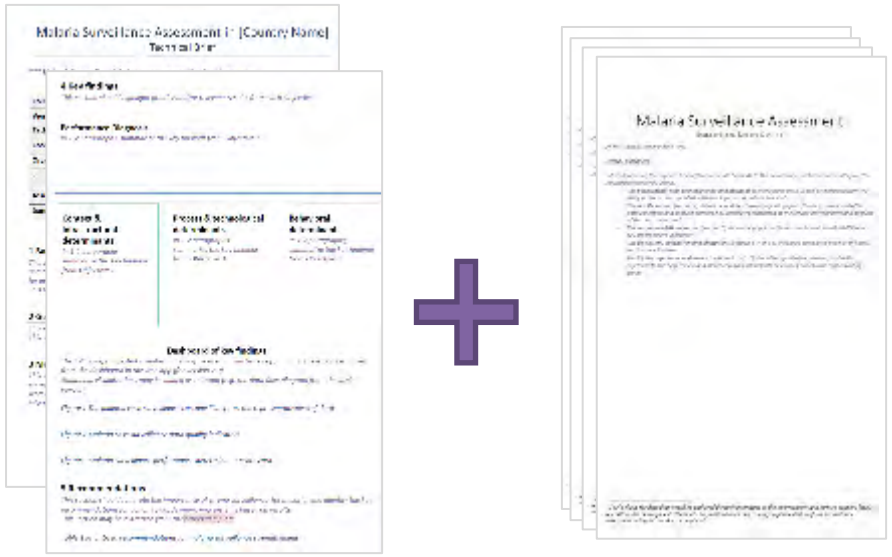
Global

Indicators

Expected outputs

- To facilitate comparability between assessments over time and across geographies, a set of **results expected from all assessments** conducted using the Toolkit should include:

  - Key tables and figures from the desk review
  - Information systems and data flow diagrams
  - Data quality assessment tables and graphs
  - A scorecard for each priority indicators
  - Results from the survey questionnaire presented as tables, graphs or maps
  - These outputs provide a high-level understanding of or first glance at the context, infrastructure, process, and technical and behavioural aspects that may be driving the surveillance system's poor or good performance.



- The **in-depth findings** from the malaria surveillance assessment can be presented in a **Technical Brief (**"2-pager) of key findings and/or a comprehensive **Report,** which includes a summary of the methods, a more in-depth description of the assessment results, and recommendations for surveillance strengthening actions based on key findings.
- A debrief presentation should also be prepared which includes the methodology, results and suggested recommendations for surveillance system strengthening.

Surveillance assessment results from 3 countries

Indicator	Burkina Faso	Democratic Republic of the Congo	Ghana
Completeness of reporting	91%	91%	98%
Timeliness of reporting	85%	66%	94%
Consistency between core variables	85%	68%	60%
Completeness of core variables within registers	64%	74%	40%
Concordance of core variables between registers and aggregated reports	32%	38%	30%
Data used for strategic, policy and operational processes	83%	64%	72%
Users with access to data	58%	96%	73%

Completeness of core variables: Survey results

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Low completeness of core variables and concordance

- Monthly data validation meetings occurred in half of the facilities surveyed.
- 67% of respondents indicated that their facility had never had an external data quality audit.
- 55% felt that they had not been adequately trained on malaria surveillance.
- 73% had access to data but only 51.2% could access DHIMS2 directly and 32.5% relied on asking the district for malaria data.
- **One major challenge was not having access to internet (50%).**

Recommendations

- Developing a single malaria data repository that includes data validation rules and dashboards for all thematic areas
- Ensuring all care seeking points can report into malaria data repository
- Increasing data use at lower levels through improved access to dashboards, refresher trainings on data analysis and use and improved SOPs
- Improving frequency of data validation meetings and add components for checking variable completeness

Global Malaria Programme

Strategic use of information to guide subnational tailoring of malaria interventions

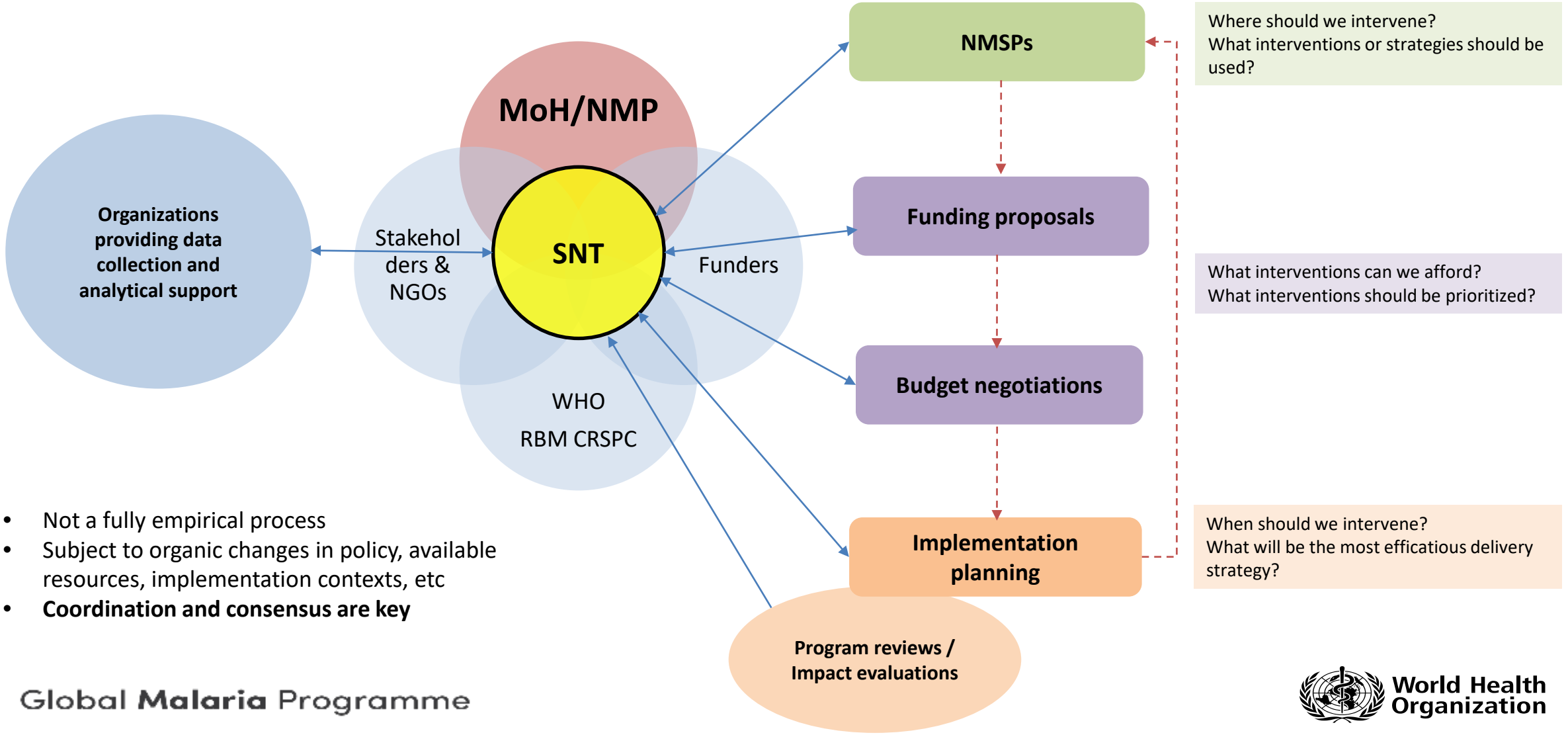
Beatriz Galatas
Strategic Information for Response Unit
MPAG Meeting, 19th April 2023

Global **Malaria** Programme

World Health Organization

SNT objectives and process

SNT = The use of local data and contextual information to determine the appropriate mixes of interventions and strategies, for a given area, for optimum impact on transmission and burden of disease



- Not a fully empirical process
- Subject to organic changes in policy, available resources, implementation contexts, etc
- **Coordination and consensus are key**

General steps per country to a successful SNT analysis

Step 1: Creation of an analysis team in country and identification of TA needs

Step 2: Data assembly and cleaning

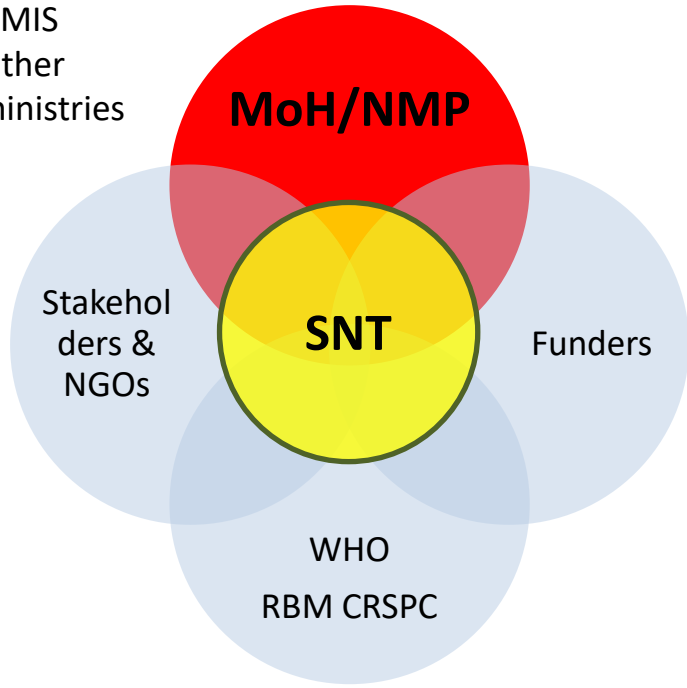
Step 3: Stratification, intervention targeting and modeling

Step 4: Consensus and development of strategic plans, funding applications, etc.

Step 1: Creation of a local analysis team

- Formation of a local team in charge of:
  - Preparing a chronogram of activities
  - Identify local focal points for different activities
  - Identify TA needs:
    - Data collection
    - Epidemiologist
    - Drafting of NSP and NFM
  - Planning, overseeing and reviewing progress on data collection, management and analysis activities through weekly calls and written communications
  - Convene partners and seek consensus locally on all outcomes
  - Translation of results into decisions

- **NMCP**
- HMIS
- Other ministries

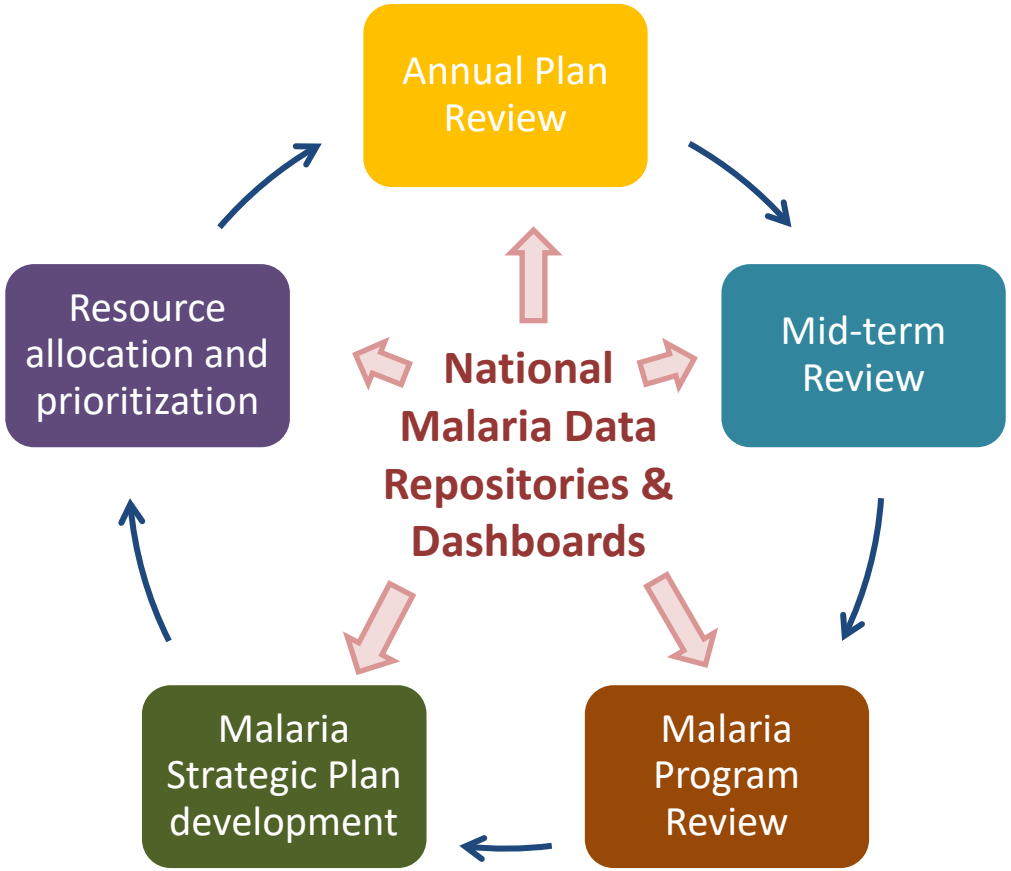


World Health Organization Africa

RBM Partnership To End Malaria

Step 2: Data assembly and cleaning

- The data needs required for stratification, targeting of interventions, prioritization, retrospective analysis to inform the MPRs and MTRs, etc **are all very similar.**
- In the absence of structured data repositories, the databases required for each new analysis **need to be updated, checked and corrected** manually, which is very time consuming
- Data repositories allow structuring and automatically update all databases required for analysis at any point during the NSP cycle so that databases can be downloaded at any point as needed.



Step 3: Stratification, intervention targeting and modeling

Term	Definition
Sub-national tailoring of malaria interventions	The use of **local data** and **contextual information** to determine the appropriate **mixes of interventions** and **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.
Optimization	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.
Prioritization	Process that aims to provide the right evidence to inform the **hard decisions countries need to make to prioritize investments for impact**, **social justice** and **equity**.
Impact projections using mathematical modeling	Process that aims to **predict the impact of different mixes of interventions, and compare them to each other**, to inform the optimization and prioritization processes. Dynamic mathematical models calibrated to the local context are used to project impact.

Step 3: Stratification, intervention targeting and modeling

Operational Unit
(district or equivalent)

WHO recommended interventions with clear targeting criteria*.

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

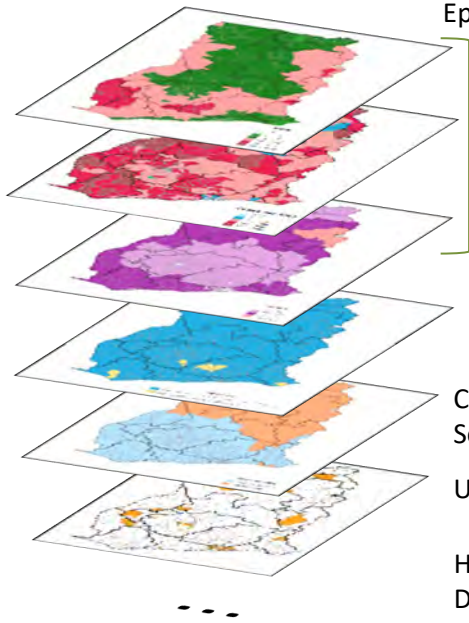
- LLIN, IRS, LSM,
- IPTp, IPTi, SMC,
- CM (Public HF, iCCM, private)

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

Malaria Strategic Plan development

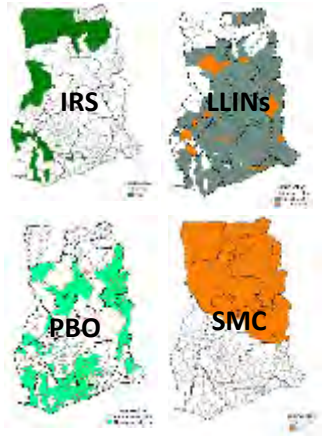
Stratification: Hierarchical ordering of one or multiple layers of information to make decisions

Indicators



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

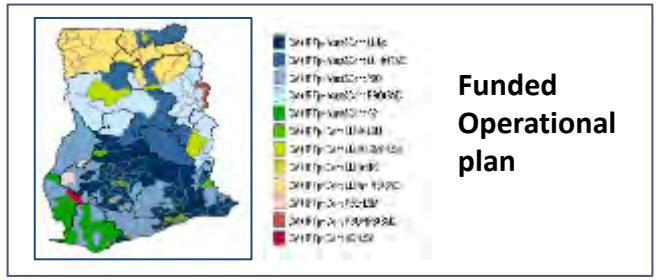
Intervention targeting: For each intervention, identify the operational unit that meets criteria + operational feasibility



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

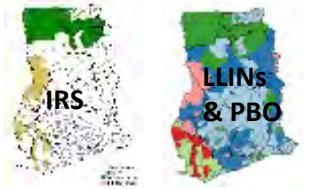


Funded Operational plan

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

Step 4: Translate analysis results into strategic plans and funding requests

Weekly calls with all relevant stakeholders to provide updates and reach to a consensus **in every step of the way**

Decisions are made regarding:

- Planning,
- TA required,
- databases available,
- indicators to be used in stratification,
- adaptation of intervention targeting criteria,
- non-analytical factors that affect decisions,
- final scenarios and questions to pose to modelers,
- model setup and interpretation of results,
- etc.

Standard chronogram of steps for Subnational Tailoring of Interventions (SNT) analysis

	Year 1											
Steps	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Presentation of methodology												
Creation of a SNT working group led by NMCP												
Data collection												
Data review and preparation for analysis												
Analysis and presentation of all available variables for decision making												
Discussion on main criteria to be used for targeting of interventions												
Analysis, presentation and review of results of intervention targeting												
Definition of scenarios to be reviewed through mathematical models for decisions making												
Mathematical modeling preparation												
Model calibration												
Modeling of specific scenarios												
Discuss scenarios												
Consensus building around final mix of interventions to be be considered in the strategic plan and for funding requests												

Expected outcomes:

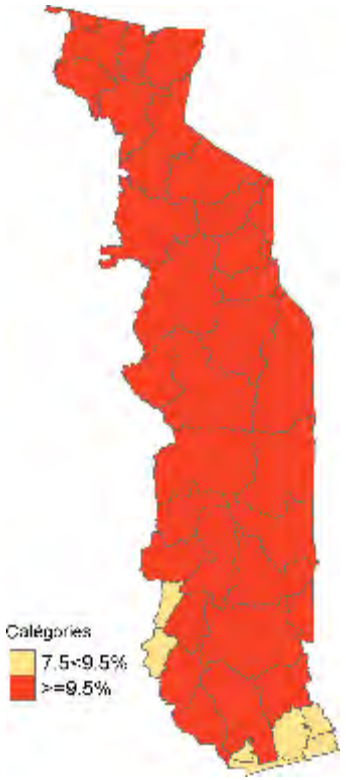
- ✓ **Updated** national malaria strategic plan guided by local evidence
- ✓ Prioritized plan submitted to funders leading to **maximum impact** within a resource envelope

