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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.

Tuesday, 5 March 2024			
	Session 5	**Open**	
10:00 – 10:05	Welcome back by the Chairperson, MPAG	Professor Dyann Wirth MPAG Chairperson	
10:05-11:05	Strategy to respond to antimalarial drug resistance in Africa – updates and identification of needs Background | Presentation	Ms Charlotte Rasmussen Technical Officer, Diagnostics, Medicines & Resistance (virtual) MPAG subcommittee on drug resistance	**For decision**
	Session 6	**Open**	
11:05-11:35	Update on development of guidelines recommendations on tafenoquine, primaquine and near-patient G6PD diagnostic test to support radical cure of *P. vivax* Background | Presentation	Dr Andrea Bosman Unit Head, Diagnostics, Medicines & Resistance Dr Peter Olumese Medical Officer, Diagnostics, Medicines & Resistance (virtual) MPAG subcommittee on *P. vivax* malaria	**For advice**
	Session 7	**Open**	
12:00-13:00	Update on malaria elimination, including zoonotic malaria Background | Presentation	Mr Elkhan Gasimov Unit Head, Elimination MPAG subcommittee on Zoonotic malaria	**For information**
13:00-13:15	Closing remarks	Dr Jérôme Salomon, Assistant Director-General, UCN	

WHO/UCN/GMP/MPAG/2024.02

Malaria Policy Advisory Group Meeting

4–5 March 2024, Yaoundé, Cameroon
Background document for Session 5

Strategy to respond to antimalarial drug resistance in Africa

Updates and identification of needs

Mutations in *PfKelch13 (K13*) associated with delayed clearance post-treatment with artemisinin-containing regimens are on the rise in the Horn of Africa and Eastern Africa. In the Horn of Africa, the 622I mutation has been identified in multiple countries, including Eritrea, Ethiopia, Sudan and Somalia. Notably, the 622I mutation is present in parasites exhibiting hrp2/3 deletions, making them challenging to detect through conventional hrp2-based Rapid Diagnostic Tests (RDTs). In Uganda, various K13 mutations seem to be proliferating, with certain areas showing a prevalence of validated markers indicating partial resistance to artemisinin in the majority of sampled parasites. Meanwhile, in Rwanda, the 561H K13 mutation is spreading, although the 675V mutation is more prevalent in western Rwanda. The 561H mutation has also been identified in Tanzania, particularly in Kagera, near the Rwandan border. With a prevalence exceeding 5% of a validated marker for artemisinin partial resistance and evidence of delayed clearance, four African countries have now confirmed artemisinin partial resistance: Eritrea, Rwanda, Uganda and the United Republic of Tanzania. In Ethiopia and Sudan, artemisinin partial resistance is suspected as studies have detected >5% patients carrying K13 mutations (622I) validated to be associated with artemisinin partial resistance but delayed clearance has yet to be confirmed.

Since the latest MPAG meeting, several initiatives have been undertaken to advance the implementation of the *Strategy for the response to antimalarial drug resistance in Africa*. In November 2023, two regional meetings for Africa were held in Uganda. The first meeting was a regional stakeholder meeting for countries across Africa aimed at aligning intervention priorities to assist countries in addressing resistance. During this meeting, key drivers of antimalarial drug resistance were discussed along with necessary interventions to respond at the country level. The second meeting focused on surveillance of drug efficacy and resistance for countries in Eastern Africa and the Horn of Africa. The meeting provided technical updates on methods of surveillance of drug resistance and efficacy, and results of country studies on drug efficacy and resistance were shared, including plans for future studies and research. Additional activities conducted include an assessment evaluating the factors that may contribute to resistance in Rwanda and devising a strategy to address these challenges.

A crucial priority is ensuring the accuracy of data generated by therapeutic efficacy studies, which inform drug policy decisions. The *Strategy for the response to antimalarial drug resistance in Africa* highlights different interventions needed to support this. These include strengthening of subregional networks for monitoring efficacy and resistance, and enhancing capacity of national teams to generate better quality and standardized data on antimalarial drug efficacy and parasite resistance. Planned activities to support these objectives encompass updating the document "Methods for Surveillance of Antimalarial Drug Efficacy," serving as a reference for national programs and investigators assessing medicine efficacy. In addition, we plan to establish a roster of consultants trained to support Therapeutic Efficacy Studies (TES) in line with WHO study protocols. Furthermore, we plan to expand the ongoing WHO External Quality Assessment (EQA) scheme for malaria molecular diagnostics, managed by UK-NEQAS, to include molecular K13 markers of artemisinin resistance.

Strategy to respond to antimalarial drug resistance in Africa – updates and identification of needs

Update for MPAG, March 2024

Charlotte Rasmussen

Global Malaria Programme

World Health Organization

Outline of presentation

- Background
- Current information on antimalarial drug resistance – brief update
- Updates on WHO activities to operationalize the *Strategy to respond to antimalarial drug resistance in Africa*
- Planned activities

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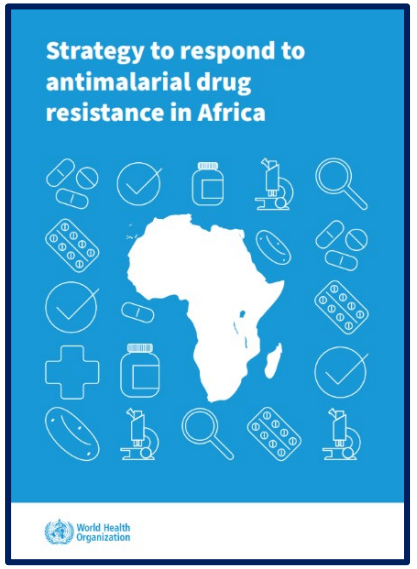
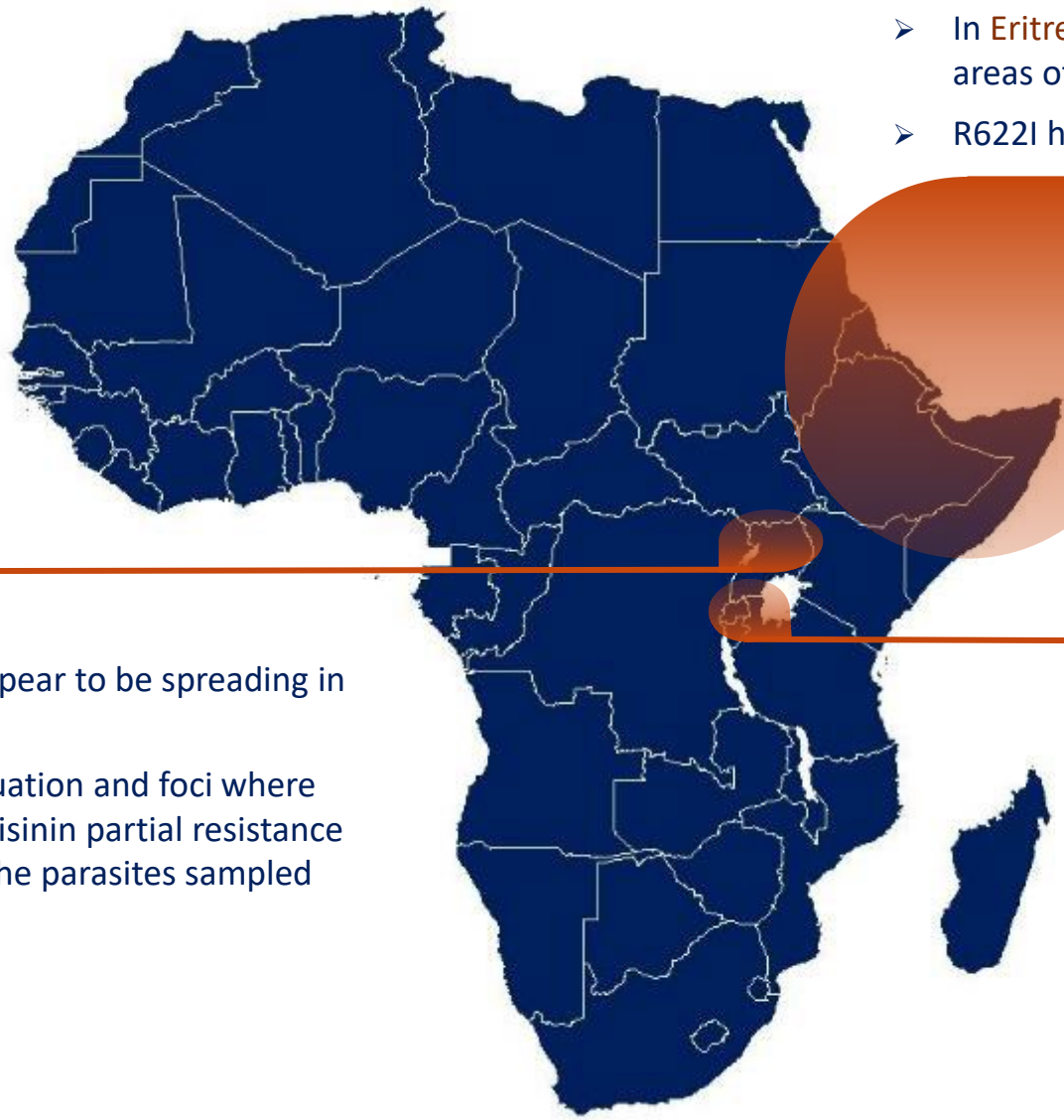
Background