Stratification of relevant indicators for intervention targeting

Epidemiological stratification

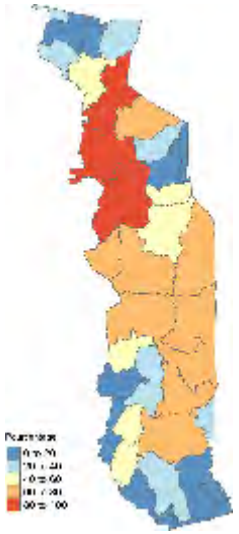
Incidence

AC U5 Mortality



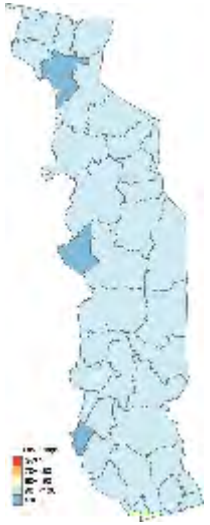
Contextual factor stratification

Access to care

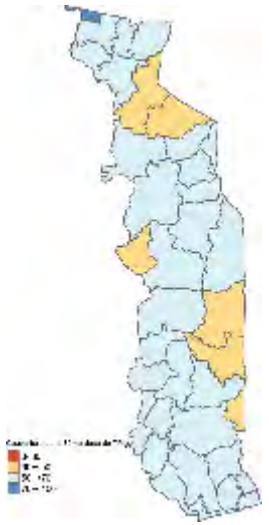


Source of care

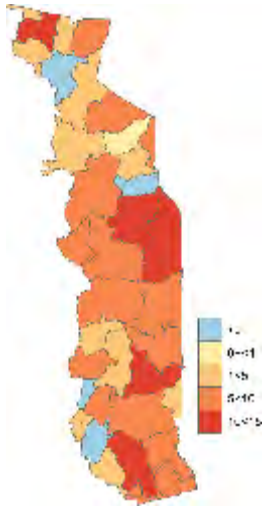
Quality of care



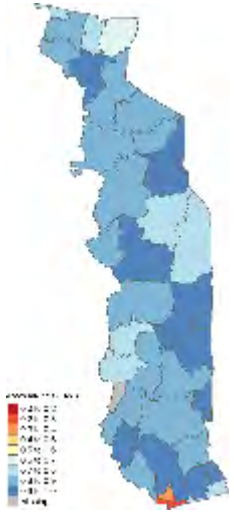
IPTp3 coverage



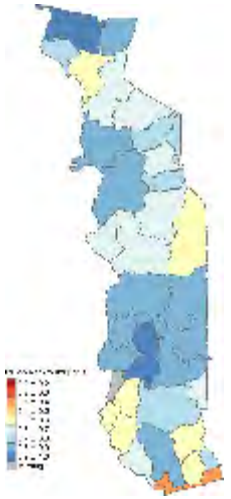
EPI coverage



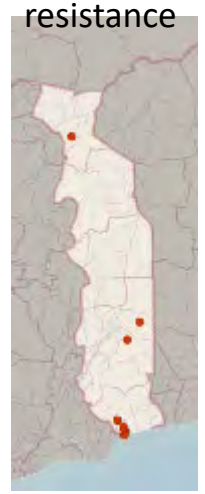
Access to ITNs



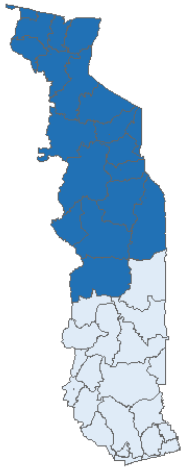
Use of ITNs



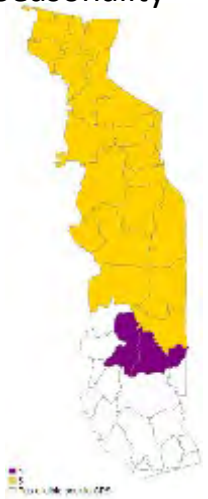
Insecticide resistance



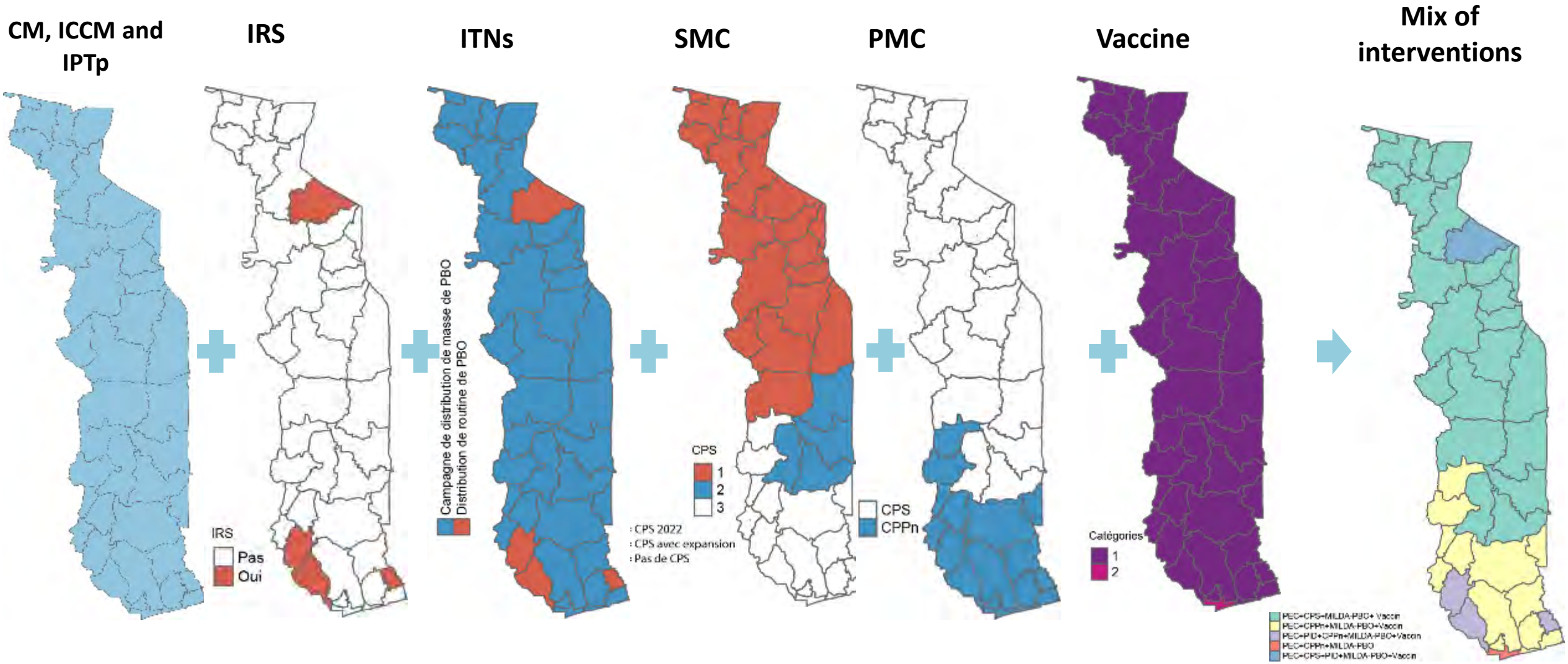
SMC coverage



Seasonality



Final mix of interventions – Strategic planning



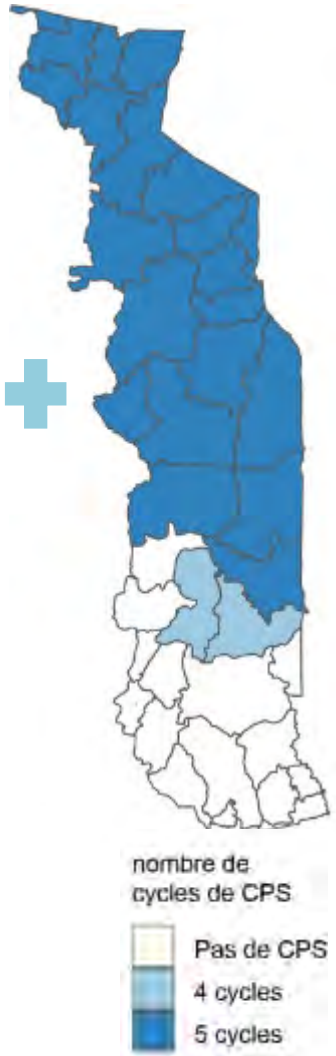
Next steps: Prioritization

CM, ICCM, IPTp

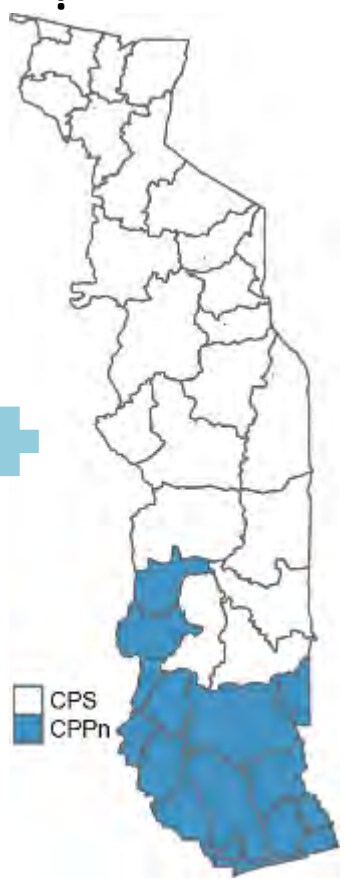
IRS ?

ITNs ?

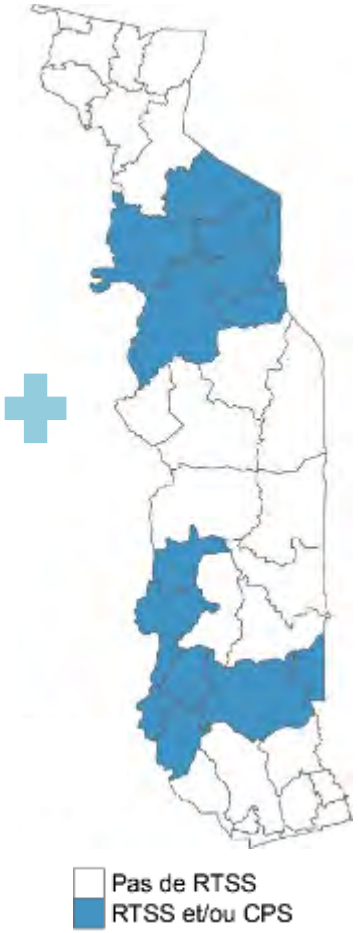
SMC ?



PMC ?

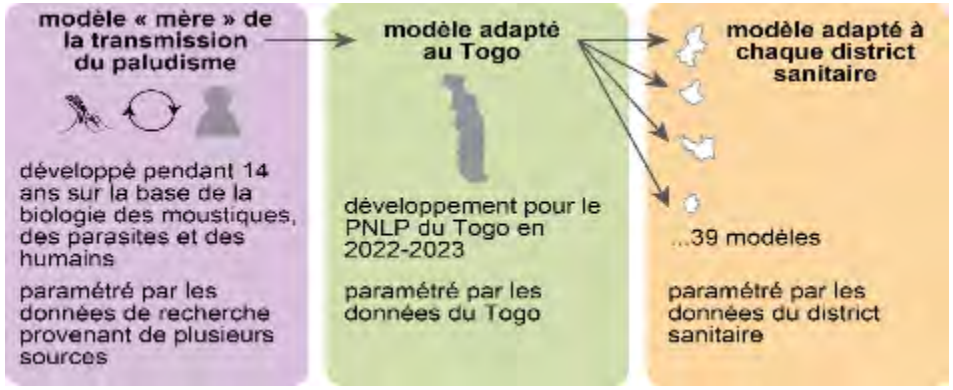


Vaccine ?



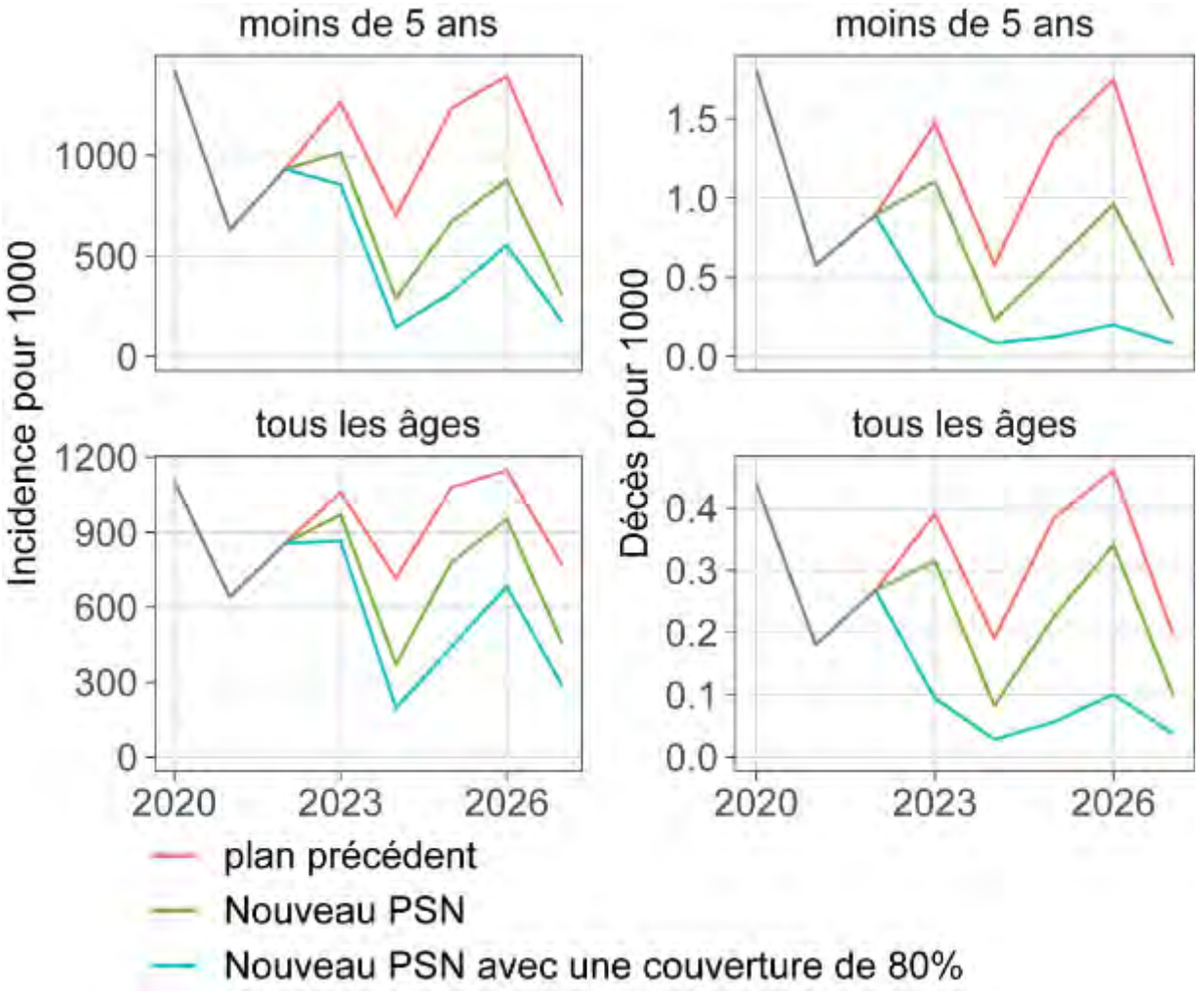
?

Mathematical modeling analysis to inform decisions



Scenarios / Questions :

1. Impact of the new NSP with current and 80% coverage.
2. Compare the new NSP with the previous plan
3. Impact of SMC in new areas (4 districts)
4. Impact of 4 vs. 5 rounds of SMC in eligible districts
5. Impact of PMC in eligible districts
6. Impact of RTS,S vaccine in eligible areas
7. Impact of IRS in areas with an incidence > 1000
8. Impact of PBOs vs standard LLINs



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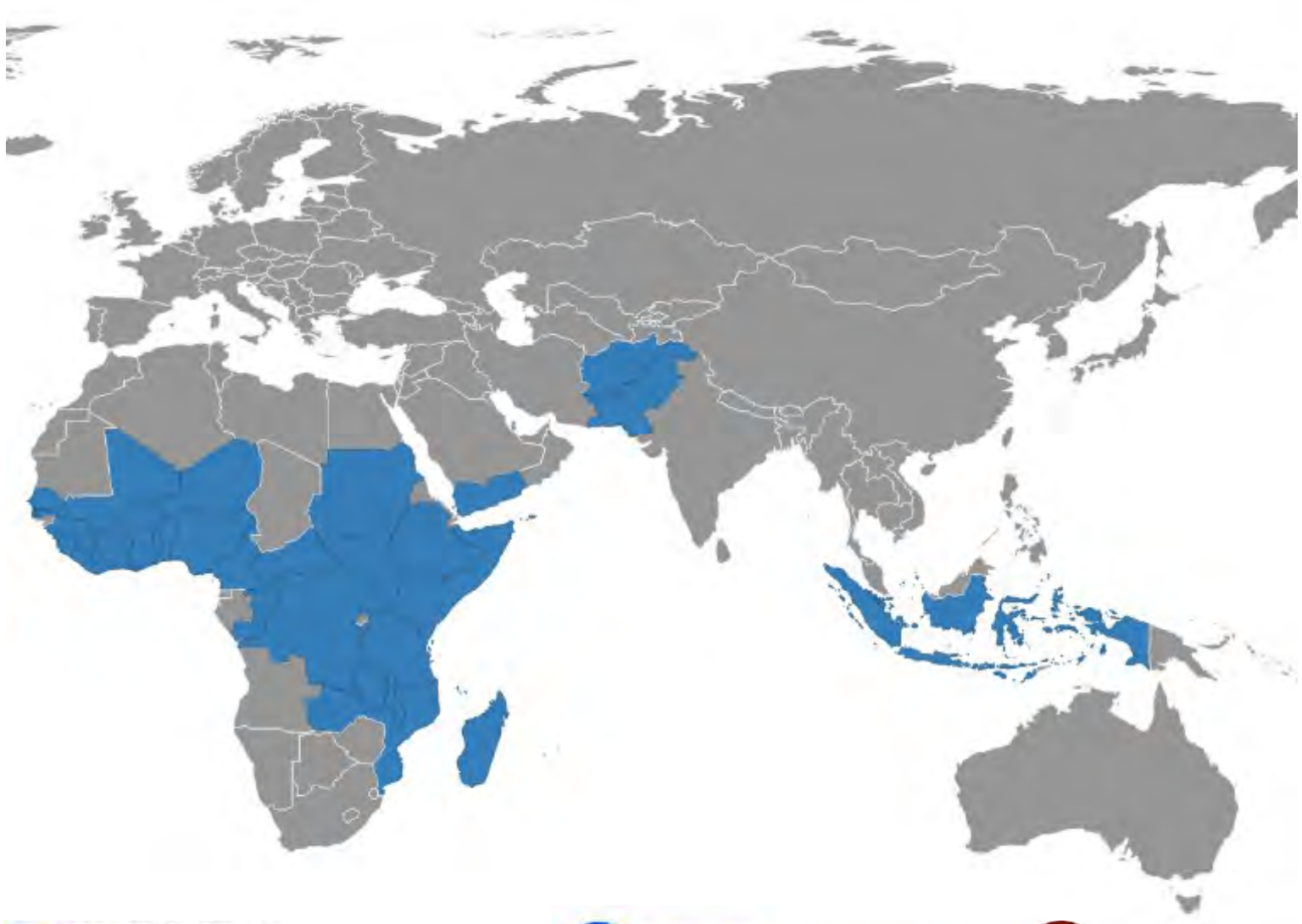
Lessons learned from SNT implementation

- **NMCP leadership is key** to enable a comprehensive review and validation of each step of the analysis, and promote a culture of evidence-informed decision-making.
- **The availability, quality and appropriateness of the routine and non-routine data** for analysis is still sub-optimal, but its use adds value to decision-making, emphasizes highlights areas of weakness, need for improvement, and its use promotes national ownership
- **More engagement with** local research institutions and funders to ensure sustainability and align over a single plan
- **Cost-effectiveness analysis** challenging due to lack of granular costing data per intervention available
- **The use of mathematical models** to support SNT is limited by quick model parametrization and calibration processes, questionable intervention effectiveness sizes, lack of robust severe malaria outputs

Countries supported

- 28 countries in AFRO
- 4 countries in EMRO
- 1 country in SEARO



SNT

World Health Organization

Clinton Health Access Initiative

map

dhis2

IHME
Measuring what matters

malaria consortium

Mathematical Modeling

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut

PATH

IDM

Northwestern University

Imperial College London

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

CDC USAID
President's Malaria Initiative

RBM Partnership To End Malaria

AFRICAN LEADERS MALARIA ALLIANCE ALMA

Global Malaria Programme

Sustainable SNT support to countries

WHO AFRO Precision Public Health Metrics unit, Communicable and non-conmmunicable disease cluster

Prof Lawrence Kazembe, PhD
Team Lead

Dr Victor Alegana, PhD
Lead, Geosciences

Dr Abde salam El Vilaly, PhD
Lead, Geoinformatics

Dr Roland Ngom, PhD
Geographic information systems expert

Mr Arish Bukhari, Masters in Information Systems
Software Engineer

A clinician and infectious disease epidemiologist

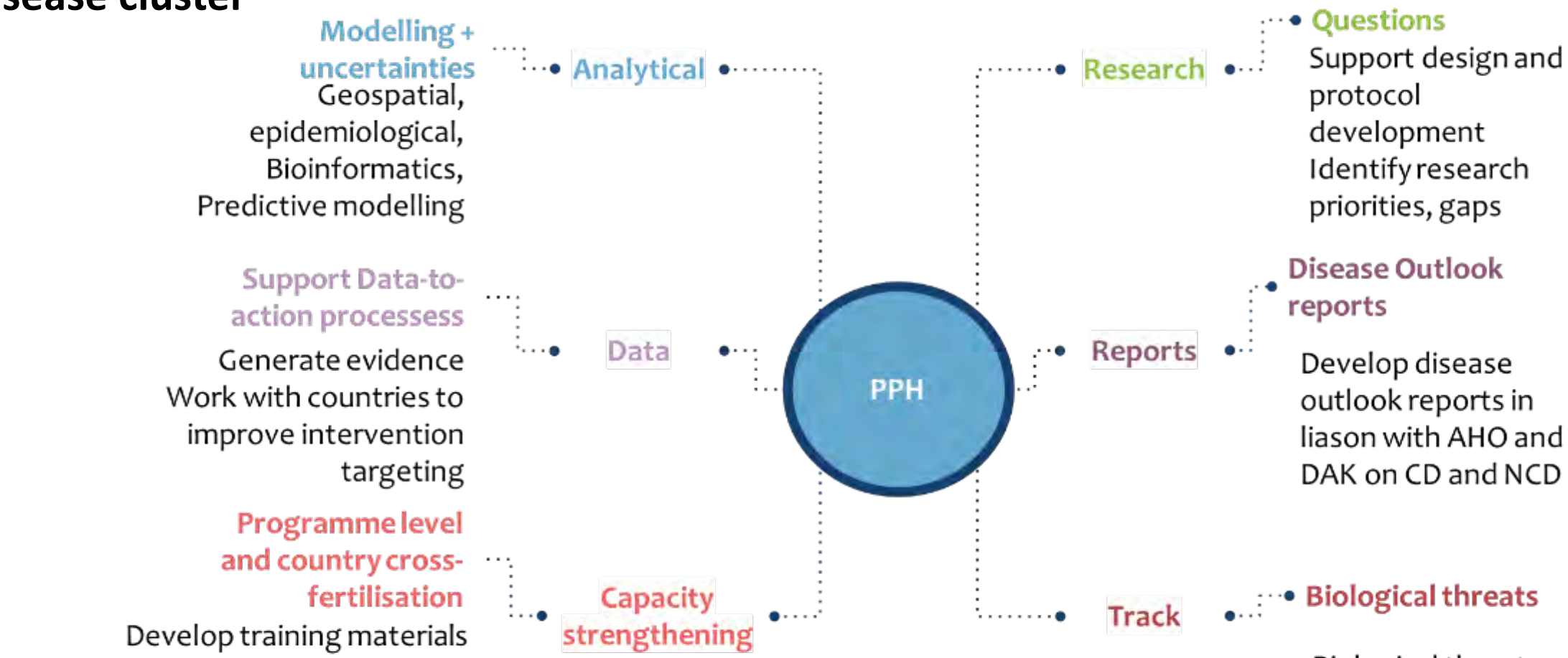
A Bioinformatics specialist

Support to the following teams in AFRO:

1. Malaria and other Tropical VBDs
2. NTDs
3. HIV & TB
4. NCDs
5. Vaccines
6. Multi-country Assigment Teams

PPHM role

WHO AFRO Precision Public Health Metrics unit, Communicable and non-conmmunicable disease cluster



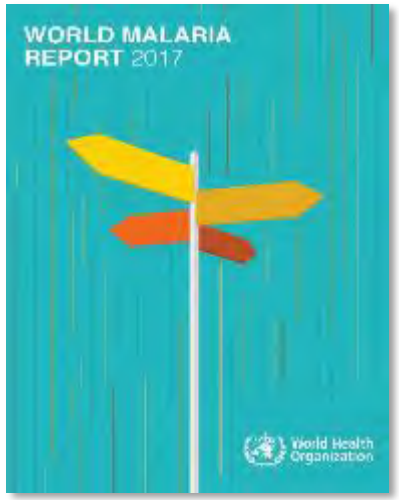
World Malaria Report

Abdisalan M Noor
Head of Unit,
Strategic Information for Response

Global **Malaria** Programme

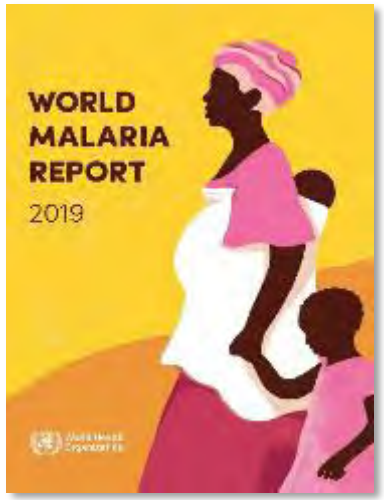
World Health Organization

Thematic series

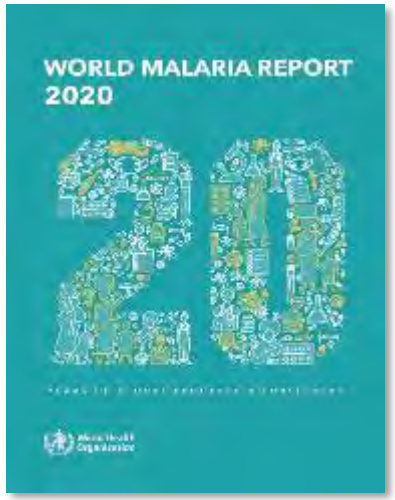


Progress at crossroads

Getting back on track – the high burden to high impact (HBHI) appraoch



Refocusing on vulnerable groups – children and pregnant women



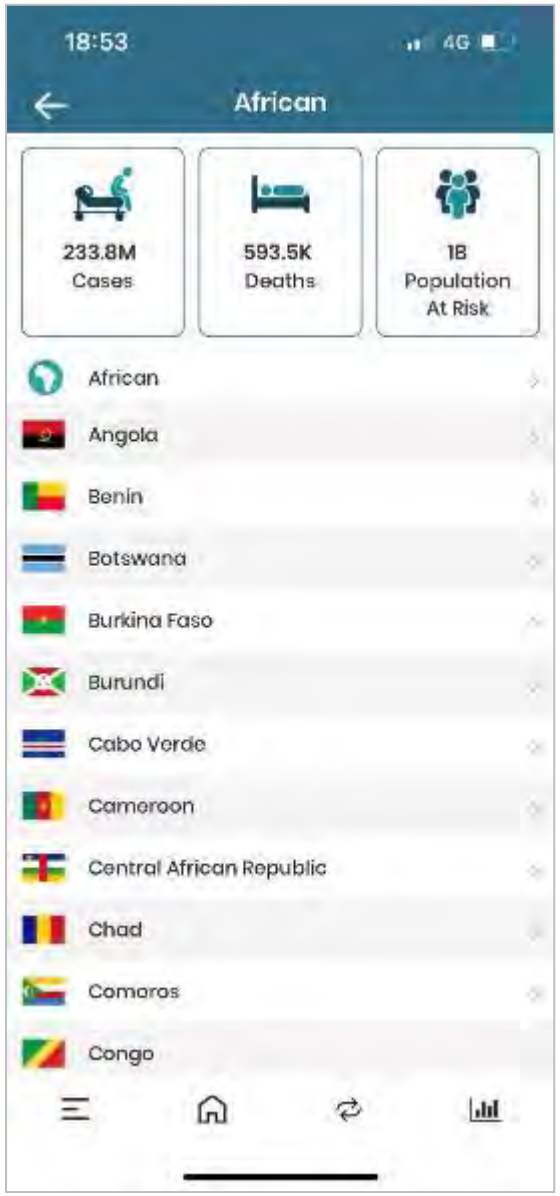
20 years of global progress and challenges & the global response to COVID-19 pandemic