- The **Strategy to respond to antimalarial drug resistance in Africa** was launched in November 2022 following an extensive process that included an MPAG review
- There is confirmed artemisinin partial resistance in 4 countries: Eritrea, Rwanda, Tanzania and Uganda. Artemisinin partial resistance is suspected in Ethiopia and Sudan
  - ➢ For **artemisinin partial resistance to be confirmed in a site**, quality evidence is needed on:
    - ✓ Presence of validated marker (≥5%) (*PfK13* mutations)
    - ✓ Evidence of delayed clearance (Day 3 + or parasites clearance half-life)

Current pattern of artemisinin partial resistance



Horn of Africa

- K13 mutation R622I detected in several countries in the Horn of Africa including Eritrea, Ethiopia, Sudan and Somalia
- In Eritrea, there is evidence of delayed parasite clearance in areas of high prevalence of R622I
- R622I has been detected in parasites with *Pfhrp2/3* deletions

Uganda

- Different K13 mutations appear to be spreading in Uganda
- Data shows an evolving situation and foci where validated markers of artemisinin partial resistance are found in a majority of the parasites sampled

Rwanda & Tanzania

- K13 mutation R561H had been found at high prevalence in studies with evidence of delayed clearance in Rwanda
- R561H has 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

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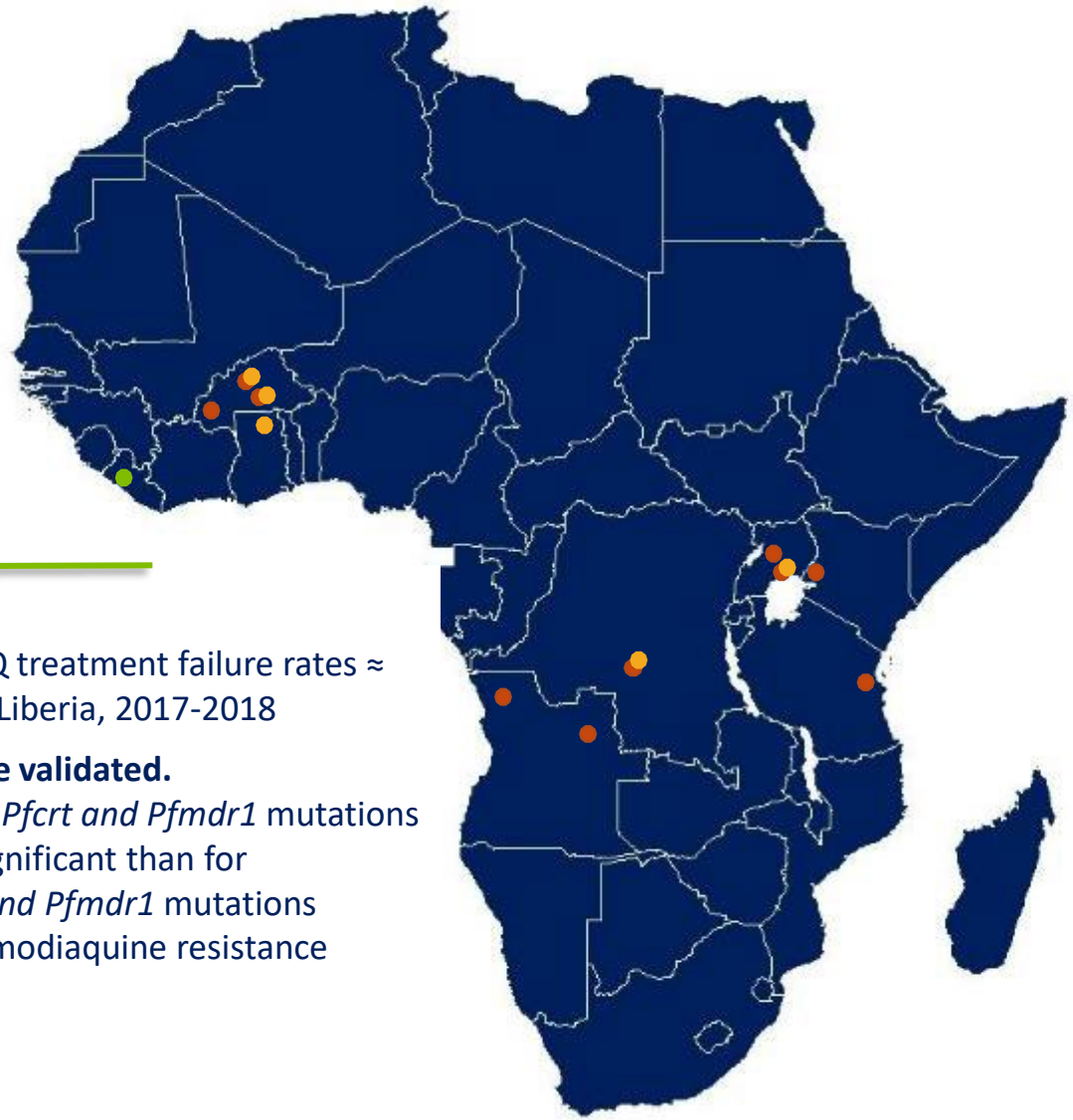
Scattered reports of high treatment failure but no confirmed partner drug resistance in Africa



TES with high failure rates from 2015 - 2023

Amodiaquine

- **Published studies:** ASAQ treatment failure rates ≈ 10% identified in TES in Liberia, 2017-2018
- **Molecular marker: To be validated.**
  IC50 affected in vitro by *Pfcrt and Pfmdr1* mutations but shift of IC50s less significant than for chloroquine, and *Pfcrt and Pfmdr1* mutations cannot be considered amodiaquine resistance markers at present

Piperaquine

- **Published studies:** DP treatment failure rates > 10% or ≈ 10% reported in Burkina Faso, the Democratic Republic of Congo, Uganda and Ghana
- **Molecular marker:** *Pfpm2–3* increased copy number and *Pfcrt* mutations validated in Asia and South America

Comments:

- Studies have used PCR-correction method a Bayesian algorithm & some concerns on quality of microscopy
- In Burkina Faso, Uganda and DR Congo, DP treatment failures in sites where AL treatment failures were also found in studies using Bayesian algorithms for PCR corrections. In Ghana, only one marker (msp2) used for PCR correction

Lumefantrine

- **Published studies:** AL treatment failure rates > 10% reported in Angola, Burkina Faso, Democratic Republic of Congo, Kenya. Since the launch of the strategy, additional reports of high treatment failure in Tanzania and Uganda
- Increased IC_{50} in Uganda
- **Molecular marker: To be validated**
  Studies show that lumefantrine selects for *Pfmdr1* N86

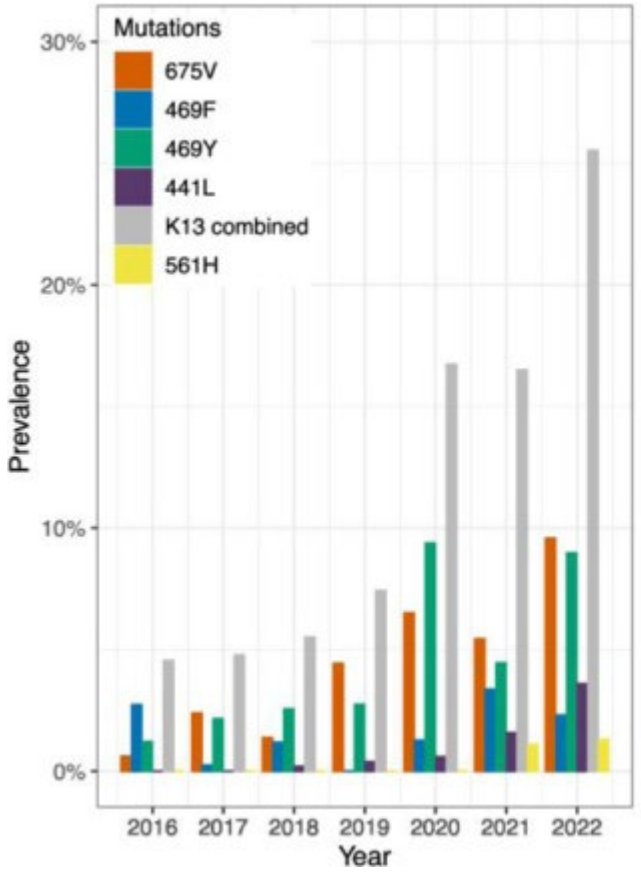
Comments: Different challenges with TES for AL

- High reinfection rates in some sites
- Short half-life -> potential misclassification of reinfections as recrudescences
- Some studies have used PCR-correction method based a Bayesian algorithm, some concerns on quality of microscopy, and some studies without supervision of evening dose

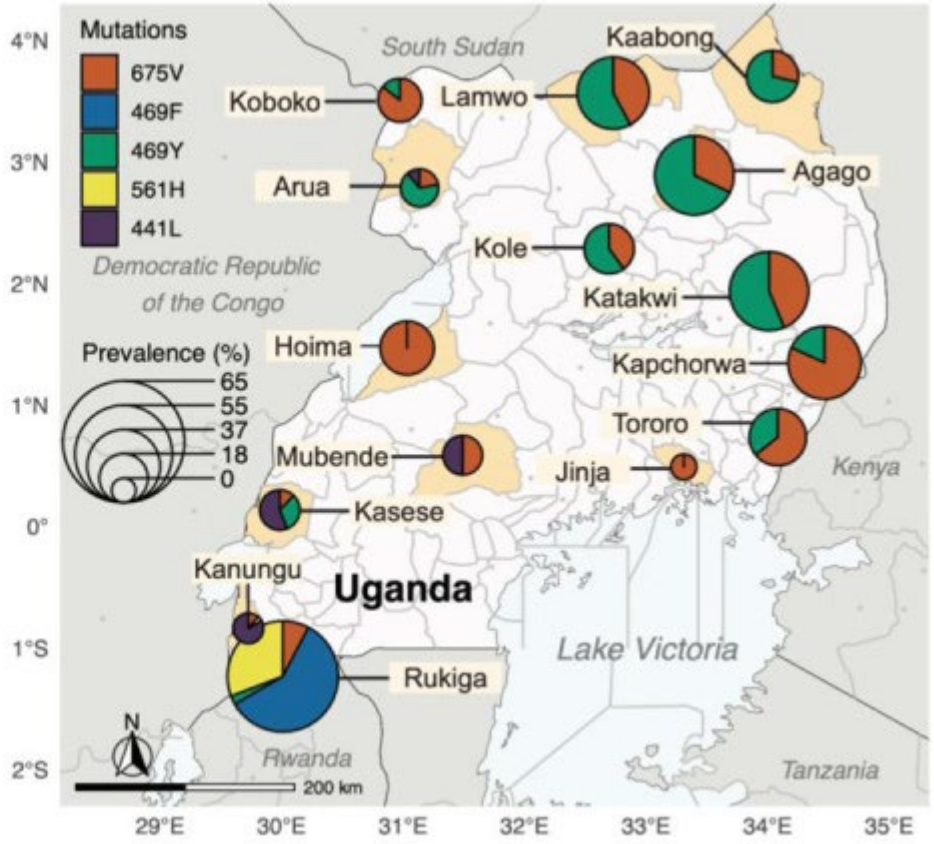
Uganda: Selection of *PfKelch13* mutations

- Some mutations in particular C469Y and C675V highly prevalent in northern Uganda while other mutations including R561H and C469F are more prevalent in southern Uganda.
- The prevalence of K13 mutations in Uganda has been rapidly increasing
- Analysis of the spread of the mutations indicate that the selection in Uganda is at a comparable rate to what was seen in the Greater Mekong subregion

Prevalence of the indicated mutations from 2016– 2022



The pie-charts represent the distribution and prevalence of mutations in 2022. Radii of pie charts proportional to the overall prevalence of the five K13 mutations at a site.



Meier-Scherling et al. Version 1. medRxiv. Preprint. 2024 Feb 4. doi: 10.1101/2024.02.03.24302209

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Updates on activities to operationalize the strategy to respond to antimalarial drug resistance in Africa

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Regional stakeholder and surveillance network meetings

WHO convened two meetings in Kampala, Uganda in November 2023:

- **7 & 8 November:** A regional stakeholder meeting to align on intervention priorities to support countries responding to resistance.
- **9 & 10 November:** Meeting on surveillance of drug efficacy and resistance for countries in Eastern Africa and the Horn of Africa.