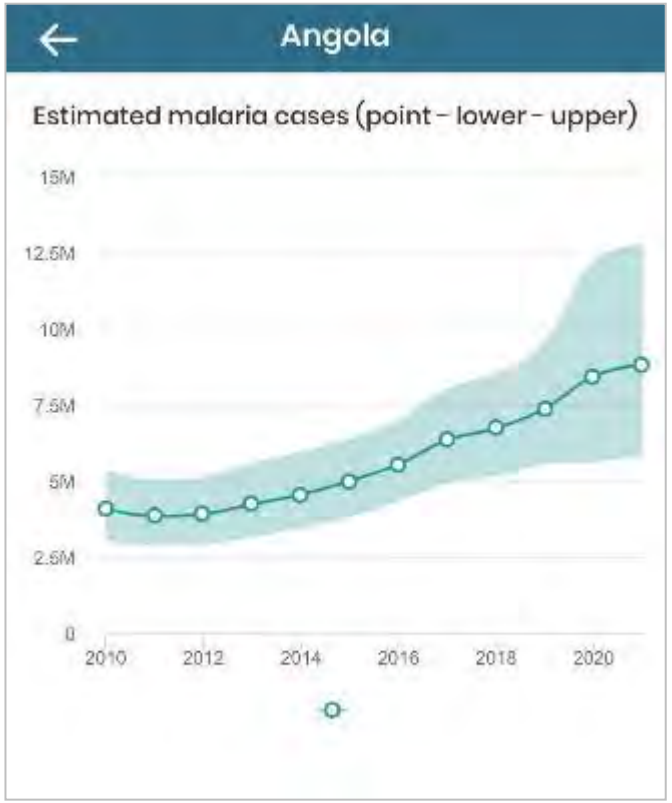
Country response during the pandemic and effects of service disruptions on burden of malaria

Response, Risks, Resilience, Research & Development

* With a focus on intervention effectiveness

Online platforms – WHO malaria toolkit App





A collaborative effort

25 partners

>200 people

WMR 2023 process

1) WMR 2022 post-launch review

2) Data submission by countries

3) WMR Technical Working Group meeting

4) WMR Editorial committee meeting – theme & outline

5) Additional data submission by partners

6) Data analysis, draft of sections

7) Internal and external review

8) Production of report – copy editing, layout design

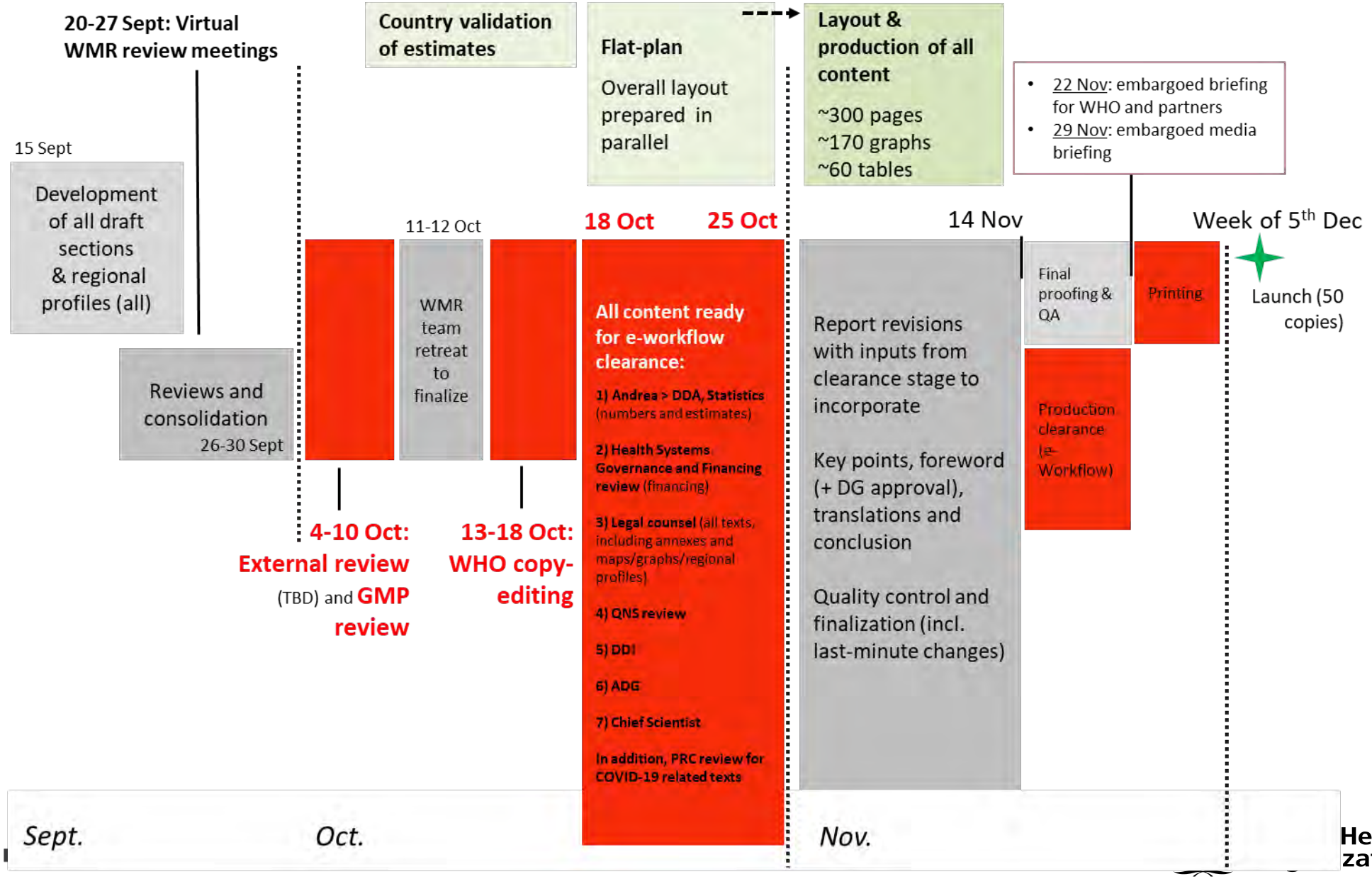
8) Early briefing to WHO 3-levels and partners

9) Preparation for report launch – key messages etc.

10) Launch

WMR 2023 process

WMR 2022 example



Funding


BILL & MELINDA
GATES foundation


The Global Fund
To Fight AIDS, Tuberculosis and Malaria

WHO Technical Consultation on the Effectiveness of Rectal Artesunate for Pre-referral Treatment in Children

Malaria Policy Advisory Group (MPAG) Meeting

Geneva, 18-20 April 2022

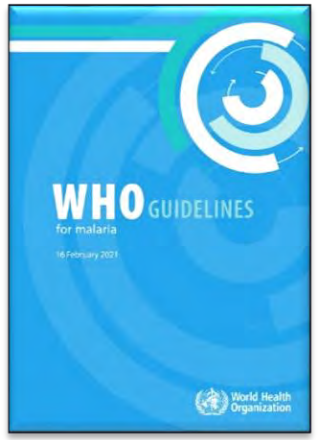
Dr Peter Olumese
Diagnostics, Medicines and Resistance Team

Global **Malaria** Programme

World Health Organization

Treatment of Severe malaria

- Therapeutic objectives
  - Main objective is to prevent the patient from dying
  - Secondary objectives are to prevent disabilities and prevention of recrudescent infection



- Death from severe malaria often occurs within hours of onset of symptoms or admission to hospital
  - Essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible

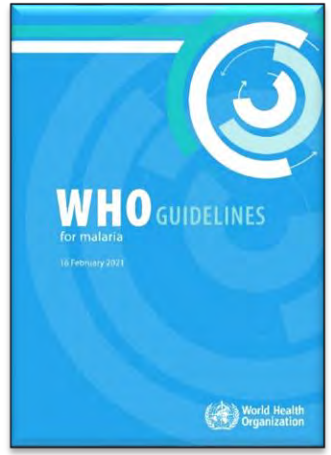
Treatment of Severe malaria (MTG 2015)

- Treat all patients with severe malaria (including infants, pregnant women in all trimester, and lactating women) with intravenous or intramuscular artesunate for at least 24 hours and until able to tolerate oral medication.
- After at least 24 hours of parenteral therapy, AND able to tolerate oral therapy, complete treatment with three-days of an ACT
- Children weighing less than 20 kg should receive a higher dose of artesunate (3 mg/kg/dose) than others (2.4 mg/kg/dose) to ensure an equivalent drug exposure.
- If artesunate is not available, use artemether in preference to quinine for treating severe malaria

Treatment of Severe malaria (2015)

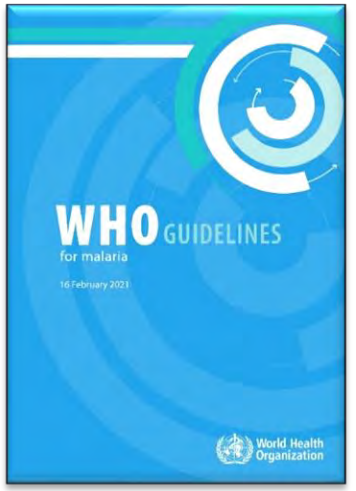
- Pre-referral treatment
  - In settings where complete treatment of severe malaria is not possible, but injections are available, give children and adults a single dose of intramuscular artesunate and refer to an appropriate facility for further care. Use artemether or quinine if artesunate is not available

  - In settings where intramuscular injections are unavailable, treat children below the age of six years with a single dose of rectal artesunate and refer immediately to an appropriate facility for further care.

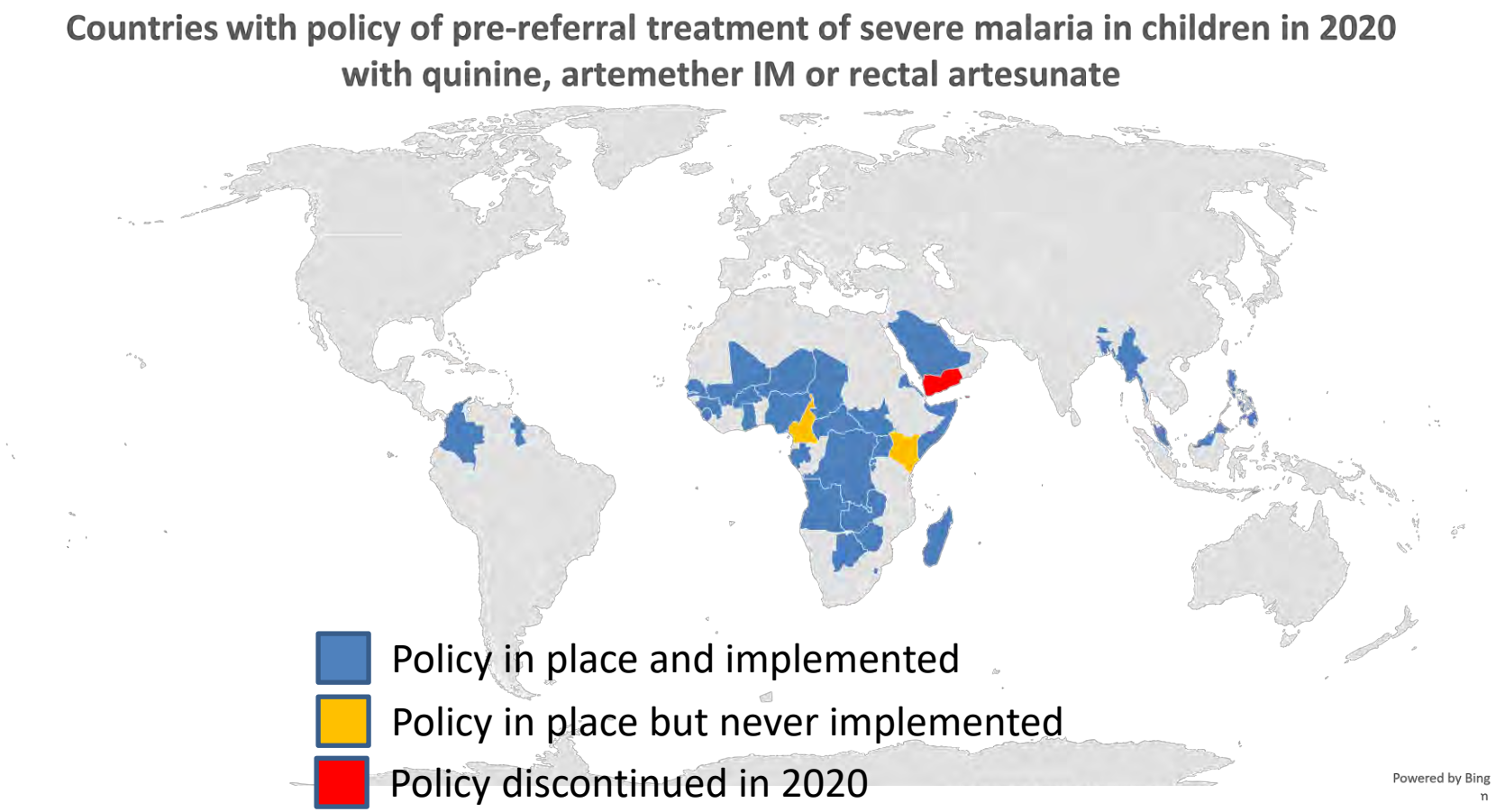


Treatment of Severe malaria (2015)

- Pre-referral treatment – follow on Action
  - Refer the patient as soon as feasible to a centre where full management is available
  - Where referral is not possible after the initial treatment:
    - Insufficient evidence on continued rectal treatment, but recommendation based on expert opinion:
      - Rectal treatment should be continued until the patient can tolerate oral medication, then
      - Administer a complete course of an effective ACT



Country uptake of pre-referral treatment policy



- In 2018, RAS became available at a quality-assured standard, with the WHO prequalification of two 100 mg products – a key factor for large-scale procurement of the commodity using multilateral funds.
- Between 2018 and 2020, about 3 million WHO-prequalified suppositories were procured by more than 20 countries.

source: NMCP data submitted to WHO for WMR2021

Background

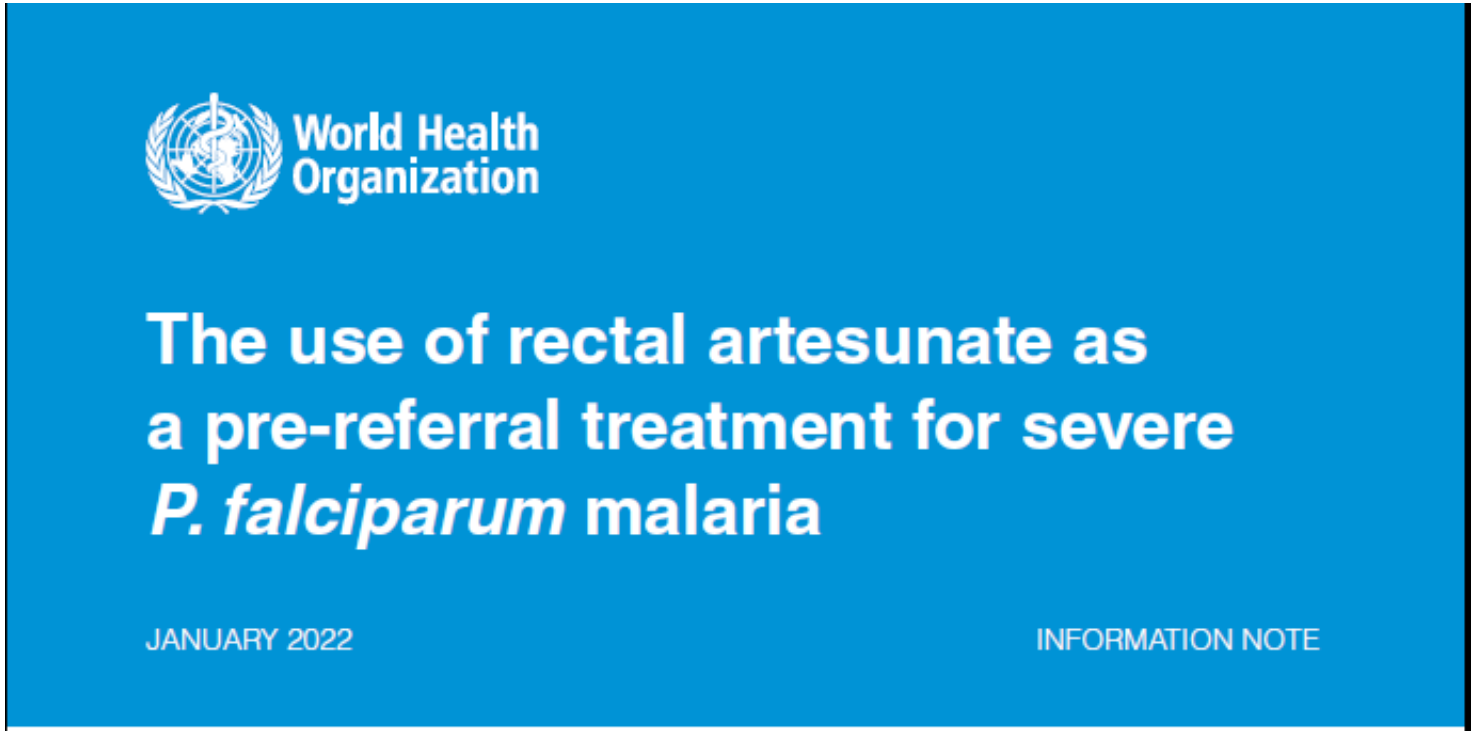
- The CARAMAL Project:
  - The purpose of the CARAMAL project is to introduce quality-assured pre-referral RAS with limited supportive interventions (referral and post referral treatment where not facilitated) to understand whether the introduction of RAS can indeed reduce severe malaria case fatality under real-world operational circumstances (DRC, Nigeria and Uganda)

  - In April 2021, WHO GMP as part of its role in the UNITAID-funded Community access to rectal artesunate for malaria (CARAMAL) project convened a Technical Consultation to review the lessons learned.
    - The aim was to evaluate the project based on preliminary unpublished reports and use the lesson learned to develop operational guidance on RAS use as pre-referral treatment of severe malaria in children.

- The same findings were also presented to the Malaria Policy Advisory Group in October 2021

WHO Information Note (28 January 2022)

In line with the MPAG recommendations in January 2022 GMP issued an information note https://apps.who.int/iris/bitstream/handle/10665/351187/9789240042513-eng.pdf?sequence=1&isAllowed=y,



WHO Information Note (28 January 2022)

The information note made some risk Mitigation recommendations as well as including the following commitment:

The WHO Global Malaria Programme, in consultation with other relevant departments, will conduct a formal evidence review and develop detailed guidance on the conditions under which the use of this tool can be implemented safely and effectively. Such guidance will be shared with countries as soon as it becomes available.

Follow on action by GMP

- In consultation with relevant departments, convening an independent technical group to undertake a technical review of all publications and study reports (including all CARAMAL -published and on-line unpublished), which have deployed RAS at programmatic level to:
  - Determine the factors required to safely and effectively deploy rectal artesunate as pre-referral treatment for severe malaria in areas where complete treatment for severe malaria is not immediately accessible.
- The outcome of the consultations will form the basis of a WHO Implementation Guidance document (Field Manual) to facilitate effective deployment of pre-referral treatment (particularly RAS) in resource limited malaria endemic countries.

Modus Operandi

- The Technical Consultation is in 2 phases:
  - Phase 1: a remote meeting on 20-21 September 2022 to review in detail all evidence (published and unpublished) by the independent experts and prepare specific follow-up questions to the study teams. Answers to which will form additional information for the 2nd phase of the technical consultation.
  - Phase 2: In-person meeting
    - 18 – 19 October 2022 in Geneva

Phase 1: Remote meeting (20-21 September 2022)

The Technical Panel:

- Conducted an in-depth review of the evidence, and generated questions directed to the respective study teams and /or Principal investigators of the studies, from areas requiring for further clarifications.

Objective of the 2nd meeting (18-19 October)

The specific objective of the meeting is:

- to review the available evidence on effectiveness of rectal artesunate for the pre-referral treatment of children with severe malaria and to generate practical guidance to enable safe and effective implementation of this intervention.
- These collectively (the review papers and any additional response to questions generated from this meeting) will form the background for the extensive consultation and recommendation in the second meeting in October.

List of publications reviewed

- **List of publications**
  - STPH (09 September 2022)
    - **4 published**
    - **7 pre-print**
  - Zambia
    - **1 published**
    - **1 pre-print**
  - Malawi
    - **1 pre-print**
  - Sierra Leone
    - **1 programme report / conference presentation**

- **Feedback answers from study teams / researchers to questions from the 1st meeting**

Summary of review and findings

RAS and Mortality (CARAMAL Study – Study design):

- The technical review identified several issues in the design of the CARAMAL study, which have left it susceptible to a number of biases and made the results difficult to interpret, particularly in terms of the impact of RAS on mortality and referral completion.
  - Though the CARAMAL study design was powered to detect a reduction in the case fatality rate (CFR) among children receiving RAS using pooled data from the three participating countries, country data was however analysed individually, (though the study was neither designed or powered for such analysis); this substantially reduced the power of the study to detect the effects of RAS.

Summary of review and findings

RAS and Mortality (CARAMAL Study – Study design):

- The primary effectiveness analysis compared RAS users to non-RAS users over the entire study period, including those enrolled before RAS roll out in the non-RAS user group
  - difficult to interpret as it included periods when RAS was not available; no adjustments for other factors including age, location, month of enrolment, etc. was made.
  - the untreated group included all severe malaria cases in the pre-RAS period, with potential temporal confounding. For example, in Nigeria
    - the CFR was substantially higher in the post-RAS period than in the pre-RAS period, including among children untreated with RAS in the post-RAS period (four-fold increase). These changes were not reported in the publication.
  - Additional analysis (technical review panel) comparing RAS users to non-users in the post-RAS period, the CFR was 19.7% for RAS users and 12.1% for non-users. However, when adjusting for confounders (including month of enrolment), the OR was 1.45 (95% CI: 0.68–3.09), showing only a moderate difference that was not statistically significant
- **Summary:** The CARAMAL study, as implemented, could not provide conclusive proof of the effectiveness of RAS in areas of high malaria burden within the existing health system framework.

Summary of review and findings

RAS and Mortality (Zambia study):

- Implementation research on scaling up the use of RAS for treatment of severe malaria at the community level in Zambia showed that the CFR decreased from 3.1% to 0.1% in the two high-intensity intervention districts and from 10.7% to 1.4% in the other districts.
  - At the end of that study, there were fewer stockouts of RAS, better knowledge of the signs of severe malaria among the community health workers (CHWs) and better knowledge of how to manage severe malaria among health workers at health facilities.
- The project confirmed that effective implementation of a community-based RAS intervention requires identification and tackling of health system bottlenecks, such as localized drug and commodity shortages, inadequate supervision of community health volunteers and weak referral systems.
  - In the Zambia setting, availability of bicycle ambulances probably had a major effect on the positive uptake of referral advice.

Summary of review and findings

Referral Completion:

- The papers suggested some evidence that children who received pre-referral RAS were less likely to complete referral. Further discussion with the investigators, however, revealed that "referral completion" meant patients going to a designated referral facility, pre-defined in the study, after referral by a CHW or PHC provider
  - The review panel noted that multiple factors may have an impact on referral completion. Often the nearest/cheapest place may be the most convenient. Referral to a recommended facility may be more costly (for the family) than going to a closer facility
  - travelling to a distant referral facility to receive ACTs that could be obtained at a local clinic/drug shop may discourage parents to complete referral
- In addition, the comparison of referral completion in a pre-RAS vs post-RAS analysis is confounded by the challenges of RAS roll-out and the fact that RAS was not available to everyone soon after roll-out, especially in Uganda and Nigeria.
- While children treated with RAS were less likely to complete referral in the post-RAS period, timeliness of referral completion was better among these children.

Summary of review and findings

Artemisinin resistance:

- The study documented clonal expansion of artemisinin-resistant Plasmodium falciparum in northern Uganda in the context of substandard treatment, such as the use of artesunate monotherapy. This finding was difficult to interpret, as it was based on a relatively small number of children and convenience sampling was used.
  - no paired day 0 and day 28 samples were collected, so no distinction could be made between recrudescence and reinfection, and ACT therapeutic efficacy could not be assessed
- The study concluded that the roll-out of pre-referral RAS was not likely responsible for the emergence or spread of artemisinin-resistant falciparum malaria:
  - K13 C469Y molecular markers for partial artemisinin resistance were present in Uganda before RAS was deployed and were widely present and increasing in the northern provinces – in some CARAMAL districts (Kole and Oyam, but not Kwania districts) and in other districts (e.g., Lamwo and Agago districts) where RAS was not deployed
  - the population-level use of RAS among all children with suspected severe malaria in the three districts in Uganda was less than 1%.
  - suggests that the inadequate use of artesunate monotherapy in different formulations (both parenteral and rectal), without completion of referral and follow-up ACT treatment, may exacerbate the selection of artemisinin-resistant strains
- Despite the limitations noted above, this study provides a signal that RAS alone, when not followed by referral and complete treatment with a full course of ACT, may select partial artemisinin-resistant parasites with the K13 C469Y mutation.

Conclusions and recommendations to GMP

- Countries that are already implementing or considering implementation of RAS for pre-referral treatment of severe malaria need to strengthen all aspects of the continuum of care for a severely sick child
  - Countries deploying RAS for pre-referral treatment of severe malaria should review, monitor and, as necessary, strengthen the whole continuum of care.
- Support for adequate supply chain management and referral systems from CHWs and facilities to treatment centres is essential for achieving the intended impact of RAS. Barriers to referral completion need to be addressed, as this will improve outcomes not only for severe malaria but also for other severe diseases.
- Effective community sensitization is needed to increase understanding of severe malaria, its causes, how dangerous it is for children, how to recognize danger signs and the need to promptly seek care if such signs are present.
- The project confirmed that effective implementation of a community-based RAS intervention requires identification and tackling of health system bottlenecks, such as localized drug and commodity shortages, inadequate supervision of community health volunteers and weak referral systems.

Conclusions and recommendations to GMP

- Malaria programmes and their partners in the public, nongovernmental organization and private sectors should ensure that health providers adhere strictly to malaria treatment guidelines and make sure that caregivers of children with severe malaria are aware of the importance of completing treatment courses. Intense efforts should be made to ensure that:
  - artemisinin-based monotherapies (both rectal and parenteral) are used for treating severe malaria cases only as per WHO guidelines;
  - RHFs treat severe malaria patients with parenteral artesunate and a full course of an effective ACT;
  - appropriate supportive management excludes or treats other concurrent infections that could be causing danger signs in a child with low-density parasitaemia; and
  - initial rectal and/or injectable artemisinin-based monotherapy is always followed by a full oral course of an effective ACT.
- Antimalarial resistance surveillance should be strengthened at the population level across Africa, and most urgently in East Africa, with:
  - prioritization of interventions to holistically address the drivers of resistance selection; and
  - prompt response in line with the WHO Strategy to respond to antimalarial drug resistance in Africa when resistance is detected.

Next steps

- Publication of the Technical Consultation report
- Finalization and publication of the WHO Implementation Manual for Effective Deployment of Rectal artesunate as pre-referral treatment of malaria.
- Release of an updated WHO Information Note on the use of rectal artesunate for the pre-referral treatment of severe malaria.
- Support countries in the effective deployment of RAS, through strengthening of the quality of care across the entire continuum of care and services.

Technical Consultation on community-based delivery of IPTp

Malaria Policy Advisory Meeting

19 April 2023

Silvia Schwarte

e-mail: schwartes@who.int

Global **Malaria** Programme

World Health Organization

Outline

- Background and WHO recommendations
- WHO Technical Consultation – meeting report
  - IPTp3
  - ANC
  - SP resistance
- Development of field guide

Outline

- **Background and WHO recommendations**
- WHO Technical Consultation – meeting report
  - IPTp3
  - ANC
  - SP resistance
- Development of field guide

WHO Guidelines for malaria – IPTp (prior to 3 June 2022)

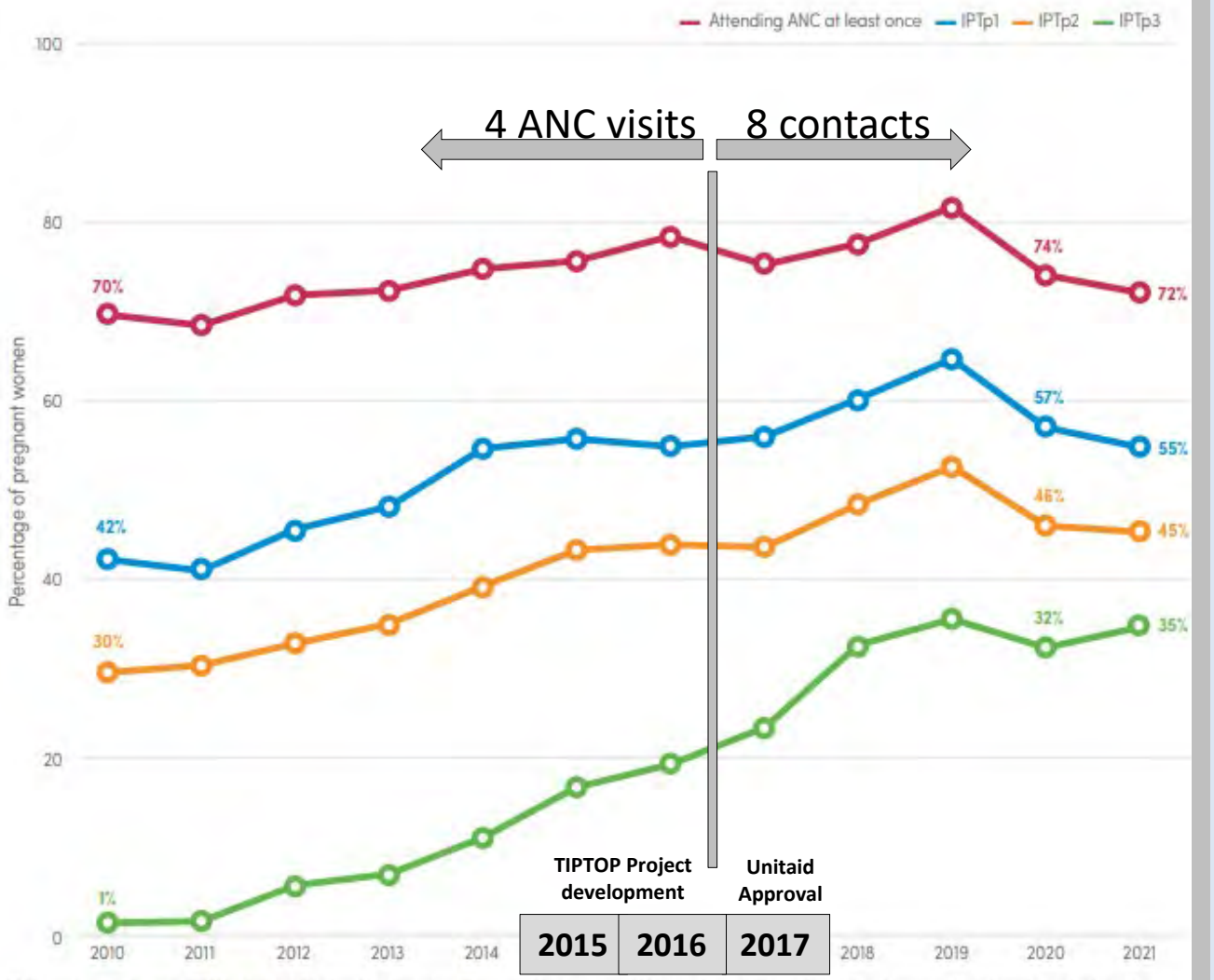
4.2.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

In malaria-endemic areas in Africa, provide intermittent preventive treatment with SP to all women in their *first or second pregnancy* (SP-IPTp) as part of antenatal care. Dosing should **start in the second trimester** and doses should be given **at least 1 month apart**, with the objective of ensuring that **at least three doses** are received.

World Malaria Report 2022

FIG. 7.5.

Percentage of pregnant women attending an ANC clinic at least once and receiving IPTp, by number of SP doses, sub-Saharan Africa, 2010–2021 *Sources: NMP reports, CDC estimates and WHO estimates.*



ANC: antenatal care; CDC: United States Centers for Disease Control and Prevention; IPTp: intermittent preventive treatment of malaria in pregnancy; IPTp1: first dose of IPTp; IPTp2: second dose of IPTp; IPTp3: third dose of IPTp; NMP: national malaria programme; SP: sulfadoxine-pyrimethamine; WHO: World Health Organization.

- Unitaid-funded project: **TIPTOP** (Transforming IPTp for Optimal Pregnancy): Community-based delivery of IPTp (c-IPTp) through trained CHWs – complementing and not replacing ANC
- TIPTOP Consortium: Jhpiego (lead grantee), ISGlobal (research partner)
- Project countries: DRC, Madagascar, Mozambique, Nigeria
- Project duration: **5 years** (2017 – 2022)
- MMV-Unitaid Supply Side Grant
- WHO-Unitaid Enabler Grant for malaria
- **April 2022**: TIPTOP submits Evidence Report to WHO

WHO recommendation (as of 3 June 2022)

4.2.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

Intermittent preventive treatment of malaria in pregnancy (2022)

In malaria-endemic areas, pregnant women of *all gravidities* should be given antimalarial medicine at predetermined intervals to reduce disease burden in pregnancy and adverse pregnancy and birth outcomes.

- Sulfadoxine-pyrimethamine (SP) has been widely used for malaria chemoprevention during pregnancy and remains effective in improving key pregnancy outcomes.
- IPTp-SP should start **as early as possible in the second trimester** and not before week 13 of pregnancy.
- Doses should be given **at least one month apart**, with the objective of ensuring that **at least three doses** are received.
- Antenatal care (**ANC**) contacts remain an important platform for delivering IPTp. **Where inequities** in ANC service and reach exist, **other delivery methods** (such as the use of community health workers) **may be explored**, **ensuring that ANC attendance is maintained** and underlying inequities in ANC delivery are addressed.
- IPTp is generally **highly cost-effective**, **widely accepted**, feasible for delivery and justified by a large body of evidence generated over several decades.

https://app.magicapp.org/#/guideline/6287

Last updated 3 June 2022

Outline

- Background and WHO recommendations
- **WHO Technical Consultation – meeting report**
  - **IPTp3**
  - **ANC**
  - **SP resistance**
- Development of field guide

WHO Technical Consultation

Meeting objectives

- ❑ Assess the **effectiveness and impact** of c-IPTp on IPTp coverage and ANC attendance
  - – review, discuss and assess the evidence generated in the context of the TIPTOP project
  - – review, discuss and assess the evidence obtained from additional (non-TIPTOP) countries where c-IPTp was piloted
- ❑ Discuss molecular markers of **SP resistance** monitored in the TIPTOP project
- ❑ Agree on **best practice** for implementation of c-IPTp, if proven successful

The full report is accessible via https://www.who.int/publications/i/item/9789240068230

Meeting participants

- Technical Consultation Expert Members: Constance Bart-Plange, Romano Nkumbwa Byaruhanga, Kassoum Kayentao, *Rose Leke (Co-Chair)*, Lucy Paintain, Stephen Rulisa, Issaka Sagara, Allan Schapira, *Larry Slutsker (Co-Chair)*
- Participants from TIPTOP countries (DRC, Madagascar, Mozambique, Nigeria) and non-TIPTOP countries (Burkina Faso, Malawi, Senegal, Sierra Leone)
- TIPTOP Consortium: Jhpiego, ISGlobal
- MMV (Supply Side Grant)
- Institut Pasteur Paris (TIPTOP resistance monitoring)
- Observers: CDC, USAID, BMGF, Global Fund, Unitaid
- WHO: HQ (GMP, Maternal and Perinatal Health, Child Health and Development), Country offices, Regional Office of the African Region

TIPTOP Household Survey Results – IPTp3 coverage increase

IPTp3+ coverage, comparing baseline and endline in the three districts

DRC

Zone	Baseline	Endline	□	*P* value
Kenge	21.8	64.9	+198%	<0.0001
Bulungu	23.9	77.7	+225%	<0.0001
Kunda	18.4	51.1	+177%	<0.0001
Overall	21.2	65.2	+207%	<0.0001

Kenge: test district; Bulungu: first expansion district; Kunda: second expansion district.

MDG

Zone	Baseline	Endline	□	*P* value
Mananjary	23.3	70.1	+201%	<0.0001
Toliary II	19.1	68.8	+261%	<0.0001
Vohipeno	36.6	84.1	+130%	<0.0001
Overall	27.9	74.9	+169%	<0.0001

Mananjary: test district; Toliary II: first expansion district; Vohipeno: second expansion district.

NGA

Zone	Baseline	Endline	□	*P* value
Ohaukwu	11.3	71.2	+533%	<0.0001
Akure South	10.2	56.5	+453%	<0.0001
Bosso	14.2	54.5	+284%	<0.0001
Overall	11.5	62.7	+448%	<0.0001

Ohaukwu: test district; Akure South: first expansion district; Bosso: second expansion district.

Differences between baseline and endline were significant in each district in the Democratic Republic of the Congo, Madagascar and Nigeria

TIPTOP Household Survey Results – IPTp3 coverage increase

IPTp3+ coverage, comparing baseline and endline in the three districts

MOZ

Zone	Baseline	Endline	Δ	*P* value
Nhamatanda	63.3	69.4	+9.6%	<0.01
Meconta	45.0	58.0	+28.8%	<0.001
Murrupula	49.1	48.7	-0.7%	NS
Overall	52.7	58.6	+11%	<0.0001

Nhamatanda: test district; Meconta: first expansion district; Murrupula: second expansion district.

- Only two of the three districts experienced a modest increase
- Baseline IPTp3+ coverage was significantly higher
- Possible reasons: e.g. low **ratio** of CHWs to people served compared with other countries, with a multitude of tasks) and contextual factors in districts (e.g. **cyclone, security issues**)

TIPTOP Household Survey Results – ANC4+ coverage

Overall increases

- **Democratic Republic of the Congo:** overall increase (40.1% to 49.3%)
  with a non-significant increase in one district
- **Madagascar:** overall increase (44.8% to 66.2%)
  with a non-significant increase in one district

Mixed results

- **Nigeria:** overall **no significant difference** (69.2% to 68.4%)
  with significant increase in one district, and a non-significant *decrease* and a significant decrease in two districts

  Absence of significant increase could be related to a high baseline coverage of ANC4+, with a potentially limited opportunity for further increases
- **Mozambique:** overall **non-significant difference** (38.6% to 37.1%)
  with a non-significant decrease in one district and a *significant* increase and a significant decrease in two districts

  Mixed results may be due to district-specific contextual factors

TIPTOP Household Survey Results – Early ANC and ANC1+

Early ANC attendance

The introduction of c-IPTp did not lead to an increase in early ANC attendance, defined as start of ANC visits before 14 weeks gestational age

- Democratic Republic of the Congo: from 16.4% to 18.4%
- Madagascar: no change, at 11.1%
- Mozambique: from 12.1% to 12.5%
- Nigeria: from 25.1% to 25.8%

ANC1+ coverage

- Significant increases in the **Democratic Republic of the Congo** (from 89.0% to 94.5%) and **Madagascar** (from 85.8% to 94.2%)
- No significant differences in **Nigeria** (from 91.1% to 92.4%) and **Mozambique** (from 91.5% to 92.8%)

TIPTOP Conclusions – HHS and routine monitoring

Household survey (HHS)

c-IPTp is associated with:

- a dramatic reduction in the proportion of women **not receiving any IPTp**
- an increase in the **proportion of women receiving more doses** of IPTp
- an increase in the mean **number of IPTp doses** per pregnant woman
- More modest increases were evident for ANC attendance:
  - fewer women did not attend **any ANC visits**, and
  - more women attended **more frequently**

Routine monitoring

- Data show **similar findings** to the household surveys: c-IPTp improved overall IPTp coverage without a negative impact on ANC use

Experiences from additional (non-TIPTOP) countries

Examples for challenging and enabling factors from Burkina Faso, Malawi, Senegal, Sierra Leone

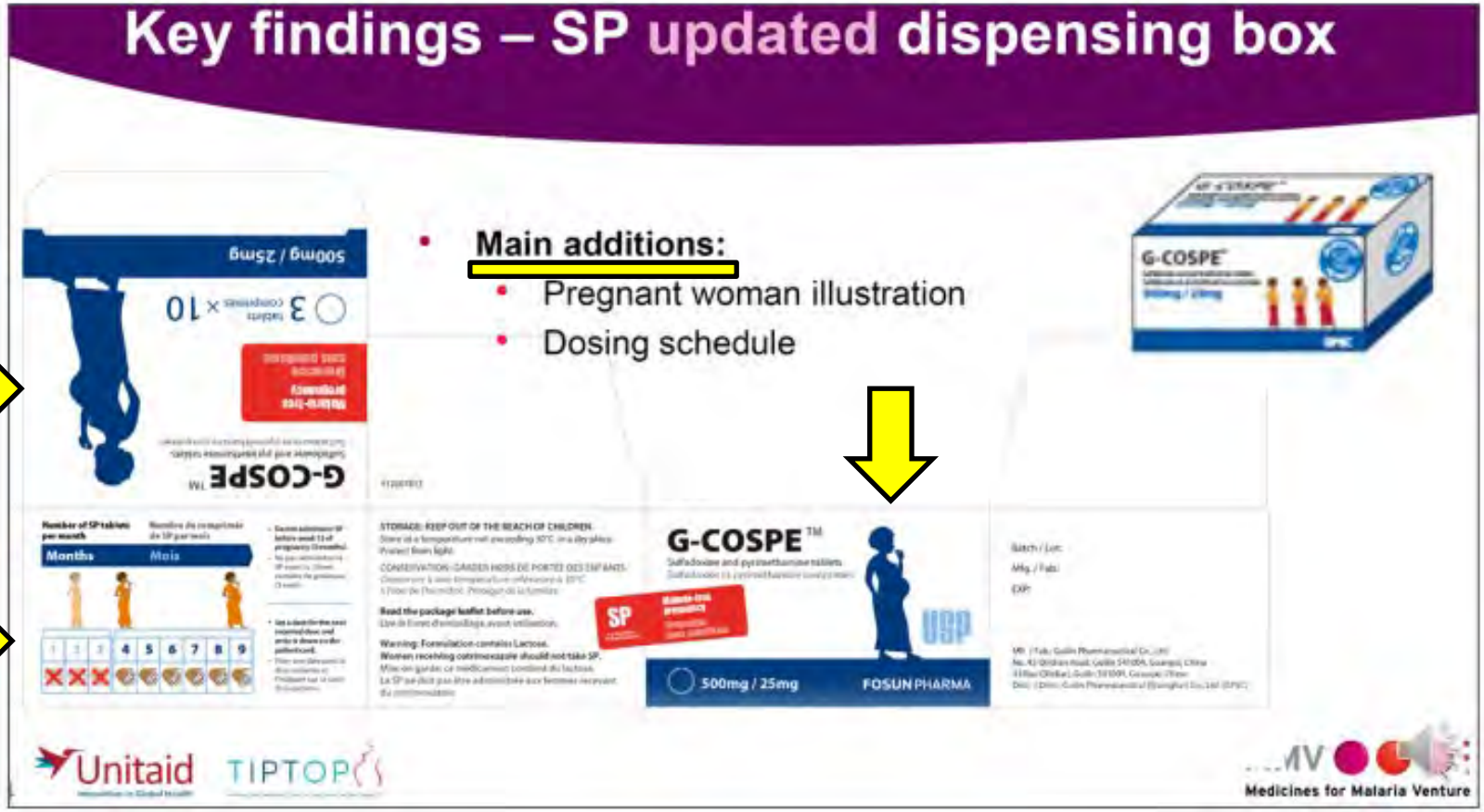
Challenges

- CHWs **workload**
- CHWs **travel distance**
- Insufficient **supportive supervision**
- **Data entry; aggregated data** in templates / forms
- **Male versus female** CHWs
- Identify women **early** in pregnancy
- Need for CHW **follow-up of pregnant** women at home if they did not present at scheduled visits
- Recruitment of **new** CHWs who were not familiar with this intervention; high **attrition** rate
- Insufficient **funding** to continue c-IPTp after piloting
- ...

Enablers

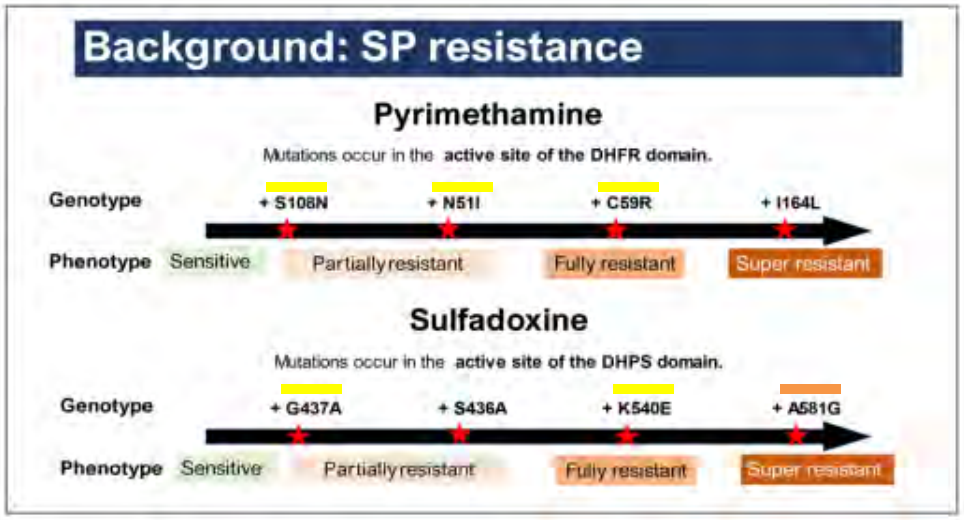
- Uninterrupted **availability of SP**, supply well **integrated** in national system
- Low **IPTp coverage** at c-IPTp start
- **Community ownership**; **collaboration** with village leaders and women leaders and other partners
- c-IPTp approach strengthened **credibility of CHWs**, and the acceptability of, and adherence to, IPTp-SP for pregnant women
- **Ratio** of CHWs to population as well as scope of care adjusted to easy- and hard-to-reach areas
- ...