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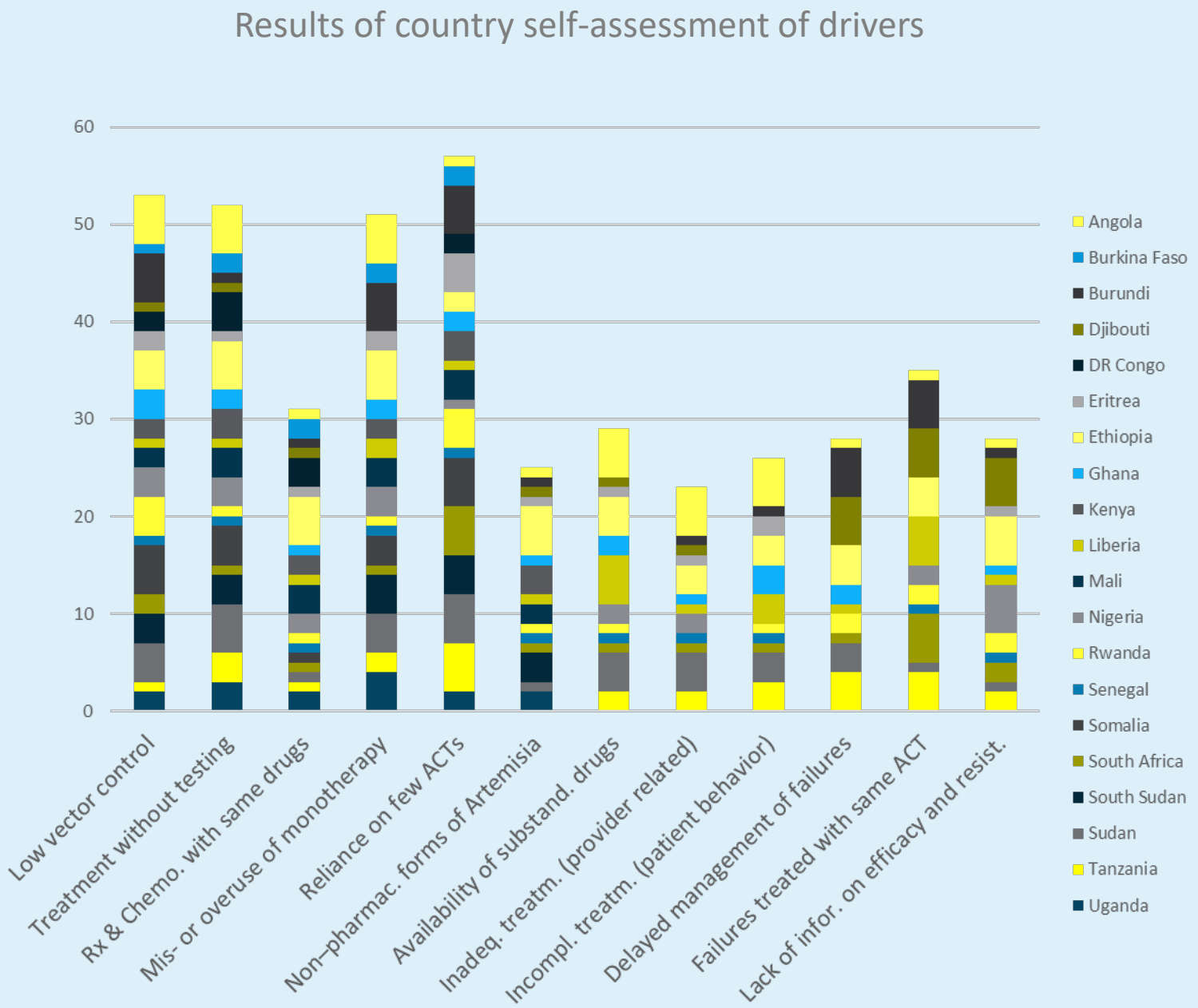
Regional stakeholder meeting

- Main aims were to present the strategy, discuss drives of drug resistance and activities needed in countries
- In preparation to the meeting, countries had been asked to rate different potential drivers in their country using a survey tool developed by WHO/GMP to help inform the discussion



Conclusions from regional stakeholder meeting

- Strengthen and support subregional networks to generate data for drug policy
- Support in-country consultations to develop and implement national plans of action to respond to the threat of drug resistance
- Develop a platform for coordinated action of all stakeholders in the fight against antimalarial drug resistance
- Mobilize resources to support the national action plans on antimalarial drug resistance

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Network meeting on surveillance of drug efficacy and resistance for countries in Eastern Africa and the Horn of Africa

- Main aims were to provide technical updates, present country data, discuss gaps and plan for further studies
- There are large gaps in data availability, as well as in capacities and funding to generate data
- The proceedings included group work to develop recommendations to strengthen efficacy and resistance surveillance

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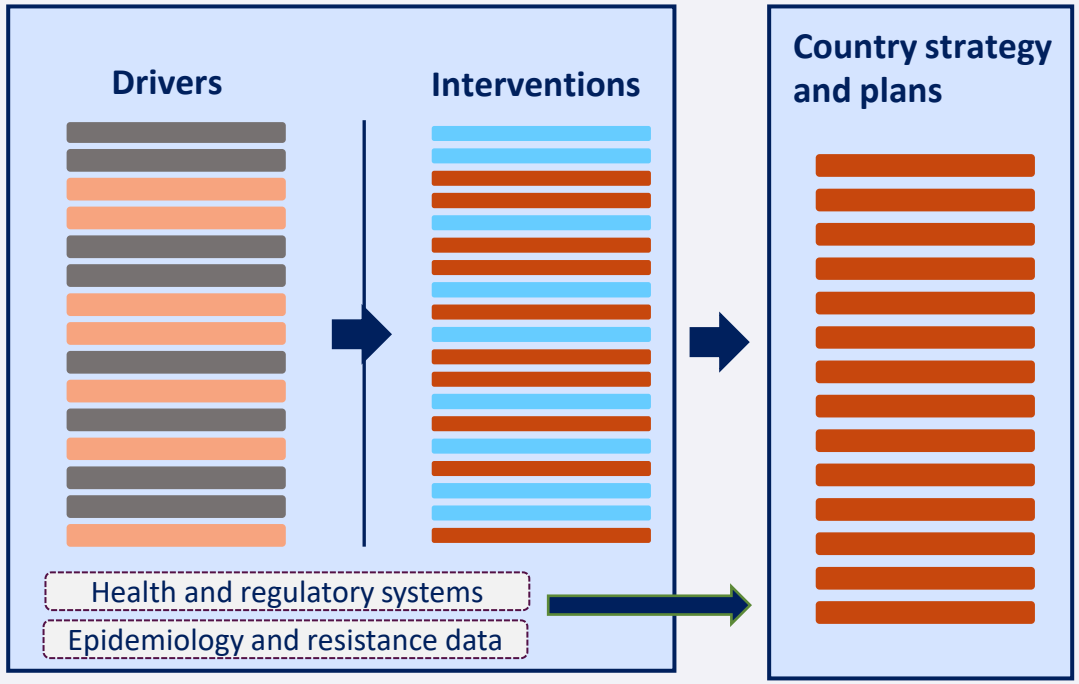
Recommendations from group work

- **Revise the 2009 TES manual for surveillance of antimalarial drug efficacy and resistance including digitalizing data collection tools**
- **TES should be a NMCP/MOH led activity for better ownership, implementation and sustainability**
- Factor TES in for every individual country NSP for securing funding
- Build capacity of NMCP on molecular surveillance
- Assure TES quality, especially in microscopy, through continued training and ECAMM certification of the study microscopists
- Quality-assured materials for the TES (including filter papers, the medicines etc.) should be centrally resourced (from WHO)
- **Support countries for QC/QA and data validation to generate reliable TES data to inform treatment policy**
- Continue to build on the existing networks and strengthen their collaboration for experience sharing
- **Regional coordination and collaboration for data and knowledge sharing**

Strategy to respond to antimalarial drug resistance – country assessment

- To help prioritize interventions in the local context, the strategy proposes country assessments looking at factors that could drive resistance in a given context, and the systems in place and data available
- This assessment will inform country specific strategies and plans



Country assessment: Rwanda

- **Objective:** to develop a context specific strategy to respond to the threat and emergence of partial artemisinin and partner drug resistance
- **Two phases:**
  - Initial assessment of current situation
  - Development of country specific strategy
- Assessment was done from August 2023 and assessment draft presented in Uganda meeting in November 2023.
- Assessment consists of **three sections:**
  - Status of resistance and epidemiology
  - Drivers of resistance
  - Review of health and regulatory systems