Adapted SP packaging – Increasing acceptability of SP for IPTp



- ❑ Introduced in DRC and NGA – study on end user experiences and perceptions
- ❑ Imagery indicates SP is for pregnant women (PW) and contributes to its perceived safety
- ❑ Unexpected effect: PW have preference for SP with updated packaging – could affect perception of SP with different or no packaging (e.g. at HF), or perceptions of /confidence in other medicines provided at ANC visits
- ❑ Next step: manufacturers to adopt new packaging

Resistance monitoring (I)



Quintuple mutant – associated with clinical and parasitological SP treatment failure

- Triple mutant dhfr (N51I + C59R + S108N)
- Double mutant dhps (G437A + K540E)

Sextuple mutant – SP ineffective in IPTp

- Plus dhps + A581G

- Analysis of endline samples provided **similar results** to the baseline samples
- Proportions of **Pfdhfr/Pfdhps haplotypes differed significantly between each country**. Some **changes in proportions of Pfdhfr and Pfdhps mutants** in the Democratic Republic of the Congo, Madagascar and Nigeria **could be attributed to the intervention.**

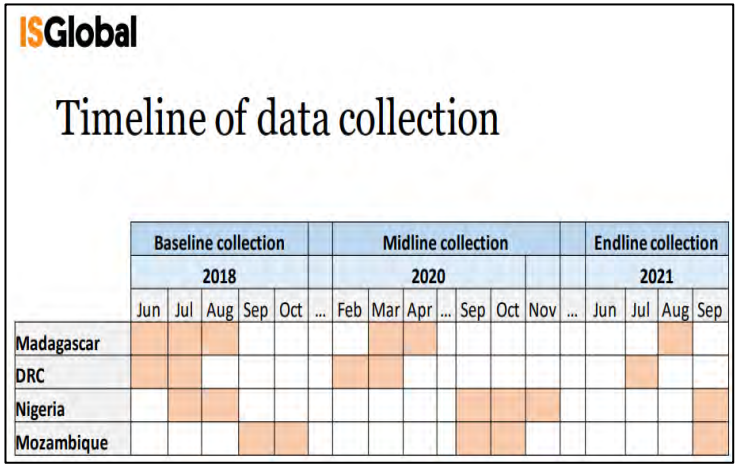
  In the Democratic Republic of the Congo, this may be for the **Pfdhfr 51I** mutant (96.4% at endline) and the **Pfdhps 613S** mutant (0.6% in the test area at endline).
  In Madagascar, it may be for the **Pfdhfr 108N** mutant (87.9% in the test area at endline).
  In Nigeria, it may be for the **Pfdhps 437A** mutant (20.0% in the test area at endline).
- **Quintuple mutants: not found** in the baseline or endline samples
- **Sextuple mutants:** The was **not detected** in the Democratic Republic of the Congo or Madagascar. The frequency of this mutant remained low in Nigeria (<10%), with no differences between test and control areas or baseline and endline.

Resistance monitoring (II)

- IPTp has been shown to be effective even if there is some mutations, but not when the sextuple haplotype is present. Most important mutation for SP resistance development is the Pfdhps 581G mutant, and there were no signals of concern.

- A recent review by Plowe* showed that resistant mutants do not predict effectiveness of IPTp for prevention. The association between SP effectiveness for prevention and the sextuple mutation has not really been established yet.

- TIPTOP study results on resistance genes obtained 3 years after the start of c-IPTp – possible it takes more time for an increase in SP resistance to become clear – continue monitoring the regular markers associated with SP resistance



* Plowe CV. Malaria chemoprevention and drug resistance: a review of the literature and policy implications. Malar J. 2022 Mar 24;21(1):104. doi: 10.1186/s12936-022-04115-8

Outline

- Background and WHO recommendations
- WHO Technical Consultation – meeting report
  - IPTp3
  - ANC
  - SP resistance
- **Development of field guide**

Development of WHO field guide on c-IPTp

Q4/2022	First draft by Emmanuel Otolorin
Dec 2022/Jan 2023	Revision by Experts
Jan/Feb 2023	Incorporation of comments
Mar/Apr 2023	WHO GMP review and finalization
Apr/May 2023	Technical editing and layout
May/Jun 2023	Publication and dissemination

Update on the WHO/TDR Technical Consultation on seasonal malaria chemoprevention;

SMC with sulfadoxine-pyrimethamine plus amodiaquine in children: a field guide (2nd edition)

Malaria Policy Advisory Group (MPAG) Meeting 18 – 20 April 2022

18-20 April 2023
Geneva, Switzerland

Dr. Peter OLUMESE,
Global Malaria Programme
WHO, Geneva, Switzerland.

Global **Malaria** Programme

World Health Organization

Seasonal Malaria Chemoprevention- *(WHO Malaria Guidelines)*

Strong recommendation for, moderate-certainty evidence

Updated

In areas of seasonal malaria transmission, children belonging to age groups at high risk of severe malaria should be given antimalarial medicines during peak malaria transmission seasons to reduce disease burden.

- Eligibility for seasonal malaria chemoprevention (SMC) is defined by the seasonality of malaria transmission and age groups at risk of severe malaria. Thresholds for assessing these criteria change over time and location. Malaria programmes should assess the suitability of SMC based on the local malaria epidemiology and available funding. The added value of a seasonally targeted intervention is likely to be greatest where transmission is intensely seasonal.
- Monthly cycles of sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) have been widely used for SMC in African children under 5 years old and have been shown to be efficacious, safe, well tolerated, available and inexpensive *[182]*.

Practical information - *(WHO Malaria Guidelines)*

- WHO recommends a combination medicine for SMC that is different from that used for first-line malaria treatment.

- The component medicines should have closely matched pharmacology, such that no component is present in the absence of other components for more than a minimal amount of time in order to reduce the risk of new infections encountering only a single drug.

- Implementation
  - *Please refer to the Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: A field Guide*

Chemoprevention recommendations – shift in approach

- The updated chemoprevention recommendations provide greater flexibility to NMPs to adapt control strategies to suit their settings.
- No longer specify strict age groups, transmission intensity thresholds, numbers of doses or cycles, or specific drugs.
- NMPs are encouraged to consider local data to determine how best to tailor chemoprevention strategies to local needs and determine which age groups should be targeted where, for how long, how frequently, and with which drugs.
- Further guidance on specificities will be provided through implementation field manuals, based on current available evidence.

WHO Technical consultation to update of SMC field manual

Background and Objectives

21-23 November 2022
Room M505, WHO, Geneva

Global **Malaria** Programme

World Health Organization

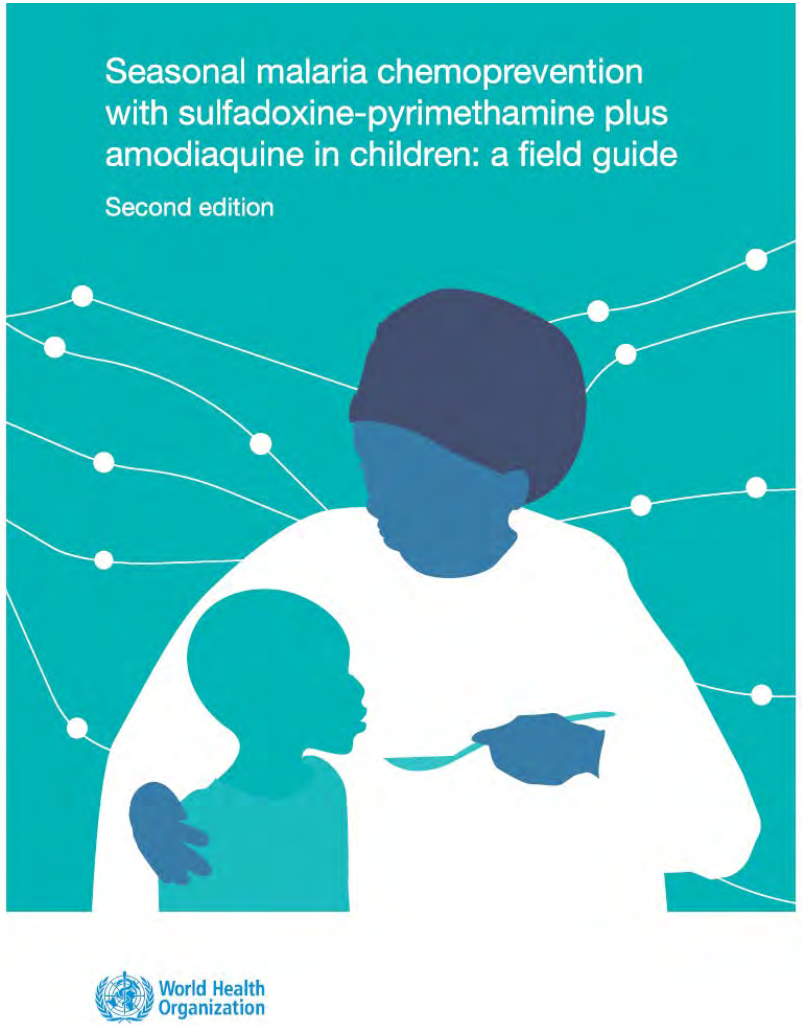
Objective of the meeting

- Update implementation field guide (2013) to reflect current Guidelines recommendation
  - specify age groups, transmission intensity thresholds, numbers of doses or cycles, or specific drugs.

Background and process

- SMC was recommended by WHO in 2012
- WHO published the first edition of the Field manual for seasonal malaria chemoprevention in 2013 to support SMC implementation
- Since then, SMC has been adopted as policy and implemented on a large scale in 13 African countries.
- Best practices for SMC implementation based on the experiences of African countries since 2013 have been compiled in this updated field guide.
- The goal is to share these best practices to improved SMC implementation, coverage, and monitoring and evaluation.
  - Examples of materials and tools, and links to resources are included to support managers and health workers conduct successful SMC activities and prevent malaria among vulnerable children.

Implementation field guide



further guidance (Field Guide 2nd ed, 2023)

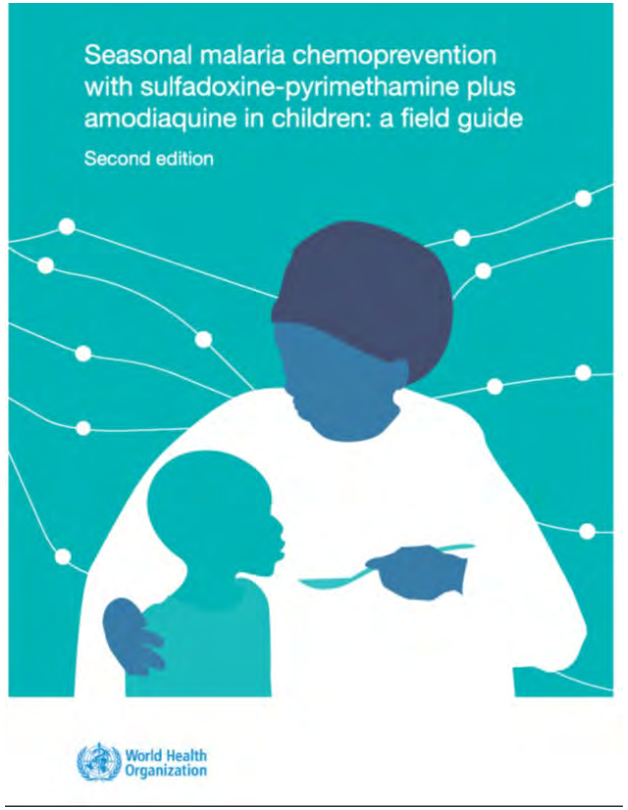
- Target area:
  - malaria transmission is highly seasonal and the majority (>60%) of clinical malaria cases occur within 4 consecutive months
  - the clinical attack rate of malaria (without SMC) is at least 0.1 episodes per child during the transmission season in the target group

- Target population
  - Children in age groups at high risk of severe malaria are eligible. In most countries with intense seasonal malaria transmission, these are children below 5 years of age.

further guidance (Field Guide 2nd ed, 2023)

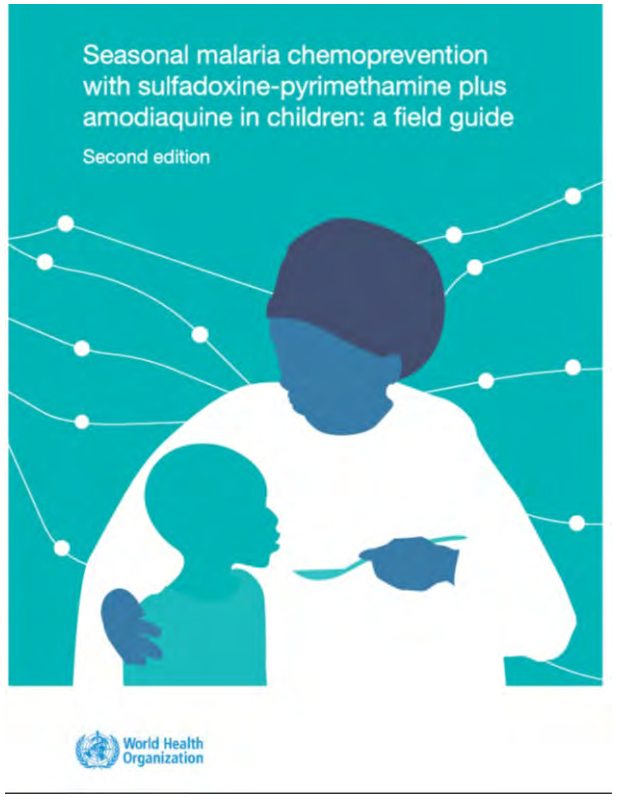
- Number of cycles
  - SMC courses should be given at 28-day intervals, beginning at the start of the transmission season and continuing for 3–5 cycles, depending on the local context.
    - In some settings, three cycles may be sufficient.
    - Add a fifth cycle if a month on either side of the 4-month season contributes more than 10% of the annual burden
    - Gains from adding a sixth SMC cycle appear to be minimal and not cost effective
- Recommended medicines
  - The combination of SP+AQ is currently recommended for SMC.

SMC with SP+AQ in Children: a field guide; second edition, 2023



SMC with SP+AQ in Children: a field guide; second edition, 2023

- 4. Planning and implementation ……. 13
  - Same as in the first edition, building on lessons learnt over 10 years of deploying SMC
  - 4.1 Distribution strategies
  - 4.2 Preparing an SMC implementation plan
  - 4.3 SMC implementation
  - 4.4 Roles and responsibilities at various levels
- 5. Monitoring and evaluation …….. 28
  - Update on previous M&E chapter and lessons over the 10 years implementation of SMC
  - Also incorporated updated performance framework for SMC produced by the Monitoring and Evaluation Subgroup of the SMC Alliance
- References …….. 48
- Tools …….. 50



Seasonal Malaria Chemoprevention with SP+AQ in Children: a field guide (2nd edition)

SMC Alliance review and planning meeting 2023

28 Feb, 1-2 March 2023
Conakry, Guinea

Global **Malaria** Programme

World Health Organization

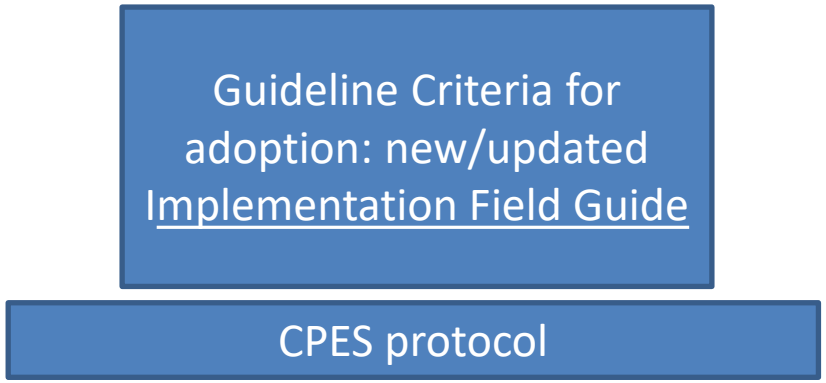
Next Steps

- Final print ongoing
- Translations
- Dissemination and uptake
- Supporting countries in updating national tools and guidance based on this global field guide.

Unpacking the other chemoprevention recommendations

Seasonal Malaria Chemoprevention (example)

- Criteria/data for intensity of malaria transmission
- Criteria/data for seasonality
- Criteria for number of cycles
- Criteria/data for target age group determination
- Protocol for measuring protective effectiveness



Prototype for other recommendations – Field guidance documents

- SMC
  - Implementation Field manual 2nd edition *(Updated, publication in process)*
- IPTp at community level
  - New field manual *(finalization in process)*
- PMC
  - Projects and early implementation underway to provide the evidence required for expansion of IPTi beyond the current recommendation and transition to PMC. – Development of updated implementation field manual – *(planned)*.
- IPTsc and PDMC
  - Deployment studies and experience required to develop implementation guidance documents
  - Implementation Guidance – *(planned)*

Malaria Policy Advisory Group Meeting

18—20 April 2023, Geneva, Switzerland
Background document for Session 7

Update on *An. stephensi* regional strategy

Anopheles stephensi is a malaria vector in south Asia. This vector has been found in Africa since 2012, and its distribution in Africa appears to be spreading. This trend is of concern, as it may result in increased malaria, particularly in urban settings, thus adding to the burden and requiring limited malaria resources to be stretched even further.

Anopheles stephensi is able to use a variety of larval sites, ranging from river margins to borrow pits. Most importantly, it is able to use man-made sites such as wells, cisterns, and tires in urban settings. While adult *An. stephensi* mosquitoes seem to prefer taking blood meals from cattle and goats, they will bite humans when their preferred hosts are not available. *An. stephensi* mosquitoes in Africa have been shown to be effective malaria vectors *(1)*.

Distribution of *An. stephensi*

Since the October 2022 Malaria Policy Advisory Group meeting, *An. stephensi* has been reported in three additional countries. In Kenya, *An. stephensi* was found in two counties (Turkana and Marsabit) in collections from 2022. In Eritrea, it was found in two locations in the north-western part of the country in collections from 2022. Finally, *An. stephensi* was detected in two sites in Ghana, near Accra, in collections from 2022. The invasive vector has now been reported in eight countries in Africa (Djibouti, Eritrea, Ethiopia, Ghana, Kenya, Nigeria, Somalia and Sudan). How long the vector has been present in these sites and the extent of its spread across the continent remain unclear.

Some of the sites have yet to be added the Malaria Threats Map *(2)*, but they will be added once details have been provided to the World Health Organization (WHO).

Update of the vector alert

An initial vector alert was issued in 2019 to provide guidance to countries on surveillance and control of *An. stephensi (3)*. An update to the vector alert *(4)* was made in late 2022 to provide guidance to countries on activities to conduct before *An. stephensi* is found in the country and activities to conduct once *An. stephensi* has been detected. The update provided additional information on methods for identification, surveillance, control, and strategy.

Partnership convening

A recent partnership convening was held in Addis Ababa from 8 to 10 March 2023. This meeting gathered members of national malaria control programmes, researchers, funders, and policy-makers to further the aims of the *WHO initiative to stop the spread of Anopheles stephensi in Africa (5)*. This meeting provided updates on the surveillance, control and development of policy against *An. stephensi* in 13 countries (Chad, Djibouti, Eritrea, Ethiopia, Ghana, Kenya, Mauritius, Nigeria, Somalia, South Sudan, Sudan, United Republic of Tanzania, and Yemen). Nine of the participating countries (eight in Africa and Yemen) reported finding *An. stephensi*, whereas four countries had not conducted specific surveillance for *An. stephensi* and/or had not detected it.

Four funding organizations provided updates on their activities and their priorities for future funding. Unitaid will take *An. stephensi* into account as it develops grants relating to its malaria priority of introducing and optimizing prevention tools. Bill & Melinda Gates Foundation will continue its support

of Oxitec's development of self-limiting *An. stephensi*, attractive targeted sugar bait operational trials, the malaria Vector Atlas project, and projects relating to mosquito identification. The United States President's Malaria Initiative (PMI) is leading the coordination of United States government activities against *An. stephensi*. PMI has developed a webpage sharing its activities and documents. Its support is limited to PMI countries; however, it is collaborating with other countries as well. PMI has conducted larviciding for the first time in Ethiopia in response to the threat of *An. stephensi*. The United States Centers for Disease Control and Prevention is also providing support for *An. stephensi* surveillance and control. Finally, the Global Fund to Fight AIDS, Tuberculosis and Malaria reported on ways it supports countries for *An. stephensi* control and described the thematic review of countries' entomological surveillance systems that is under way. The review is being undertaken in seven countries affected by or considered at risk of *An. stephensi* invasion, namely Djibouti, Eritrea, Ethiopia, Somalia, South Sudan, Sudan, and Yemen.

Researchers presented key aspects of *An. stephensi's* biology and control. Fitsum Tadesse (Armauer Hansen Research Institute [AHRI]) reported on a case-control study conducted in Dire Dawa, Ethiopia, where a local outbreak of malaria was linked to *An. stephensi*. Anne Wilson (Liverpool School of Tropical Medicine) reported on activities of the "Controlling Emergent *An. stephensi* in Sudan and Ethiopia" (CEASE) project. Matt Thomas (University of Florida) presented an invasion biology perspective on *An. stephensi*'s spread in Africa. Meshesha Balkew (PMI VectorLink) provided an update on PMI VectorLink's work on *An. stephensi*'s biology and control in Ethiopia. Tamar Carter (Baylor University) discussed her laboratory's work on the population genetics of *An. stephensi*. Charlie Whittaker (Imperial College) provided a modelling analysis of the seasonality of *An. stephensi*. Finally, Gonzalo Vazquez-Prokopec (Emory University) provided insights into the control of urban *An. stephensi* based on the control of *Aedes aegypti*.

On the second day of the meeting, there was a site visit to Adama, Ethiopia, approximately 90 km south of Addis Ababa, where *An. stephensi* has been found. The visit started at AHRI's Malaria Research and Training Center. There were presentations from AHRI staff about the institute and its history. AHRI staff then led participants on a field visit to see potential *An. stephensi* larval sites in Adama.

On the final day, participants broke into four groups to discuss important areas of work for *An. stephensi* control. These included surveillance, vector control, social and behaviour change, and strategy/integration of *An. stephensi* activities into national malaria control programmes.

Key unknowns/research priorities

There remain several key areas where the lack of knowledge on *An. stephensi* hampers an organized response. These include:

- A comprehensive understanding of the distribution of *An. Stephensi*: understanding which countries *An. stephensi* has already invaded an important first step to provide baseline data to monitor any potential further spread. It is also essential to understand the distribution of *An. stephensi* within countries, particularly in terms of its penetration into peri-urban or rural areas;
- Understanding *of An. stephensi*'s mechanism of spread: the means of transportation by which *An. stephensi* has invaded African countries and the life stage (egg/larvae/adult) that is travelling are unknown. Understanding how the vector has invaded the continent and the various countries it has been reported from would help in devising ways to prevent further spread. Population genetics may be a useful tool in this regard, and careful observation of transportation hubs and vehicles may also be useful;
- The impact of *An. stephensi* on malaria transmission: while some studies appear to indicate an important role of *An. stephensi* in urban malaria transmission, other analyses show little

impact. More detailed assessment of the recent evolution of urban malaria in areas with *An. steph*ensi (noting travel history) would be very useful for understanding its importance as a malaria vector;

- Optimal vector control for *An. Stephensi*: while randomized controlled trials may be excessively expensive to conduct in urban settings (which often have low prevalence), entomological impact studies could be done to see which methods work best. Larviciding and larvivorous fish are the most widely used methods in India and these interventions should be assessed in Africa;
- Overlap of *An. stephensi* and *Ae. aegypti* larval sites: overlap could allow for increased opportunities for integration of surveillance and control of these disease vectors. Examples of this integration should be shared if possible.

Upcoming activities

In 2023, the WHO Global Malaria Programme Vector Control and Insecticide Resistance Unit aims to complete a "deep dive" into the history of successes and failures in *An. stephensi* control, and will undertake at least one case study of integrated mosquito surveillance and control with the aim of informing action as envisaged under the Global Vector Control Response. The quarterly update calls and updates to the Malaria Threats Map will also continue in 2023.

References

1. Tadesse FG, Ashine T, Teka H, Esayas E, Messenger LA, Chali W, et al. *Anopheles stephensi* mosquitoes as vectors of *Plasmodium vivax* and *falciparum*, Horn of Africa 2019. Emerg Infect Dis. 2021;27:603–7. doi:10.3201/eid2702.200019.
2. Mapping tool on tracking biological challenges to malaria control and elimination [website]. In: Global Malaria Programme. Geneva: World Health Organization (https://www.who.int/teams/global-malaria-programme/surveillance/malaria-threats-map, accessed 28 March 2023).
3. Vector alert: *Anopheles stephensi* invasion and spread: Horn of Africa, the Republic of the Sudan and surrounding geographical areas, and Sri Lanka: information note. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/326595, accessed 28 March 2023).
4. Vector alert: *Anopheles stephensi* invation and spread in Africa and Sri Lanka. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/365710, accessed 28 March 2023).
5. WHO initiative to stop the spread of *Anopheles stephensi* in Africa. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/363318, accessed 28 March 2023).