Country assessment in Rwanda – some findings

Artemisinin partial resistance

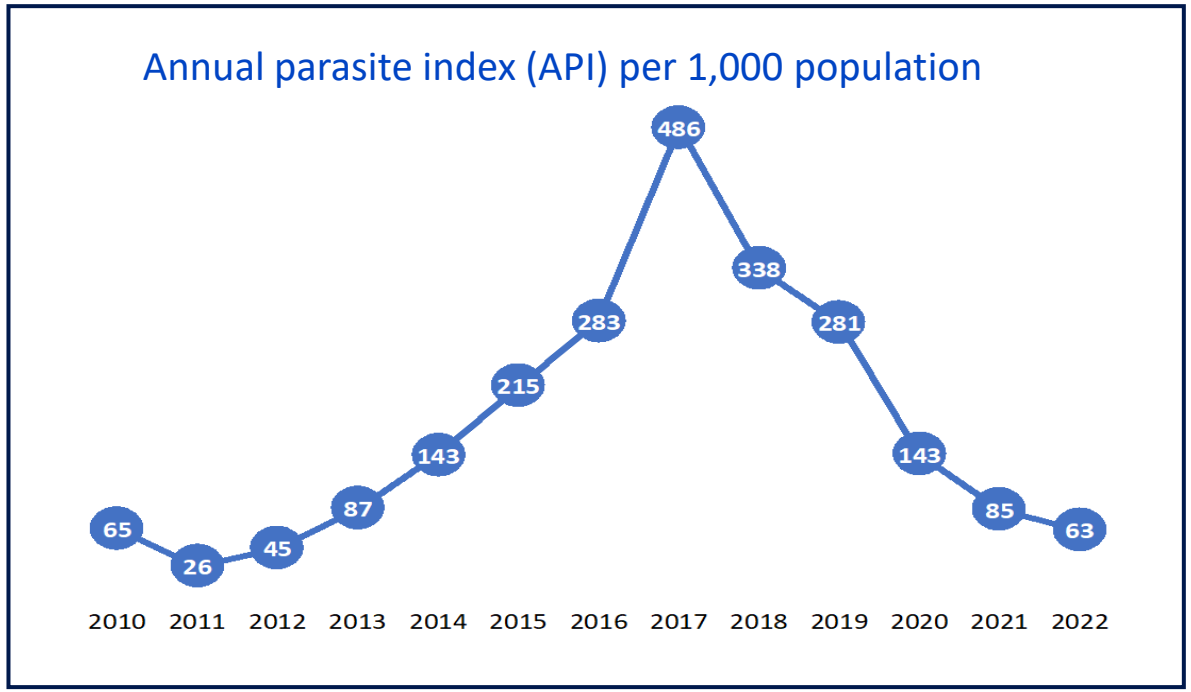
In 2022, **prevalence of *PfK13 R561H* mutation above 20% is well documented** in areas close to the Rwanda borders in South-West Uganda and North-West Tanzania. This mutation was first detected in a Chinese worker in 2011 and later isolated in samples of the 2014-2015 DHS in the South-East close to the Tanzanian border.

Province	District	Site	Year	N	Pfkelch13 R561H (%)	N	Day 3 + (%)	Failure PP (%)
Kigali	Kicukiro	Masaka	2018	52	17	50	15	3
Kigali	**Kigali**	**Kigali**	**2018**	**73**	**22**	**17**	**28**	**6**
Eastern	Kayonza	Rukara	2018	82	19	69	14	6

The latest TES results from 2021-23 are still being analyzed

Shifting levels of transmission

Very low transmission levels around 2010 with low population immunity followed by 5 years of fast increased transmission in 3 provinces were **favorable conditions for emergence and early expansion** of artemisinin partial resistance.



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Findings in the Rwanda assessment

Access to services
"….access to health services for malaria patients is facilitated by mechanisms to mitigate most of the usual socio economic and geographical barriers. …. **but some gaps still exist. "**

Coverage of parasitological diagnosis
" ….ABER has been maintained at high levels over the last years (40 per 100 population in 2022) despite the recorded fast decreasing transmission."

Adherence to treatment guidelines
"…almost all confirmed malaria cases receive the recommended AL first line treatment…. "

Quality of antimalarials
"….Regulation of the importation and marketing of antimalarials is managed by a stringent independent regulatory agency….The risk of illegal marketing of substandard or falsified drugs in shops is likely to be minimal….**The magnitude of the use of non-pharmaceutical forms of Artemisia by some communities is unknown and should be explored.**"

Management of failures
"…**unsuccessful procurement of quality assured DHA-PQ. As a result, patients with a treatment failure are likely to be repeatedly treated with AL. "**

Population movements and migrations
"…could not find evidence that population movements from neighboring countries could be a significant source of resistant parasites…."

Adaptation of national policy
"…new 2023 edition of the national guidelines now recommend 3 different ACTs to be potentially used as first-line treatment."

Assessment to strategy

- The findings from the assessment have been used to priorities interventions based on the *Strategy to respond to antimalarial drug resistance in Africa*
- The national strategy covers topics from need for further studies to options for treatment
- The strategy is currently under review in Rwanda

Planned activities

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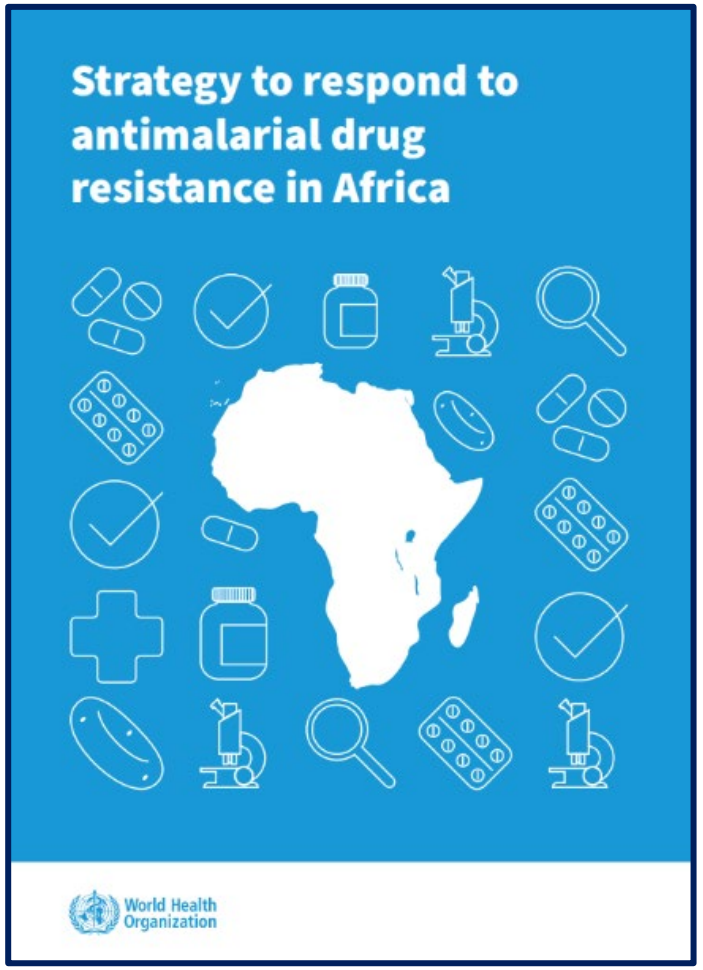
Key challenges



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Complex partner landscape - increasing the risk for both overlaps, and areas and countries not receiving needed support

Still gaps in data, delays in data sharing, and sometimes uncertainty regarding the quality and reliability of the data generated

Technical areas where there are uncertainty regarding the best way forward

Current partner landscape

- **Support for the efficacy and resistance surveillance**
  - **PMI**: Support for TES in PMI supported countries and the PARMA network
  - **The Global Fund:** Financial support for TES in some country grants
  - **Various partners:** Funding provided including for TES via partners
  - **WHO:** Normative guidance, technical support and, in the past, financial support to countries where no other funding is available or where there is an urgent need to do additional TES
- **Support for the response to resistance**
  - **CHAI:** Support for country assessments in five countries
  - **PATH:** Support for country assessments in five countries
  - **MARC SE:** Support for country work and analyses (EDCTP funded)
  - **WHO:** Continual technical support and guidance

PMI supported countries

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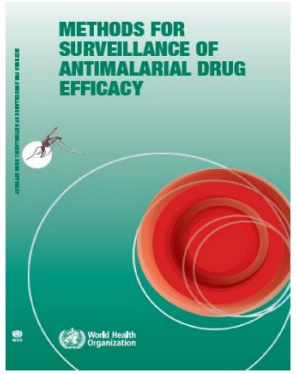
Key GMP planned initiatives

To help improve the quality and sharing of data generated on efficacy and resistance, following activities are planned:



- **Update of the document "Methods for Surveillance of Antimalarial Drug Efficacy".** Serves as a reference for national programmes and investigators involved in assessing the efficacy of medicines. Updates are needed due to changes in recommendations, updated guidance on genotyping, study monitoring, and expanded guidance on quality control.
- **Roster of consultants trained to support TES.** To safeguard the proper implementation of TES in accordance with the study protocol, it is essential to have a roster of consultants capable to ensure quality TES through initial training and site monitoring.