Update on *An. stephensi* regional strategy

Dr Seth Irish
Malaria Policy Advisory Group
18-20 April 2023

Global **Malaria** Programme

World Health Organization

Background

- *An. stephensi* spreading in Africa
- Initiative against the spread of *An. stephensi* in Africa launched in September 2022

Activities since last MPAG meeting

- WHO activities
  - Quarterly call (December 2022)
    - Rajender Sharma "*Anopheles stephensi* control in India"
  - Update to Malaria Threats Map platform
  - Update of Vector Alert
  - Partner convening in Addis Ababa (March 8-10)
- Other
  - MESA Forum: "Responding to the threat of *Anopheles stephensi* invasion in Africa"
  - IHI Masterclass: "*Anopheles stephensi* in Africa: a Masterclass with Global Experts & In-country Practitioners"

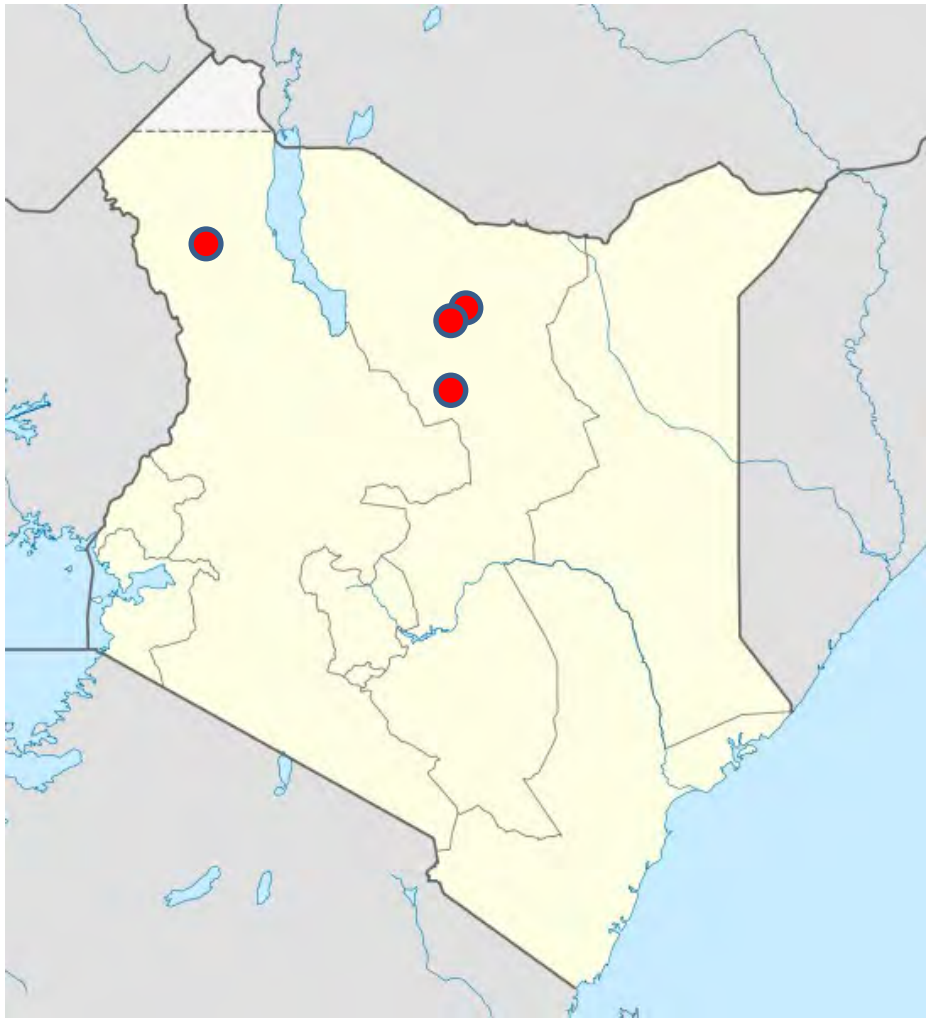
Key publications since last MPAG meeting

- PCR method for confirmation of *An. stephensi* identification
- Identification of resistance markers
- Seasonality and thermal limits of malaria transmission by *An. stephensi*.
- Evaluation of insecticides:
  - *Bacillus thuringiensis* var. *israelensis*
  - Temephos
- Modeling marine cargo traffic to identify countries at risk of invasion
- Detection of *An. stephensi*
  - Yemen
  - Kenya
- Guidance for surveys
- Sharing of larval sites by *An. stephensi* and *Ae. aegypti*

Findings since last MPAG meeting

GHANA

KENYA



Partners convening: A regional response to the invasion of *An. stephensi* in Africa

8-10 March, 2023

- 94 participants from 23 countries
- Presentations of *An. stephensi* monitoring, control, and policy from 13 countries
- Funding agencies (4) presented their priorities for *An. stephensi*–related activities
- Researchers presented findings on *An. stephensi*
  - Distribution of *An. stephensi* in Africa
  - Impact of *An. stephensi* on malaria transmission
  - Population genetics
  - Seasonal dynamics of *An. stephensi*
  - *Aedes aegypti* and *An. stephensi*

Partners convening: A regional response to the invasion of *An. stephensi* in Africa

8-10 March, 2023

- Field visit to Armauer Hansen Research Institute
- Sampling of larval sites in Adama
- Research prioritization breakout groups
  - Vector control
  - Surveillance
  - Strategy/integration of *An. stephensi* activities into NMCP activities
  - Social and behavior change

Next steps

- Continue update activities:
  - Quarterly *An. stephensi* calls
  - Updating of Malaria Threats Map
- Deep dive on past successes and failures in *An. stephensi* control

Update on HRP2 gene deletions and Global Response Plan

Dr Jane Cunningham

Malaria Policy Advisory Group (MPAG) Meeting, 18 – 20 April 2022, Geneva, Switzerland

Global **Malaria** Programme

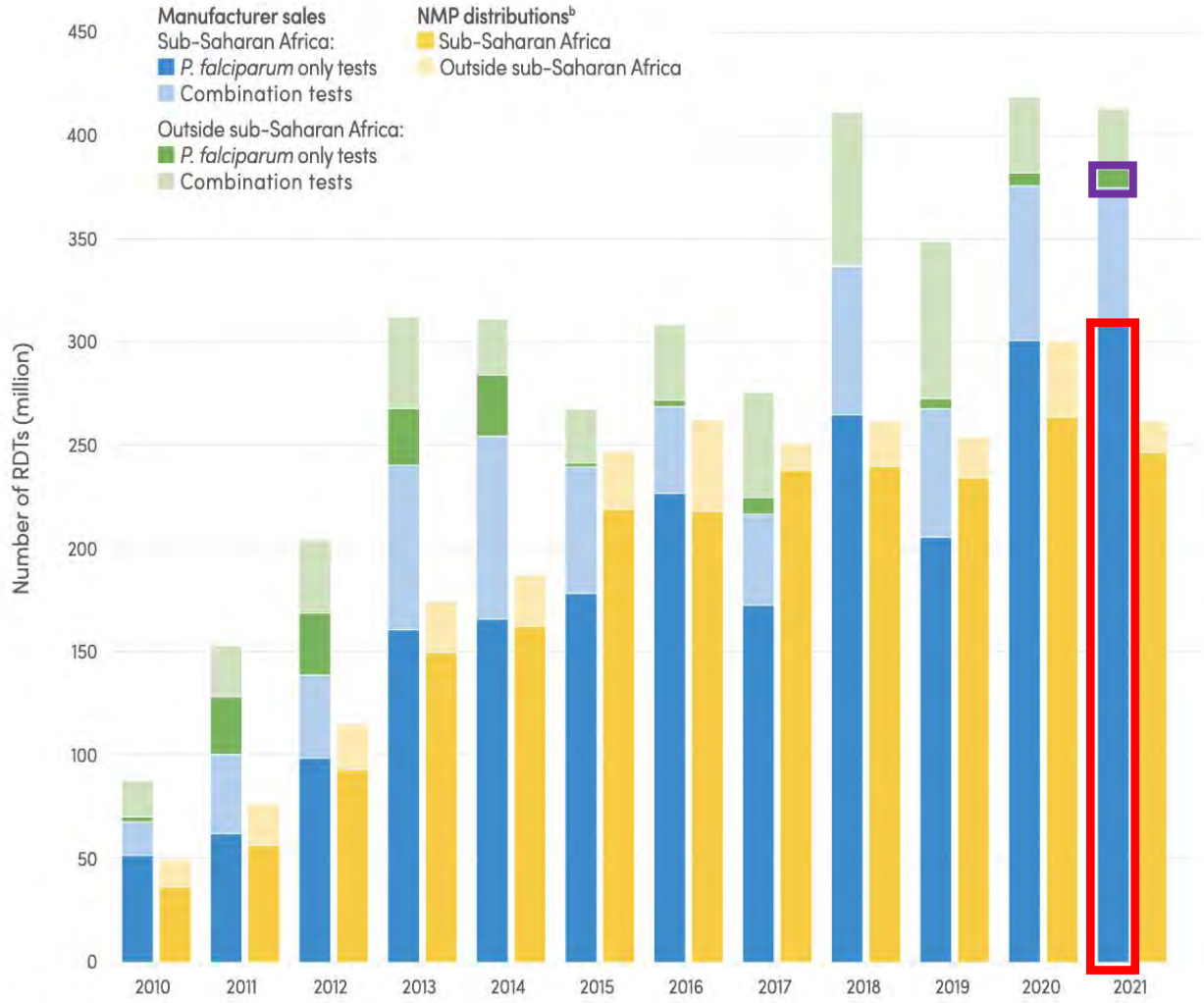
World Health Organization

- RDTs target different malaria antigens

	HRP2	pLDH	Aldolase
***P.falciparum*-specific**	+	+	
Pan-specific (all species)		+	+
***P.vivax*-specific**		+	

- The majority of RDTs used to detect *P. falciparum* target histidine rich protein-2 (HRP2)
- Partial or complete deletion of the gene that encodes for HRP2 can result in negative HRP2-RDTs

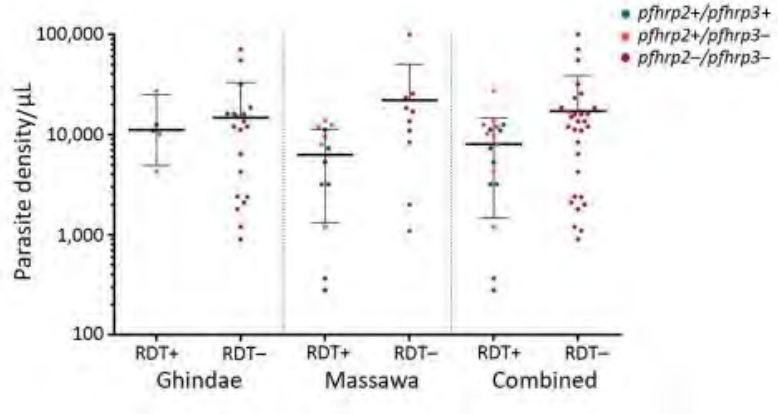
Number of RDTs sold by manufacturers and distributed by NMPs for use in testing suspected malaria cases, 2010–2021[a] *Sources: NMP reports and delivery data from eligible manufacturers.*

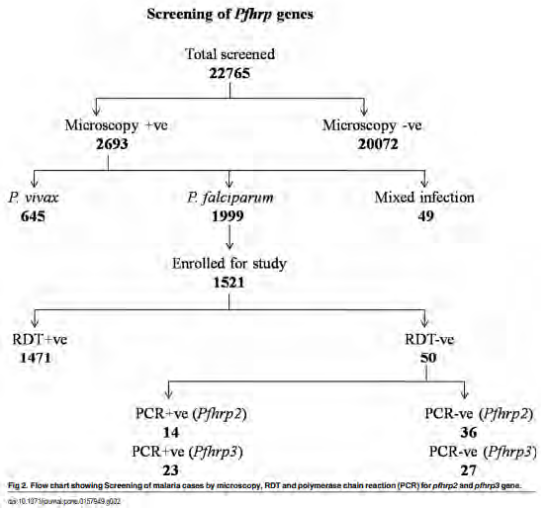


NMP: national malaria programme; *P. falciparum*: *Plasmodium falciparum*; RDT: rapid diagnostic test.
[a] NMP distributions do not reflect those RDTs still in storage that have yet to be delivered to health facilities and to community health workers.

First report pfhrp2 deletions in Peru in 2010 …Turning point in 2016

- 41% (61/148) of isolates lacked *pfhrp2;*
- 21% lacked both *pfhrp2 and 3*
- *Surveys in neighbouring countries also confirmed presence of deletions*



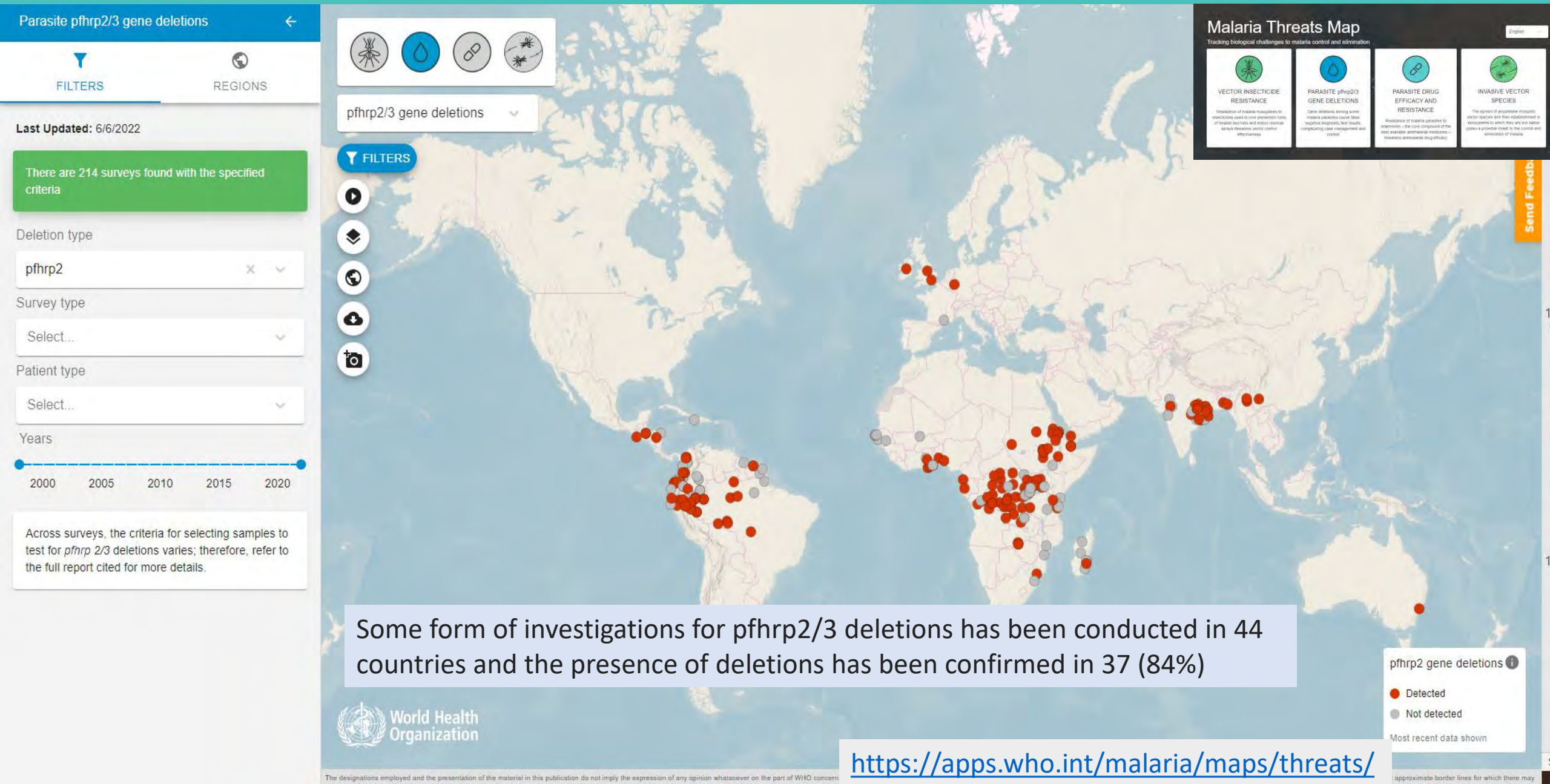


Very high prevalence of double deletions in Eritrea and overall low but heterogeneous prevalence of deletions in India (eight states)

Berhane A, et al. Major Threat to Malaria Control Programs by Plasmodium falciparum Lacking Histidine-Rich Protein 2, Eritrea. Emerg Infect Dis. 2018 Mar;24(3):462-470.

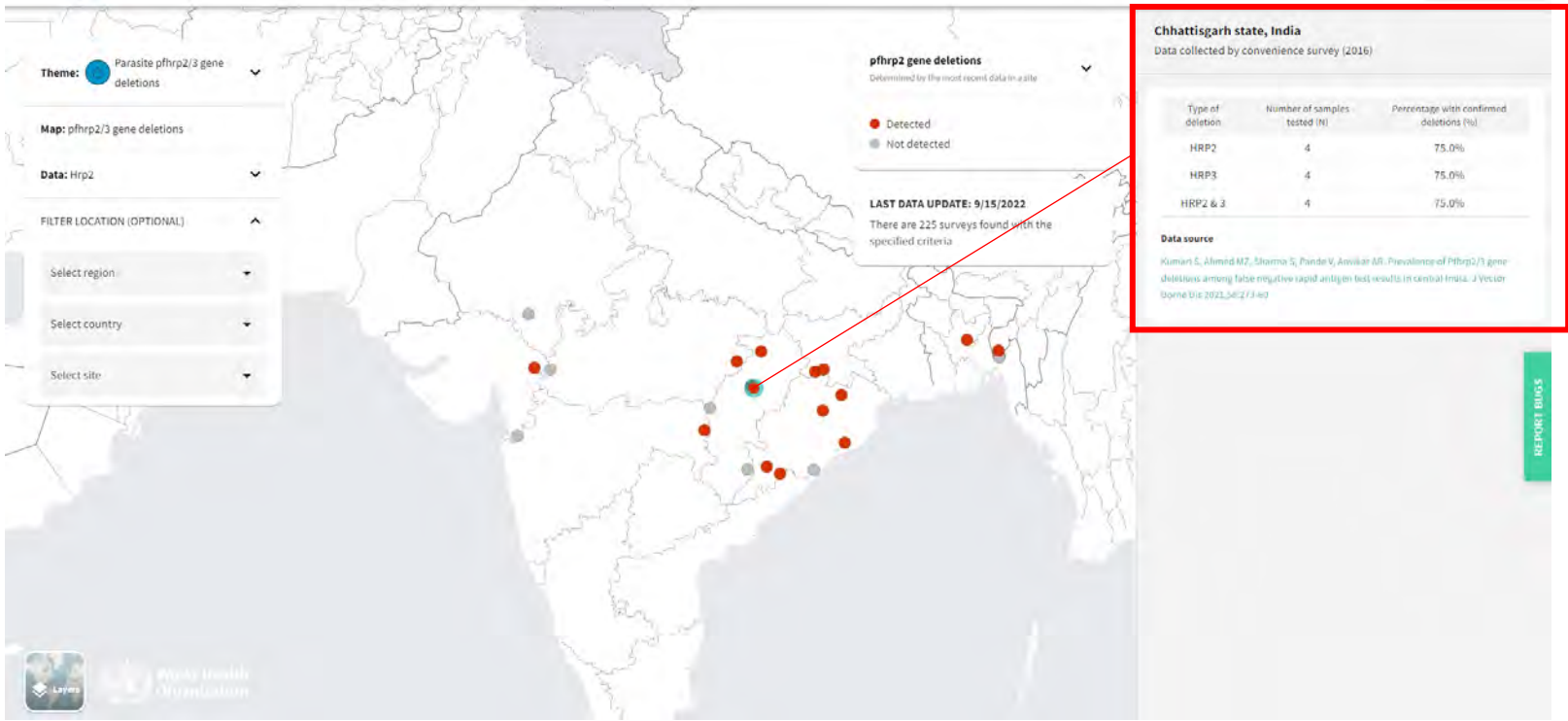
Bharti PK et al (2016) Prevalence of pfhrp2 and/or pfhrp3 Gene Deletion in Plasmodium falciparum Population in Eight Highly Endemic States in India. PLoS ONE 11(8): e0157949.

WHO Malaria Threat Maps: 2017-



Limitations

- Malaria threat maps chart what is in the published report – typically percentage of pfhrp2 deleted samples amongst those tested and NOT all *P.falciparum* cases
- Populations are different – age, symptoms/no symptoms, selection criteria for genotyping
- RDT result not always known – don't know if the deletion led to a false negative result
- Original source is required to properly interpret the results.
- <u>CANNOT CURRENTLY USE MAP TO DETERMINE WHERE POLICY SHOULD CHANGE</u>

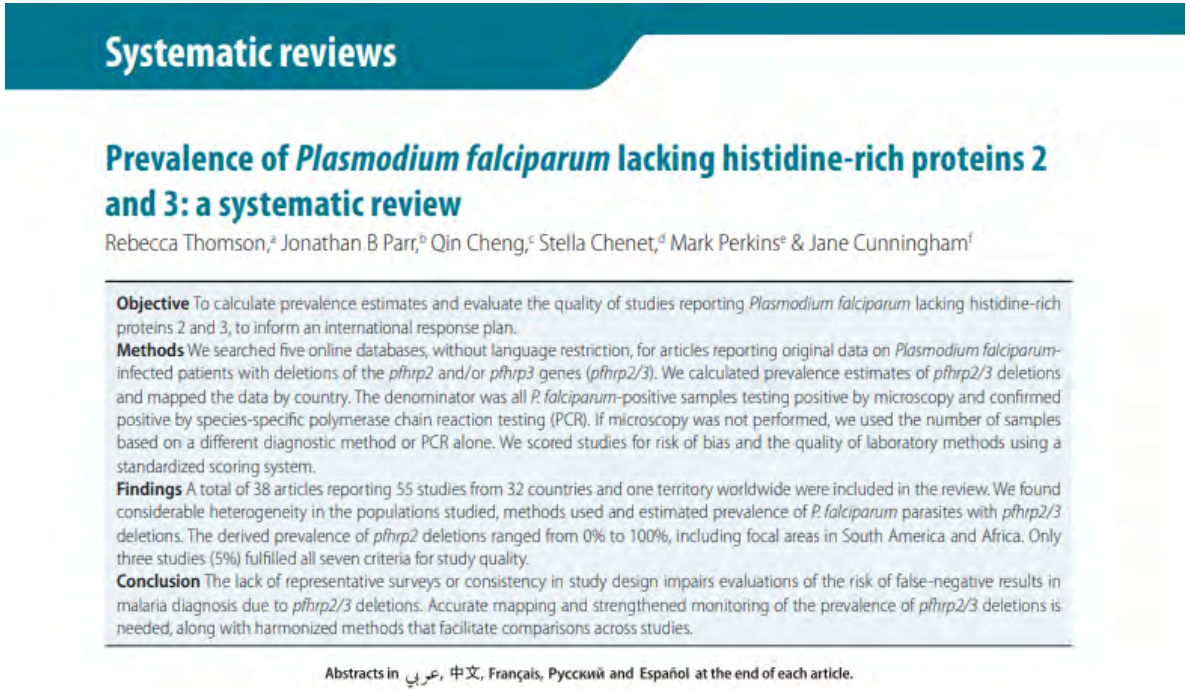


Prevalence of deletions causing false negative HRP2 RDTs = 3/85* (3.5%) not 75% !

** 203 suspects screened; 85 Pf confirmed; 4 HRP2-/micro or PCR +*

Getting at the true picture …. Still many gaps

- Prevalence estimates of pfhrp2/3 deletions and mapped the data by country
- **denominator** was all *P. falciparum-positive* samples testing positive by microscopy* and confirmed positive by species-specific polymerase chain reaction testing (PCR)
- 38 publications; 55 studies from 32 countries (01/10-08/19)
- Small sample sizes, heterogeneity in populations, lab methods and estimated prevalence (0-100%)
- 3(5%) of studies met all quality criteria



Systematic reviews

Prevalence of *Plasmodium falciparum* lacking histidine-rich proteins 2 and 3: a systematic review

Rebecca Thomson,[a] Jonathan B Parr,[b] Qin Cheng,[c] Stella Chenet,[d] Mark Perkins[e] & Jane Cunningham[f]

Objective To calculate prevalence estimates and evaluate the quality of studies reporting *Plasmodium falciparum* lacking histidine-rich proteins 2 and 3, to inform an international response plan.
Methods We searched five online databases, without language restriction, for articles reporting original data on *Plasmodium falciparum*-infected patients with deletions of the *pfhrp2* and/or *pfhrp3* genes (*pfhrp2/3*). We calculated prevalence estimates of *pfhrp2/3* deletions and mapped the data by country. The denominator was all *P. falciparum*-positive samples testing positive by microscopy and confirmed positive by species-specific polymerase chain reaction testing (PCR). If microscopy was not performed, we used the number of samples based on a different diagnostic method or PCR alone. We scored studies for risk of bias and the quality of laboratory methods using a standardized scoring system.
Findings A total of 38 articles reporting 55 studies from 32 countries and one territory worldwide were included in the review. We found considerable heterogeneity in the populations studied, methods used and estimated prevalence of *P. falciparum* parasites with *pfhrp2/3* deletions. The derived prevalence of *pfhrp2* deletions ranged from 0% to 100%, including focal areas in South America and Africa. Only three studies (5%) fulfilled all seven criteria for study quality.
Conclusion The lack of representative surveys or consistency in study design impairs evaluations of the risk of false-negative results in malaria diagnosis due to *pfhrp2/3* deletions. Accurate mapping and strengthened monitoring of the prevalence of *pfhrp2/3* deletions is needed, along with harmonized methods that facilitate comparisons across studies.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

https://www.who.int/bulletin/volumes/98/8/20-250621.pdf?ua=1

Number of lab-confirmed *pfhrp2/3* deletions

Number of *P.falciparum*-positive samples

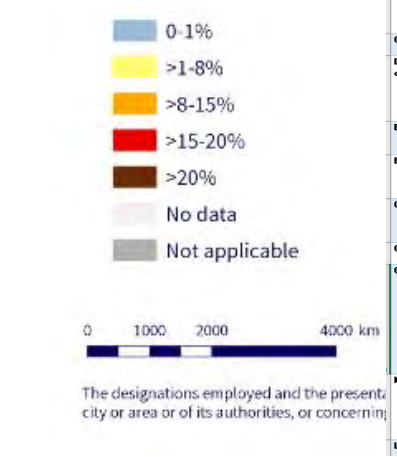
*If microscopy was not performed, the study included samples confirmed by a different diagnostic method or by PCR alone

Despite limitations – hot spots emerge

Collection of information on *pfhrp2* deletions

The WHO Response Plan to *pfhrp2* deletions calls for urgent action to determine the scale and scope of the problem and WHO has developed surveillance protocol templates to support these efforts. Tracking of surveillance activities is critical to directing resources as well as informing RDT demand forecasting and R&D. WHO has therefore developed a *pfhrp2* surveillance dashboard to be voluntarily populated by representatives of ministries of health and research groups leading surveillance efforts. Collectively this will generate a global picture of *pfhrp2/3* surveillance efforts. The contents of the dashboard will be updated monthly and freely downloadable and eventually visually integrated into the Malaria Threats Map platform.

- **Enter information into the dashboard | Download the dashboard (4 December 2022)**



Country	Name	Institution	City	Telephone	Email address	In which country will the survey be conducted?	What is the survey status?	What prompted the survey/study for pfhrp2/3 deletions?	What prompted the survey/study for pfhrp2/3 deletions? [Comment]	Describe the survey/study design: provide details including links, if protocols published	Describe the survey/study design: provide details including links, if protocols published [Comment]	Is the funding secured?	Which type of individuals will be included?	According to the protocol will initial routine HRP2-RDT results be available so that impact of pfhrp2/3 deletions on RDTs results	What is the geographical scope or sampling domain?
Brazil	Alexandre Dias Tavares Costa	FIOCRUZ (Oswaldo Cruz Foundation)	Curitiba	+554138835202 6	alexandre.costa@fiocruz.br	Brazil	Ongoing - data collection	High level of suspicion of pfhrp2/3 deletions	In fact, it is a mixture of the high level of suspicion and the opportunity to add on to other survey efforts.	Others, specify (eg. case report, convenience testing, therapeutic efficacy survey (TES) samples, discordant samples (RDT-/micro +))	Evaluation of available molecular techniques for accurate detection of pfhrp2/3 deletions. Techniques include Taqman-based qPCR, digital PCR, and Sanger sequencing.	Yes	Mixed	Yes	Transmission zone(s)
Burkina Faso	DR ISSIAKA SOULAMA	Institut de Recherche en Sciences de la Santé (IRSS/CNRST)	Ouagadoug ou	+22670757190	iss.soulama@gmail.com	Burkina Faso	Ongoing - data collection	Opportunity to add on to other survey efforts e.g. TES	We are now conducting a malaria genomic surveillance in Burkina Faso funded by Gate Foundation. pfhrp2/3 deletions analysis are pat of our obiectives	Other survey, specify type (e.g., Health Facility Survey (HFS), Demographic and Health Survey (DHS), Malaria Indicator Survey(MIS))	The study is based on two Health facilities survey.	Yes	Mixed	Yes	Transmission zone(s)
Cameroon	Nkemago Francis Nongley	Centre for Research in Infectious Diseases & University of Buea	Buea	(00237)6755797 37	nkemago.francis@gmail.co m	Cameroon	Ongoing - data analysis	pfhrp2/3 deletions confirmed in neighbouring country		Modified WHO surveillance protocol (specify deviations, if possible)		Yes	Asymptomatic	Yes	Transmission zone(s)
Democratic Republic of the Congo	MESIA KAHUNU GAUTHIER	UNITE DE PHARMACOLOGIE CLINIQUE ET PHARMACOVIGILANCE, UNIVERSITY OF KINSHASA	KINSHASA	+243 813 261 360	mesia.kahunu@unikin.ac.cd	Democratic Republic of the Congo	Ongoing - data analysis	Opportunity to add on to other survey efforts e.g. TES		Others, specify (eg. case report, convenience testing, therapeutic efficacy survey (TES) samples, discordant samples (RDT-/micro +))	Therapeutic efficacy survey (TES) samples	Yes	Symptomatic	No	Multiple administrative zones (states/provinces) - please list by name in comments, if available
Ethiopia						Ethiopia	Published	pfhrp2/3 deletions confirmed in neighbouring country		WHO pfhrp2/3 surveillance protocol template		Unknown	Symptomatic	Yes	Multiple administrative zones (states/provinces) - please list by name in comments, if available
Ethiopia	Bokretion Gidey	Ethiopian Public Health Institute (EPHI)	Addis Ababa	+251931571838	bokregidey@yahoo.com	Ethiopia	Completed but unpublished	pfhrp2/3 deletions confirmed in the country	We have one (1st phase) published data and (2nd phase) waiting for the publication.	WHO pfhrp2/3 surveillance protocol template	We use the WHO protocol since 2018.	Partial	Symptomatic	Yes	Nationwide
Ghana	Lucas Amenga-Etego	West African Centre for Cell Biology of Infectious Pathogens, University of Ghana	Accra	+233203797997	lucasmengax@gmail.com; lamengaetego@ug.edu.gh	Ghana	Planned	Other (please explain)	As part of a nation-wide malaria genomic surveillance study using NMEP sentinel health facilities.	Other survey, specify type (e.g., Health Facility Survey (HFS), Demographic and Health Survey (DHS), Malaria Indicator	Health facility survey	No	Symptomatic	Yes	Transmission zone(s)
Ghana	Anita Ghansah	Noguchi Memorial Institute for Medical Research, University of	Legon	+233 271405535	aghansah@noguchi.ug.edu.gh	Ghana	Ongoing - data collection	pfhrp2/3 deletions confirmed in the country		WHO pfhrp2/3 surveillance protocol template		Partial	Symptomatic	Yes	Other (specify)
Ghana	Samuel Blankson	West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), University of Ghana	Accra	+233243313100	soblankson@st.ug.edu.gh	Ghana	Ongoing - data analysis	pfhrp2/3 deletions confirmed in the country		Other survey, specify type (e.g., Health Facility Survey (HFS), Demographic and Health Survey (DHS), Malaria Indicator Survey(MIS))		Partial	Mixed	No	Multiple administrative zones (states/provinces) - please list by name in comments, if available
Kenya	Elly Ochieng Munde	Hospital and Health Administration Services	Mombasa	2.54726E+11	ellymunde@gmail.com	Kenya	Ongoing - data analysis	High level of suspicion of pfhrp2/3 deletions	Western Kenya is malaria endemic and was suspected to be having polyclones of P. falciparum	Others, specify (eg. case report, convenience testing, therapeutic efficacy survey (TES) samples, discordant samples (RDT-/micro +))	Convenience testing	Yes	Symptomatic	Yes	Transmission zone(s)
Libya	Walid Saadawi	National Center for Disease Control	Tripoli	+218914353443	walid_ecology@yahoo.com	Libya	Planned	Opportunity to add on to other		Other survey, specify type (e.g.,		Unknown	Mixed	Unknown	Multiple administrative zones

WHO Response Plan to *pfhrp2/3* deletions: 2019

Core response plan to pfhrp2/3 deletions

- **mapping the distribution and frequency of *pfhrp2/3* deletion mutants with harmonized protocols;**
- building an international network of laboratories to perform the complex molecular confirmation required for mapping and identify new and/or efficient screening methods ;
- supporting countries in the selection and procurement of new RDTs when a change of testing is warranted;
- advising commercial manufacturers of the priorities for new tests and providing the best available market forecasts;

https://apps.who.int/iris/bitstream/handle/10665/325528/WHO-CDS-GMP-2019.02-eng.pdf
https://www.who.int/publications/i/item/9789240002036

When to suspect HRP2 deletions ?

- In a <u>patient</u>
  - negative results on an HRP2 test line of at least two quality-assured malaria RDTs

  And

  - positive on the pan- or pf-pLDH test line, when a combination test is used

  And

  - the sample is confirmed microscopically to be positive for *P. falciparum* by two qualified microscopists.

  - Also consider travel history to areas with high prevalence of HRP2 deletions e.g. Peru, Brazil, Eritrea, Djibouti, Ethiopia

https://apps.who.int/iris/bitstream/handle/10665/258972/WHO-HTM-GMP-2017.18-eng.pdf

When should a programme be suspicious ?

- in a programme, the rates of discordance between the results of RDTs and microscopy are systematically ≥ 10–15%, with higher positivity rates in microscopy,
- when the national malaria control programme receives multiple formal complaints or anecdotal evidence of RDTs that give false-negative results for *P. falciparum*.
- When *pfhrp2/hrp3* gene deletions have been reported, the baseline prevalence should be determined in the affected country and neighboring countries

Proactive surveillance – if reports in country or neighbors

Two templates available approved by WHO Ethics Review Committee:

Focus on suspected malaria cases and "false"negative RDT results -- underestimates prevalence of *pfhrp2/3* deletions BUT identifies CLINICALLY RELEVANT deletions

- **Protocol for Surveillance** (only)

All suspected malaria cases tested simultaneously with:

2 RDTs: HRP2 ("program") & pf-LDH* ("survey")

OR

1 RDT + MIC: HRP2 ("program") & Microscopy

AND

2 Dried Blood spots (collected)

RESULTS of parallel testing:

- **Discordant samples** (HRP2- & pf-LDH+ // HRP2- & Mic+) prioritized for molecular analysis
- If resources available, include a subset of other samples for molecular analysis

- **Protocol for Surveillance + Biobanking**:

Involves asking consent for long term storage of samples -> If yes, samples are kept to support future research

*pan-LDH is alternative but will detect non-P.falciparum cases – increased discordance

Updating - WHO Response Plan and Surveillance Protocols

I. Surveillance protocol templates proposed sample sizes to determine if prevalence of false negative RDTs due to pfhrp2 deletions was > or < 5%; assuming that true prevalence was < 3% or > 8%
   I. Error in sampling design – sample increased from 370 Pf cases/ domain (admin area) to 584
   II. Issued corrigendum and began reconsidering the sampling approach to improve power (R. Verity)

II. Verify if current threshold for change to alternative RDT still valid
   I. Prevalence of false negative RDTs due to pfhrp2 deletions is > 5% = nationwide change

III. Given new tools emerging but limited suppliers; higher unit costs and challenges of regular surveillance = modelling risk based transition to alternative RDTs
   I. Which areas are at highest risk ?– prioritize surveillance vs preemptive switch
   II. Where are markets likely to shift first ?
   III. What data would support better predictions ?

Current criteria for change to alternative RDTs

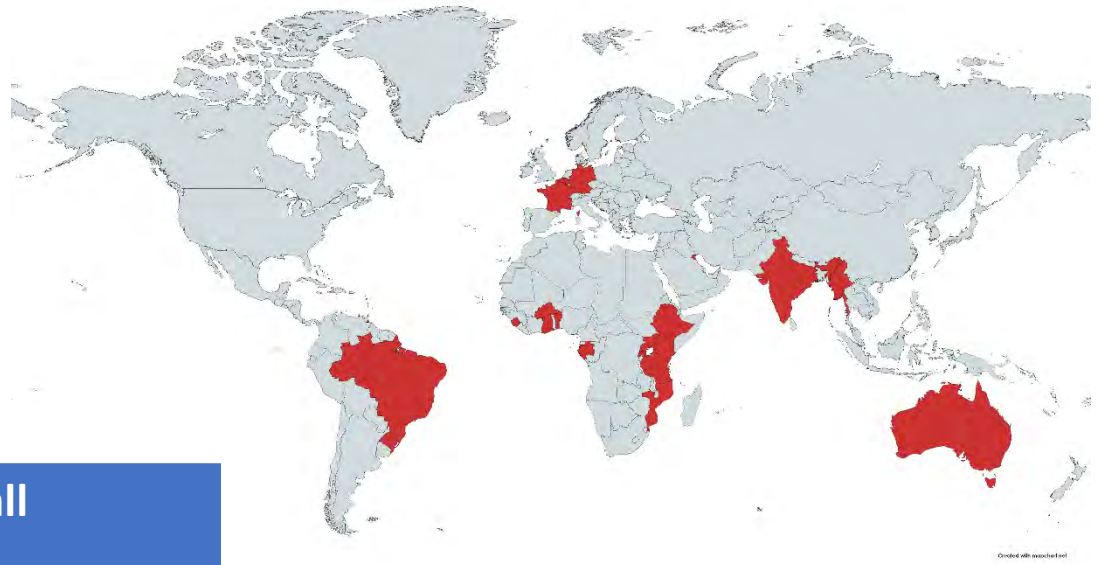
- Change when: prevalence false-negative HRP2 RDT results caused by pfhrp2-deleted parasites is > 5% - nationwide change is advised
- A threshold of 5% was selected because it somewhere around this point that the proportion of cases missed by HRP2 RDTs due to *pfhrp2* gene deletions may be greater than the proportion of cases that would be missed by less-sensitive pLDH-based RDTs

$$\text{Proportion of } P.\ falciparum \text{ cases with false-negative HRP2 RDT results due to } pfhrp2/3 \text{ deletions} = \frac{\#\text{ of confirmed falciparum patients with } pfhrp2/3 \text{ gene deletions and HRP2 RDT negative results}}{\#\text{ confirmed } P.\ falciparum \text{ cases (by either RDT or microscopy)}}$$

Comparing performance of HRP2 and pf-LDH RDTs

Literature review – 2011-2022

- Publications from 24 countries
- Micro vs PCR
- Symptomatic vs asymptomatic



Microscopy as the gold standard		PCR as the gold standard		Overall	
Delta Sensitivity %	**Delta Specificity %**	**Delta Sensitivity %**	**Delta Specificity %**	**Delta Sensitivity %**	**Delta Specificity %**
4.3	-8.8	12.9	1.3	8.0	-5.3
Taking out one study in Peru with a very high prevalence (26%) of *pfhrp2* gene deletions					
5.9		**-**		**9.0**	

Also reviewed unpublished studies using 'new' pf-LDH RDTs

Gap in performance shrinking

New tests – combination test lines (HRP2+pfLDH):
no need to consider 'trade offs'

Alternative non-exclusive HRP2 RDTs

to use where >5% of *falciparum* cases are missed by HRP2-RDTs due to *pfhrp2/3* deletions

Detect *P. falciparum*	• pan-LDH-only RDTs • combination of HRP2 and pf-LDH[a]
Detect and discriminate Pf from Pv or non-Pf infections	• Combination of pf-LDH, HRP2 and pan-LDH[a] • Combination of pf-LDH, HRP2 and pv-LDH[a] • Combination of pf-LDH, pv-LDH • Combination of pf-LDH and pan-LDH

[a] pf-LDH and HRP2 may be on the same test line or separate test lines

WHO prequalified with NOC

Product name	Product code	Manufacturer name
CareStart™ Malaria PAN (pLDH) Ag RDT	RMNM-02571	Access Bio, Inc.
CareStart™ Malaria Pf (HRP2/pLDH) Ag RDT	RMPM-0257	Access Bio, Inc.

Non WHO-prequalified tests meeting critical criteria (GF ERPD approved)

Product name	Product code	Manufacturer name
Biocredit Malaria AG Pf (pLDH)	C14RHG25, C14RHH25	Rapigen Inc.
Biocredit Malaria AG Pf (pLDH/HRP2)	C13RHG25, C13RHH25	Rapigen Inc.
Biocredit Malaria AG Pf/Pv (pLDH/pLDH)	C61RHG25, C61RHH25	Rapigen Inc.

Why surveillance instead of outright switch RDTs ?

Limited alternatives

- No WHO prequalified RDT combination tests
- ERPD approval - RapiGen – Biocredit has 3 pf-LDH based RDTs: 2 Pf-only and 1 Pf-Pv
  - New products in pipeline will have HRP2 and pf-LDH on same test line
- Do manufacturers have production capacity ?
- If manufacturer leaves the market or pivots to more lucrative RDTs what will happen?
- How are prices kept competitive ?

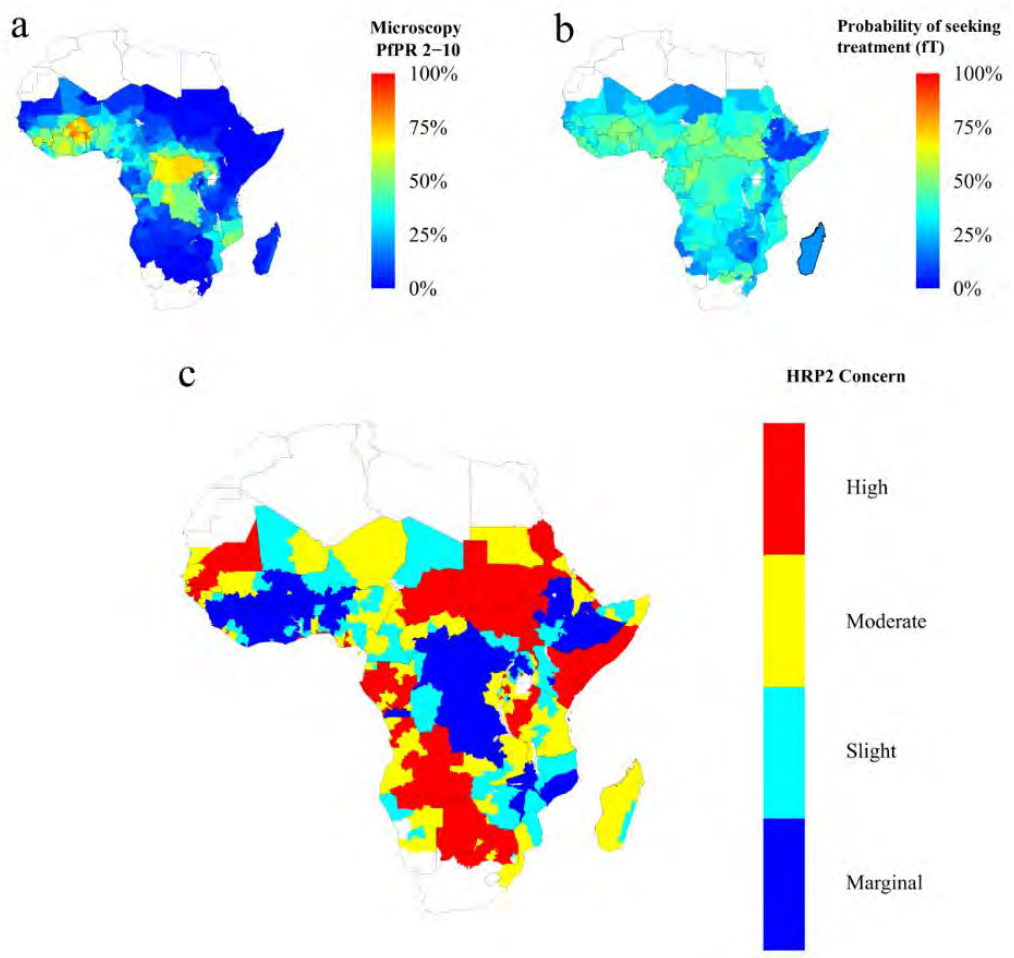
Procurement policies

- Most RDTs are purchased by donors who have strict procurement policies
- Sole sourcing must be justified

WHO risk based transition planning

- WHO planning risk based transition to non-exclusive HRP2 RDTs
  - Identify factors that put countries in Africa at increased risk of :
    - pfhrp2 deletions emerging
    - Pfhrp2 deletions having clinical impact
    - Pfhrp2 deletions spreading
  - Countries will be grouped by their risk and this will indicate where pf-LDH RDTs will be used first
  - Outputs critical for program planning; for procurers and manufacturers to forecast future demand

Predicted concern impact of *pfhrp2*-deleted mutants.