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Key GMP planned initiatives (Cont.)

- **Piloting an External Quality Assessment scheme for molecular markers of drug resistance.** In July 2023, an expert consultation organized by WHO highlighted the need for an expanded EQA scheme, that included molecular markers of drug resistance, starting with *PfKelch13*. The goal for 2024 is to pilot such a scheme with a subset of interested laboratories.
- **The Malaria Threat Maps**: Continue to develop the Malaria Threat Maps to map data availability and gaps, and facilitate data sharing
- **Support regional networks for surveillance of drug efficacy and resistance** (depending on resources): Networks can play a key role in the generation of quality data and data sharing
- **Support for data analyses and data validation from studies as needed**

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WHO consultation on MFT (multiple first-line treatments)

- GMP will convene a WHO Technical Consultation on Multiple first-line treatments (MFTs) as a face-to-face meeting **in Geneva in mid-May 2024**
- The key objective of the consultation is to **generate evidence-based guidance on MFT as potential interventions to reduce antimalarial drug resistance**
- **The consultation will focus on:**
  - Definition of MFTs
  - Review evidence on impact of MFTs on antimalarial drug resistance
  - Review implications for policy and implementation of MFTs
  - Generate MFT guidance for NMP and partners, including recommendations for research

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Example of drug interventions modelled

(Zupko et al. Nat Med 29, 2775–2784 (2023))

Table 2 | Summary of the primary drug therapy interventions examined using the simulation

Intervention	Therapy
AL extension	AL (4-d course)
	AL (5-d course)
	AL (3-d course on days 0, 1 and 2) followed up with a second course on days 7, 8 and 9; labeled 'AL789'
AL replacement	ASAQ
	DHA–PPQ
MFTs	ASAQ (75%)+DHA–PPQ (25%)
	ASAQ (50%)+DHA–PPQ (50%)
	ASAQ (25%)+DHA–PPQ (75%)
	AL (75%)+ASAQ (25%)
	AL (50%)+ASAQ (50%)
	AL (25%)+ASAQ (75%)
	AL (75%)+DHA–PPQ (25%)
	AL (50%)+DHA–PPQ (50%)
	AL (25%)+DHA–PPQ (75%)
Sequential courses of 3-d ACT	AL on days 0, 1 and 2, followed by ASAQ on days 3, 4 and 5; labeled 'AL, then ASAQ345'
	AL on days 0, 1 and 2, followed by DHA–PPQ on days 3, 4 and 5
	ASAQ on days 0, 1 and 2, followed by AL on days 3, 4 and 5
	DHA–PPQ on days 0, 1 and 2, followed by AL on days 3, 4 and 5
	AL on days 0, 1 and 2, followed by ASAQ on days 7, 8 and 9; labeled 'AL, then ASAQ789'
	AL on days 0, 1 and 2, followed by DHA–PPQ on days 7, 8 and 9
	ASAQ on days 0, 1 and 2, followed by AL on days 7, 8 and 9
	DHA–PPQ on days 0, 1 and 2, followed by AL on days 7, 8 and 9
Switch to DHA–PPQ, followed by switch to MFT	DHA–PPQ (3 years), then AL (50%)+ASAQ (50%)
	DHA–PPQ (3 years), then 5-d course of AL (50%)+ASAQ (50%)
Triple ACT (TACT)	ALAQ
	ASMQ–PPQ

The table above shows the non-standardization or understanding of what is MFTs and its potential application

Thank you

For more information, please contact:
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Malaria Policy Advisory Group Meeting

4–5 March 2024, Yaoundé, Cameroon
Background document for Session 6

World Health Organization

Update on development of guidelines recommendations on tafenoquine, primaquine and near-patient G6PD diagnostic test to support radical cure of *P. vivax*

The Global Malaria Programme has convened two Guidelines Development Group (GDG) meetings to develop guidelines recommendations on the use of 8-aminiquinolines and near-patient G6PD tests for radical cure of *P. vivax* and *P. ovale*. On 14–15 November 2023, the GDG on malaria chemotherapy reviewed the evidence and generated recommendations on tafenoquine and primaquine as anti-relapse therapy. For primaquine this included a review of the standard WHO recommendations of primaquine daily for 14 days as well as the recommendation on high dose primaquine for 7-days, and the safety of primaquine administration to infants aged < 6 months and women breastfeeding infants aged < 6 months. On 30 November–1 December 2023, the GDG on malaria diagnostics reviewed the evidence to recommendations on near-patient diagnostic tests for G6PD deficiency. Since then the systematic review of G6PD tests has been further refined and cost-effectiveness analysis completed and these have informed the second meeting of the GDG on G6PD tests, convened on 26 and 29 February 2024. The GDG on G6PD developed recommendations on the use of qualitative and semi-quantitative G6PD tests, comparing diagnostic accuracy with quantitative spectrophotometric G6PD assays as reference test, at the critical thresholds critical to inform administration of 8-aminoquinolines, i.e. < 30%, 30–70%, and > 70% G6PD activity.

The recommendations on single low-dose primaquine to reduce the transmissibility of *P. falciparum* were not reviewed by the GDG as the current WHO guidelines already provides recommendations for areas of low transmission to reduce the transmissibility of treated falciparum malaria infections as well as for areas with artemisinin-resistant falciparum malaria, that a single low dose of primaquine of 0.25 mg/kg should be given with an artemisinin-based combination therapy (ACT) to patients with *P. falciparum* malaria (WHO guidelines for malaria, pp 109 and 208, 2023 https://www.who.int/teams/global-malaria-programme/guidelines-for-malaria, accessed on 22 February 2024).

Following the elaboration of the new guidelines for malaria sections, the inputs from the external review group and the submission to the WHO Guidelines Review Committee, the plan is to finalise new recommendations on the use of tafenoquine, primaquine and near-patient G6PD tests by April 2024. In line with the "Master plan for developing recommendations on the use of tafenoquine and companion quantitative point-of-care G6PD in vitro diagnostics" (WHO internal document, 2019) these new recommendation will be released when near-patient G6PD tests will be included in the WHO prequalification lists for in-vitro diagnostics. The aim of the master plan is to coordinate "one WHO" to the generation of WHO guidelines recommendations on the use of tafenoquine and companion G6PD point-of-care tests *(3)*; the WHO prequalification lists of finished pharmaceutical products and in vitro diagnostics; and the Model Lists of Essential Medicines and Essential In Vitro Diagnostics.

Following the inclusion tafenoquine and near-patient G6PD tests in the WHO prequalification lists and the release of the new guidelines, GMP will convene a Technical Consultation to develop a field guide on the case management of *P. vivax*, providing practical guidance to support the implementation of the new WHO recommendations on 8 amino-quinolines and near-patients G6PD tests.

Update on development of guidelines recommendations on tafenoquine, primaquine and near-patient G6PD diagnostic test to support radical cure of *P. vivax*

Dr Andrea Bosman and Dr Peter Olumese, GMP Diagnostic, Medicines and Resistance Unit

25th meeting of the WHO Malaria Policy Advisory Group

4 – 5 March 2024

World Health Organization

Outline of the presentation

- Guidelines recommendations and prequalification
- Tafenoquine and primaquine
  - Process & timelines for guidelines recommendations
  - Drug regimens reviewed
  - PICO questions and systematic reviews
- Near-patient G6PD tests
  - Process & timelines for guidelines recommendations
  - PIRT questions and tests reviewed
- Plans to develop field guide on case management of P. vivax malaria
- Coming soon: PPC of tests for detecting the risk of P. vivax relapses

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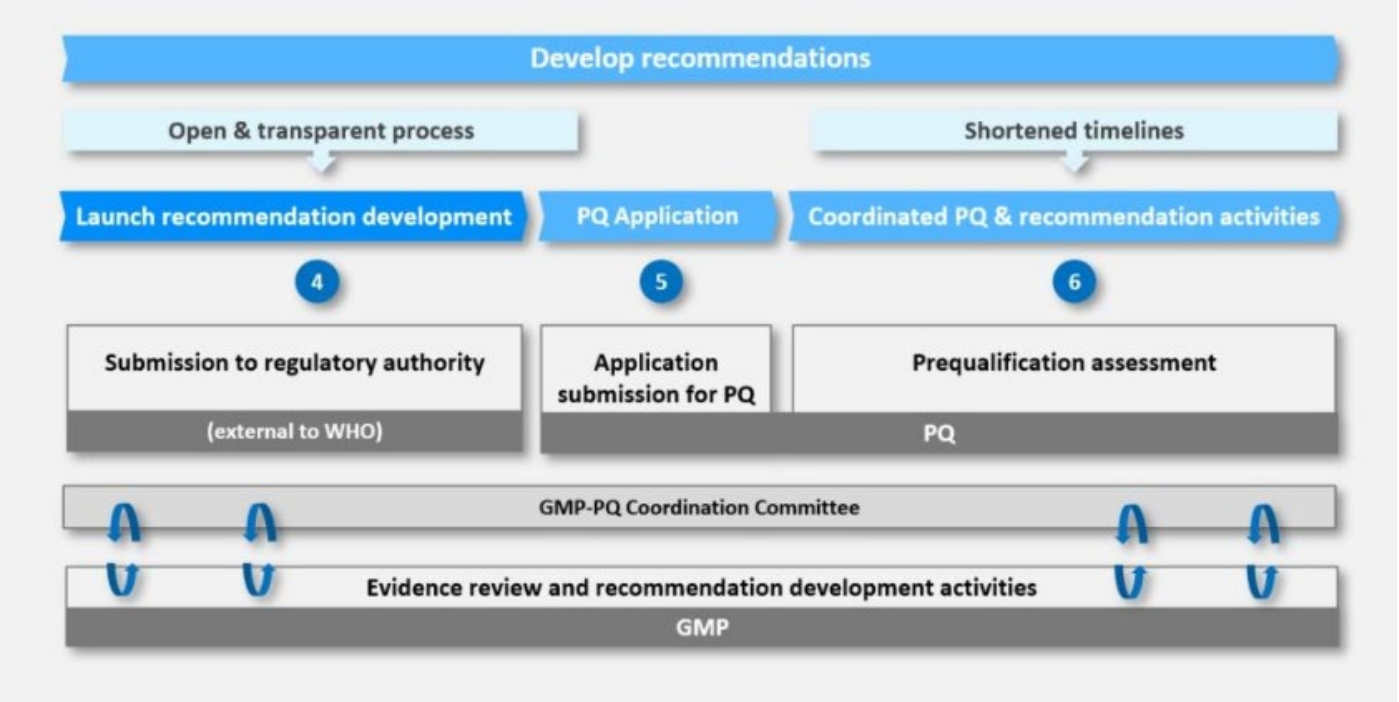
Reminder…

- Based on the review of development of WHO malaria recommendations, in Nov 2019 GMP and the Department of Essential Medicines Health Products developed and Master Plan for Developing Recommendations on the Use of Tafenoquine and companion Quantitative Point-of-Care G6PD In Vitro Diagnostic(s)
- Aim to coordinate activities as 'one WHO' on recommendations on the use of tafenoquine and companion G6PD POCT as part of:
  - WHO Guidelines for Malaria,
  - WHO prequalification list of prequalified finished pharmaceutical products and in-vitro diagnostics
  - Model List of essential medicines and essential diagnostics.



https://www.who.int/teams/global-malaria-programme/guideline-development-process/recommendation-pathway

World Health Organization

Timelines for WHO recommendations on tafenoquine and primaquine

14-15 Nov 2023

GDG meeting:
review evidence,
formulation
of recommendations

Systematic reviews on
- **Tafenoquine**
- **Primaquine**

Feasibility study (Brazil)

Nov - Dec 2023

Recommendations drafted by GDG

Jan – Feb 2024

Editing,
internal review

Mar 2024

External review group

April 2024

Guidelines Review Committee

May 2024

Publication of recommendations on the use of tafenoquine and primaquine, if positive guidelines recommendations and PQ listing of quantitative near-patient G6PD tests

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8-aminoquinoline anti-relapse treatment dose regimens

Primaquine	Total	Weekly	Adult dose
Weekly regimen	mg/kg	mg/kg	mg
Dose 8 weeks	6.0	0.75	45 mg/week

Primaquine	Total	Daily	Adult dose
Daily regimen	mg/kg	mg/kg	mg
Low Dose 14 days	3.5	0.25	15 mg/day
Low Dose 7 days	3.5	0.5	30 mg/day
High Dose 14 days	7.0	0.5	30 mg/day
High Dose 7 days	7.0	1.0	60 mg/day

Tafenoquine	Total	Adult dose
	mg/kg	mg
Single dose	5.0	300 mg

Reviewed by GDG

Low

Moderate

High

World Health Organization

PICO question on tafenoquine anti-relapse therapy

Topic	PICO Question	Inclusion criteria				Critical & important Outcomes	Current status
		Studies	Participants	Intervention	Control		
Single-dose tafenoquine for radical cure of *Plasmodium vivax* malaria (to be recommended with a near-patient quantitative G6PD test)	Is single dose tafenoquine an alternative to standard dose primaquine for preventing relapses in patients with a G6PD activity of >70% who have received chloroquine therapy for acute *P. vivax* infection?	All eligible studies Including Phase IV studies for safety review	Patients with a G6PD activity of >70% treated for *P. vivax* malaria with chloroquine	Single dose tafenoquine (300mg)	Standard Primaquine treatment 0.25mg/kg daily for 14days or 0.5mg/kg daily for 7 days or 0.5mg/kg daily for 14 days or placebo	*P. vivax* relapse defined as reappearance of *P. vivax* parasitemia <6 months after treatment Safety of tafenoquine	New evidence review

World Health Organization

PICO question on primaquine anti-relapse therapy

Topic	PICO Question	Inclusion criteria				Critical & important Outcomes	Current status	Other considerations/ questions
		Studies	Participants	Intervention	Control			
Anti relapse treatment: Primaquine efficacy	Is high total dose primaquine (7.0 mg/kg) more efficacious than low total dose primaquine (3.5 mg/kg) at preventing relapses to day 180 in patients with uncomplicated vivax malaria?	Clinical trials and cohort studies	Malaria patients with *P. vivax* uncomplicated disease	PQ at high total dose (7.0 mg/kg)	PQ at standard/ low total dose (3.5 mg/kg)	First vivax recurrence by day 180	Update evidence review	Impact of duration of treatment Impact by geographic region Impact of schizontocidal drug Age <5 years
Anti-relapse treatment: Primaquine – tolerability and safety	Does intermediate (0.5 mg/kg) or high (1.0 mg/kg) daily dose primaquine cause more gastrointestinal symptoms or adverse haemoglobin changes compared to low (0.25 mg/kg) daily dose primaquine?	Clinical trials and prospective cohort studies.	Malaria patients in vivax endemic regions with uncomplicated disease and G6PD activity >=30%.	Daily PQ dose of 0.5 mg/kg Daily primaquine dose 1.0 mg/kg	Daily PQ of 0.25 mg/kg	Vomiting or diarrhoea or anorexia on Days 2-3 and 5-7 Vomiting within 1st hour Hb change on Days 2-3 Hb drop >25% to <7 g/dL on Days 1-13	Update evidence review	G6PD activity: >=30%, 30-<70% and >=70% Sex Food intake GI symptoms in relation to age