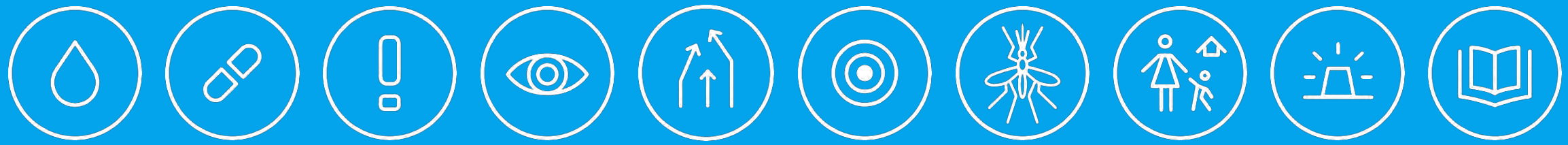
Source: Watson et al eLife 6:e25008

Acknowledgements

- Rebecca Thomson
- Oliver Watson
- Members of pfhrp2 gene deletion reference laboratory network

Update on antimalarial drug resistance in Africa

Update for the Malaria Policy Advisory Group
April 2023



Charlotte Rasmussen
Diagnosis, Medicine and Resistance Unit

Global **Malaria** Programme

World Health Organization

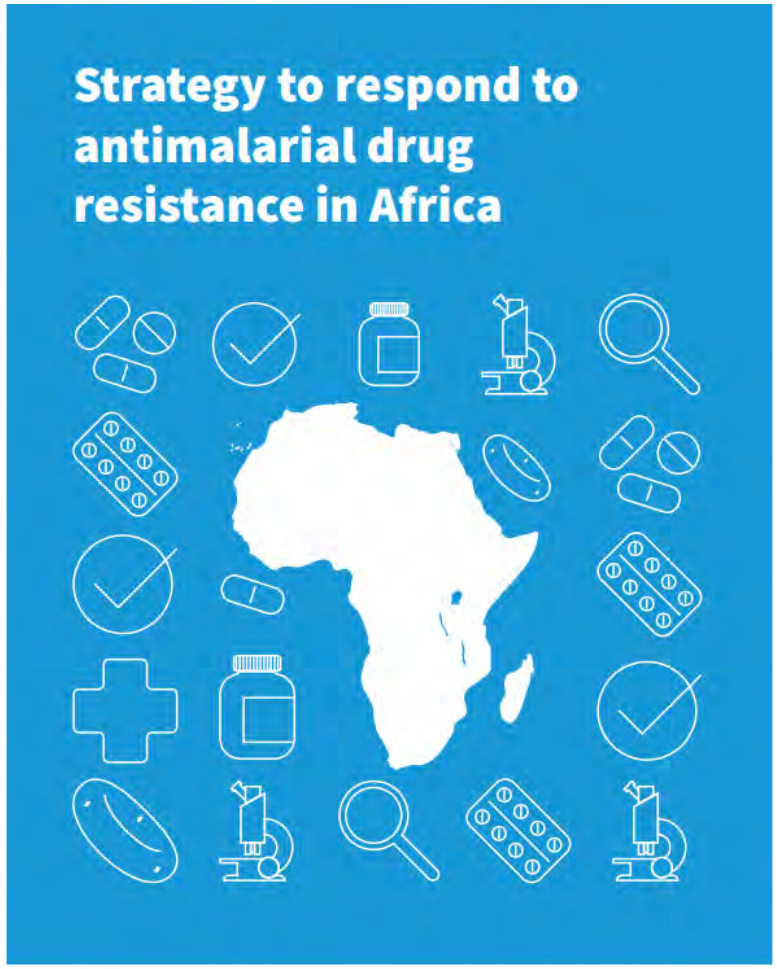
Outline of the presentation

- **Background**
  - **Development of the *Strategy to respond to antimalarial drug resistance in Africa***
  - **Status of resistance at launch of Strategy**
- **Resistance situation in Africa**
  - **New data since the launch of the Strategy**
- **Strategy implementation**
  - **Ongoing and planned WHO activities**

World Health Organization

Background

Context



- Launched November 2022
- Strategy developed due to:
  - Growing evidence of antimalarial drug resistance in Africa
  - Reliance on a few ACTs (artemether-lumefantrine 85% of courses procured by GF)
  - Potential devastating consequences of drug resistance in Africa
- Strategy development process included:
  - 5 technical working groups
  - Input from diversified panel of stakeholders
  - Two consultations
  - MPAG review

In early 2022, experts on drug resistance reviewed the data on antimalarial drug resistance in Africa | Situation still under control, but measures should be implemented to avoid ACT treatment failure

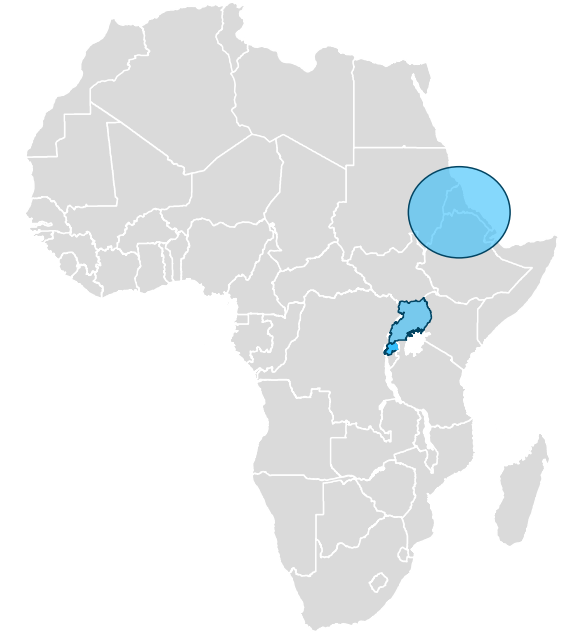
- Artemisinin partial resistance confirmed in Rwanda, Uganda, and Eritrea
- Lack of geographical coverage of data

- Fitness cost and parasite genetic background expected to play a key role in the ability of resistance to spread
- Spread potential likely to differ from the Greater Mekong Subregion

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

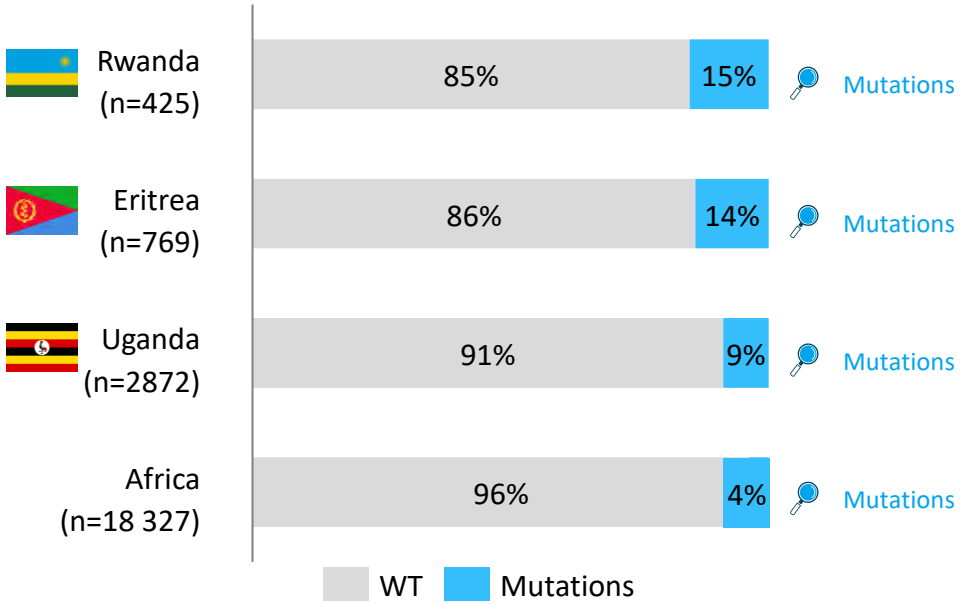
- Potential risk of issue underestimation by local stakeholders (≠ GMS)
- Communication and advocacy will play a key role

Conclusion of review in 2022: Molecular markers of artemisinin partial resistance found at high prevalence in 3 African countries



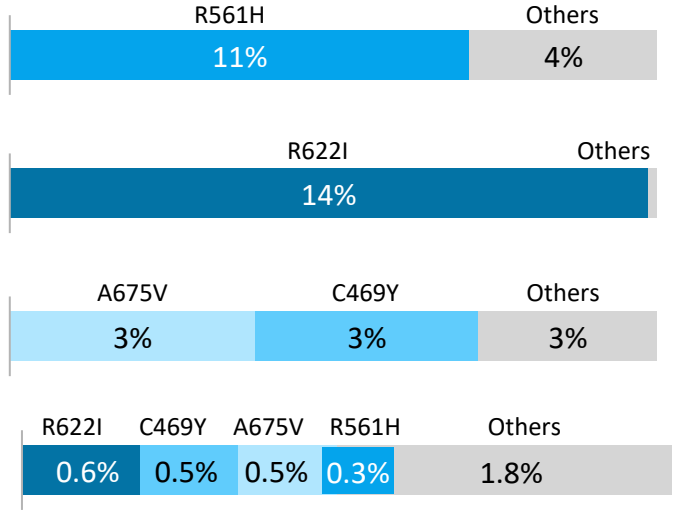
Countries with >5% K13 mutations

Wild Type still significantly dominant



n = number of samples collected

Various K13 mutants identified in different countries



Note: Wild Type refers to a phenotype, genotype, or gene that predominates in a natural population of parasites

Conclusion of review in 2022: So far, no confirmed partner drug resistance in Africa[1]

Partner drug	Current evidence	Molecular markers of resistance	Comments
Amodiaquine	• Treatment failure rates > 10% identified in two TES in Liberia in 2017-2018	To be validated in Africa	• IC_{50} affected in vitro by *Pfcrt* and *Pfmdr1* mutations but shift of IC_{50}s less significant than for chloroquine, and *Pfcrt* and *Pfmdr1* mutations cannot be considered amodiaquine resistance markers at present
Lumefantrine	• Treatment failure rates > 10% reported in 4 countries (Angola, Burkina Faso, Democratic Republic of Congo and Uganda) between 2009 and 2019 • Increased IC_{50} in Uganda	To be validated	• Studies show that lumefantrine selects for *Pfmdr1* mutations (N86) • Short half-life → potential misclassification of reinfections as recrudescences • Studies have used PCR-correction method based on microsatellites and a Bayesian algorithm rather than WHO recommended method • Concerns on quality of microscopy • In Burkina Faso, Uganda and DR Congo, AL treatment failures in sites where DP treatment failures were also found
Piperaquine	• Treatment failure rates > 10% reported in 3 countries (Burkina Faso, Uganda and Democratic Republic of Congo)	To be validated in Africa (Pfpm2–3 increased copy number and *Pfcrt* mutations validated in GMS and South America)	• Studies have used PCR-correction method based on microsatellites and a Bayesian algorithm • Concerns on quality of microscopy • In Burkina Faso, Uganda and DR Congo, AL treatment failures in sites where DP treatment failures were also found

[1] Excluding sulfadoxine-pyrimethamine

Resistance situation in Africa - Updates

K13 mutation R622I – evidence from the Horn of Africa countries

- **K13 mutation R622I detected in several countries in the Horn of Africa**
- **Only in Eritrea is there evidence of delayed parasite clearance in areas of high prevalence of R622I**
- **R622I has been detected in parasites with *Pfhrp2/3* deletions**

Eritrea

- TES from 2019 showed evidence of delayed clearance
- Samples from 2019 taken for *Pfhrp2/3* deletion testing showed 11.7% of sampled parasites carried R622I. R622I more frequent in parasites with *Pfhrp2/3*-deletion*
- Tentative data available from TES in 4 sites in 2022 with ASAQ. One site shows increasing proportion of patients being day 3+. Markers and PCR correction being done.

TES of artesunate-amodiaquine in Eritrea 2019 (PCR corrected, 28 days of follow-up)

	n	Day 3+ %	Treatment failure %	R622I %
Agordat	88	0	0	28.3
Tokombia	71	10.2	4.7	32.1
Shambuko	83	5.7	3.6	9.5
Guluj	94	1.1	2.2	24.4

*Mihreteab et al. *Plasmodium falciparum kelch13 mutations in Eritrea and associations with pfhrp2 and pfhrp3 deletions.* Abstract for ASTMH

R622I – evidence from the Horn of Africa countries

Ethiopia

- Samples collected 2018-19 for *Pfhrp2/3* surveillance showed 8.0% (n=609) with R622I (see figure and reference). R622I less frequent in parasites with *Pfhrp2/3* deletions
- One TES done in 2021 with AL >98% efficacy and no Day 3+ patients

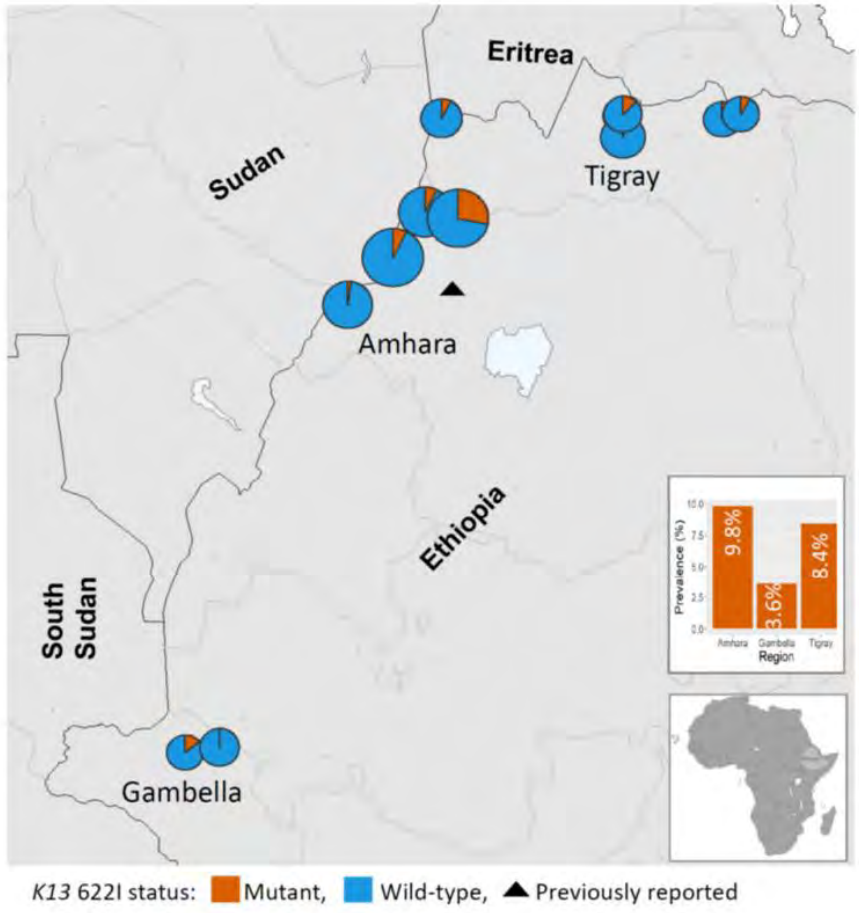
Sudan

- R622I detected in 2016/17 and 2019/20. Majority of R622I detected in one site close to border with Eritrea and Ethiopia (where 5% of samples carried R622I in 2019/20)

Somalia

- R622I detected in one case in 2017 and pooled analysis of samples from molecular markers surveillance in 2021/22

Prevalence of K13 622I in Ethiopia 2018-19



Fola et al. *Clonal spread of Plasmodium falciparum candidate artemisinin partial resistance Kelch13 622I mutation and co-occurrence with pfhrp2/3 deletions in Ethiopia.* Article in pre-print

K13 mutation R561H – Evidence from Rwanda and Tanzania

- **K13 mutation R561H had been found at high prevalence in studies with evidence of delayed clearance in Rwanda**
- **R561H has now also been detected in Tanzania in a study with a high proportion of patients with delayed clearance indicating the presence of artemisinin partial resistance in Tanzania**

Rwanda

- TES from 2018 showed evidence of delayed clearance and R561H as most prevalent K13 mutation
- New TES are underway

TES of artemether-lumefantrine in Rwanda 2018
(PCR corrected, 28 days of follow-up)

	n	Day 3+ %	Treatment failure %	R561H%
Rukara	66	13.6	5.8	19.5
Masaka	50	15.4	4	17.3
Muganza	76	0	2.6	1.2

Tanzania – recent data

- A TES was done in 2022 in Kagera close to Rwanda
- Study was initiated in this area based on molecular surveillance identifying R561H
- All patients kept as in-patients for the first 3 days
- The study found:
  - high proportion of parasites with R561H
  - high number of patients being day 3+ and slow parasite clearance time
- ACTs remain efficacious. However, in the AL group there was high reinfection rate

TES in Kagera 2022 (PCR corrected, preliminary data 28 days of follow-up)

	n	Day 3+ %	Treatment failure %	R561H%
AL	59	12.5	3.4	24.1 (28/116)
ASAQ	86	19.3	0	20.5 (18/88)

Uganda

- **Extensive molecular surveillance ongoing**
- **Data shows an evolving situation and foci where validated markers of artemisinin partial resistance are found in a majority of the parasites sampled***

- Four main mutations detected:
  - C469Y and A675V mutations increasing prevalence in northern Uganda since 2016, with gradual spread around the country by 2021-22
  - Additionally, C469F and R561H have been detected at high prevalence in a specific region of southwestern Uganda
  - Analysis of parasite background shows independent emergences with extensive recombination after emergence

*Conrad et al. *Evolution of artemisinin partial resistance in Ugandan malaria parasites.* Forthcoming article

Kenya

- **Some potentially concerning signs, but more quality data needed**

TES in Siaya County, Kenya 2016-2017, PCR corrected,

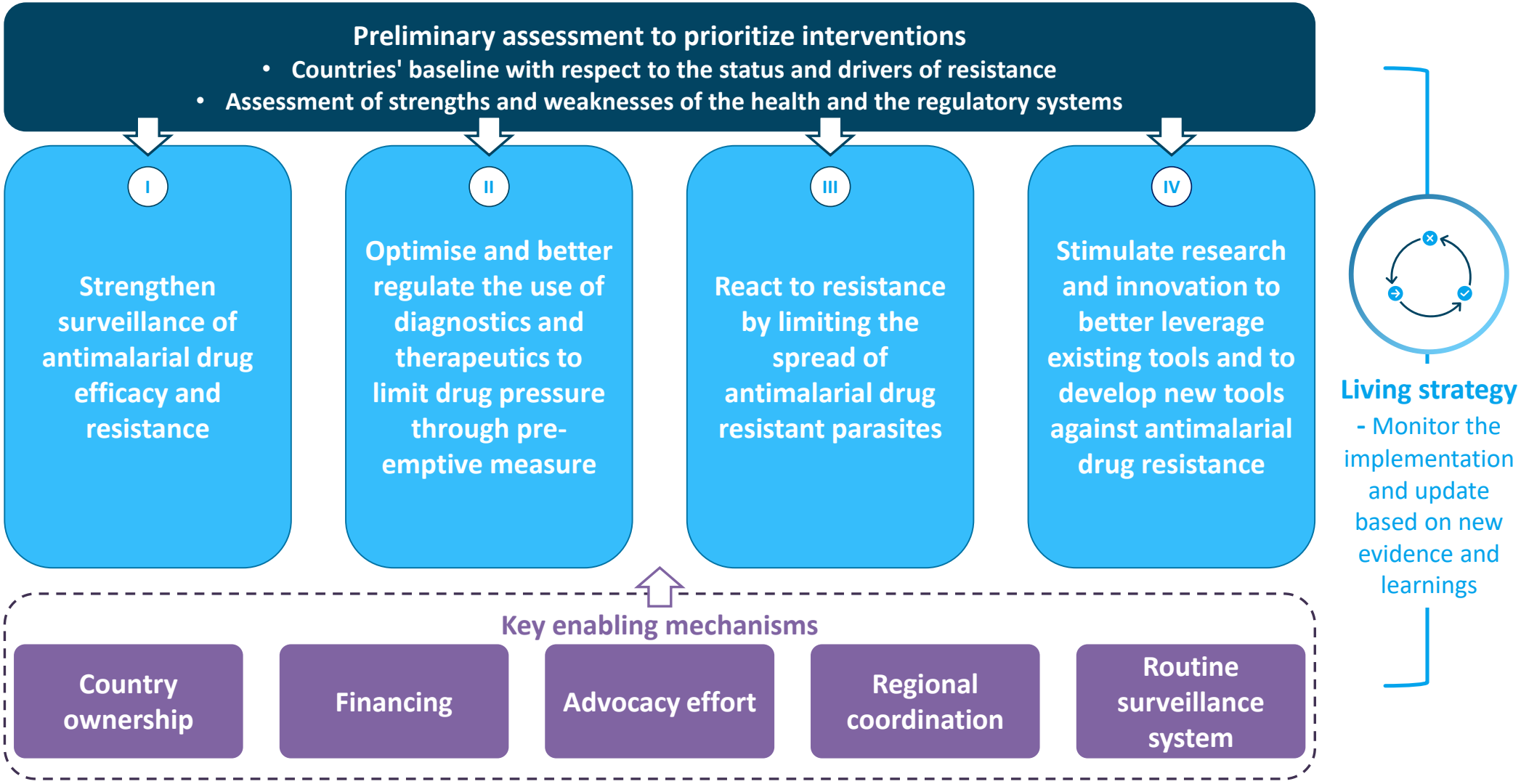
	Days of follow-up	n	Day 3+ %	Treatment failure %
AL	28	144	0.7	11.5
DP	42	115	0	7.0

- A TES was done in 2016 - 2017 in Siaya County, Kenya:
  - Data published in late 2022
  - The study found:
    - Low Day 3+
    - >10% failure rate for artemether-lumefantrine
  - Evening artemether-lumefantrine dose not supervised by study personal
- Another TES with AL conducted in nearby Kisii in 2021 reporting lower treatment failure rate (5.6%). Classification of recrudescence and reinfection not in accordance with WHO recommendations
  - Study identified different K13 mutations

Strategy implementation

Strategy to respond to antimalarial drug resistance in Africa

Interventions to mitigate risks and respond to resistance



Interventions by pillar

I Strengthen surveillance of antimalarial drug efficacy and resistance

1. Enhance capacity and capabilities to generate better quality and standardized data on antimalarial drug efficacy and parasite resistance
2. Increase coverage of surveillance systems for efficacy and resistance
3. Increase collection of additional, more detailed data at select sites
4. Improve data dissemination systems to facilitate a reactive and coordinated response to resistance data

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

1. Develop national treatment policies that promote deliberate use of existing treatments to prevent and react to the emergence and spread of resistance
2. Promote the availability of a diversified drug portfolio in countries
3. Prevent exposure to subtherapeutic drug levels driven by substandard and falsified ACTs by promoting drug quality
4. Remove non-recommended monotherapies and ensure that other monotherapies are used in accordance with WHO guidelines
5. Promote equitable access to quality drugs
6. Promote equitable distribution of and access to high-quality diagnostics to reduce drug pressure
7. Empower patients, HCWs and other stakeholders to make informed decisions, and provide appropriate treatment

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

1. Ensure optimal malaria vector control intervention coverage in priority areas
2. Leverage preventive measures to reduce transmission of antimalarial drug-resistant parasites
3. Limit the risk of increased transmission of resistant parasites
4. Strengthen cross-border collaboration on malaria activities to ensure coordinated resistance management

IV Stimulate research and innovation to better leverage existing tools and develop new tools against resistance

1. Identify innovative approaches using currently available drugs to delay the development and spread of resistance
2. Identify areas and populations where drug resistance is deemed more likely to develop and spread
3. Develop new treatments and diagnostics with the objective of delaying the emergence and spread of resistance
4. Identify and develop innovative tools to limit malaria infection and transmission
5. Conduct modelling and research to better understand and track resistance

Strategy implementation | Generate better quality and standardized data on antimalarial drug efficacy and parasite resistance

Ongoing and planned WHO activities

- Roster being created for consultants trained to support TES. This will help promote the adherence to WHO standard protocol and the generation of quality and standardized data
- Supporting quality of malaria microscopy including through ECAAM (malaria microscopy external competency assessment)
- External Quality Assessment scheme to be established for markers of resistance
  - Plan for a virtual expert meeting by July to discuss parameter of the EQA scheme (targets, materials)

Strategy implementation | Increase coverage of surveillance systems for efficacy and resistance & improving data dissemination

Ongoing and planned WHO activities

- Providing support to TES focusing on countries with no recent data
- Continually update the malaria threat maps
- Launched two dashboards for the collection of planned and ongoing studies and surveys of drug efficacy and resistance. This will help map gaps and direct resources
- Support expanded use of molecular surveillance
- WHO plans to reconvene subregional networks of antimalarial drug resistance and efficacy surveillance
  - Tentative plan for 2 meetings this year and 3 meetings early next year

https://www.who.int/teams/global-malaria-programme/surveillance/malaria-threats-map

Ongoing and planned WHO activities

- Discussion with countries for support for country specific response and plans
- WHO plan to convene a regional stakeholder meeting to align on intervention priorities to support countries responding to resistance
  - Tentative plan to convene in late August /Early September