PICO question on primaquine

Topic	PICO Question	Inclusion criteria				Critical & important Outcomes	Current status	Other considerations/ questions
		Studies	Participants	Intervention	Control			
Primaquine for infants aged < 6 months and breastfeeding women	Is it safe to administer primaquine to infants aged < 6 months and women breastfeeding infants aged < 6 months to reduce transmission and to prevent relapses?	Safety surveillance Case reports	Children and lactating women with uncomplicated *P. falciparum* or *P. vivax* malaria	Infants <6 months Women breastfeeding infants aged <6 months	Infants >6 months Women breastfeeding infants aged >6 months	Safety (serious adverse events, haemolysis and vomiting) Drug levels in breastmilk	New evidence review	G6PD status
Single low dose primaquine for reducing spread of artemisinin resistance	In areas threatened by artemisinin resistance, a single low dose of primaquine of 0.25 mg/kg should be given with ACT to patients with *P. falciparum* malaria	RCTs Cohort studies Observation	*P. falciparum* malaria infected patients	In moderate to high transmission intensity areas	In low transmission areas	Gametocyte carriage (qPCR, microscopy) Mosquito membrane	Update evidence based on IPD meta-analysis	Age Seasonality of malaria Pre-treatment: - Parasite density PQ dose

In areas with artemisinin-resistant falciparum malaria it is strongly recommended that single low dose primaquine (as a gametocytocide) be added to all falciparum malaria treatment regimens (WHO Guidelines for Malaria, pp 109 and 208, 2023 https://www.who.int/teams/global-malaria-programme/guidelines-for-malaria, accessed on 22 February 2024).

Timelines for WHO recommendations on near-patient G6PD tests

Editing, internal review

External review group

Guidelines Review Committee

30 Nov – 1 Dec 2023 | **Dec – Jan 2024** | **26 – 29 Feb 2024** | **Mar 2024** | **April 2024** | **May 2024** | **June 2024**

1ST GDG meeting: review evidence,

2ND GDG meeting: review evidence, formulation of recommendations

Publication of recommendations, if PQ listing of G6PD near patient semi-quantitative tests

Cost-effective analysis
Completion of systematic review

Systematic reviews on
- **Qualitative G6PD point-of-care tests**
- **Quantitative G6PD point-of-care tests**

Literature review of contextual factors (feasibility, acceptability, gender and equity)
Linked evidence modelling of the impact of G6PD testing strategies on treatment outcomes of *P. vivax*

World Health Organization

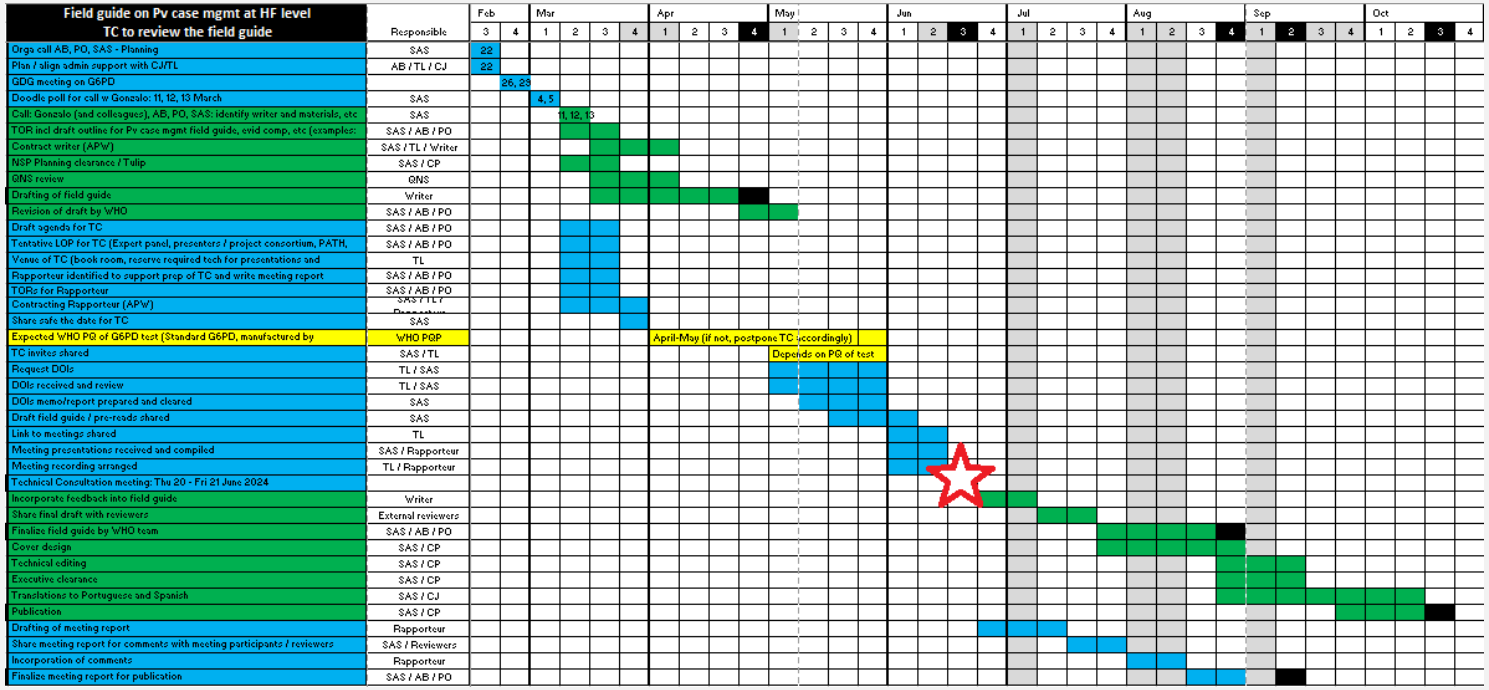
PIRT question on near-patient G6PD tests

Topic	PICO Question	Inclusion criteria				Critical & important Outcomes	Current status	Other considerations/ questions
		Studies	Participants	Index test	Reference Standard			
Use of near-patient qualitative or quantitative G6PD tests to support safe and effective *P. vivax* and *P. ovale* anti-relapse treatment	In patients undergoing G6PD activity testing, how accurate are near-patient tests for G6PD deficiency compared to quantitative spectrophotometric G6PD testing at the thresholds* critical to inform administration of 8-aminoquinolines to prevent relapses of P. vivax and P. ovale? * <30% vs 30-70% vs >70% G6PD activity	All eligible studies	Patients undergoing G6PD testing	- G6PD FST - CareStart G6PD - BinaxNOW G6PD - WST8/1-methoxy PMS assay - Standard G6PD by SD Biosensor - CareStart G6PD Biosensor by AccessBio	Quantitative spectro-photometric assay The reference G6PD activity (100%) calculated as adjusted male median of study samples for each spectro-photometric assay	Sensitivity and specificity at 30% and 70% G6PD activity in males and females	New evidence review	Gender Age G6PD prevalence Endemicity of malaria Location (e.g. Africa, Asia) Venous vs capillary Reference standard

PIRT = Population, Index Test, Reference Test, Target Condition

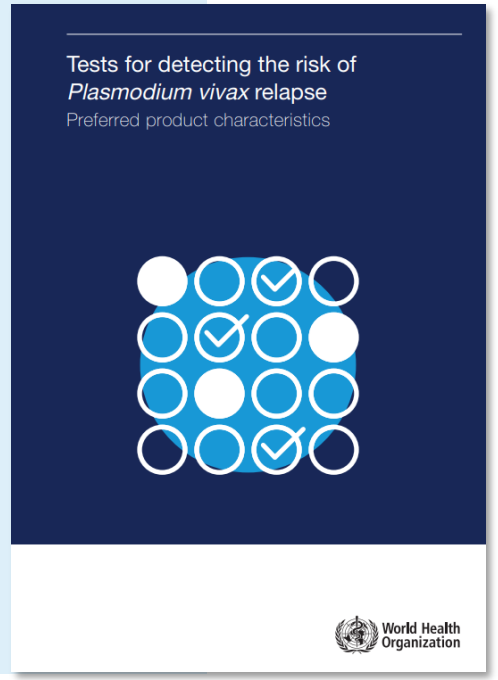
Following publication of recommendations on tafenoquine and primaquine, and PQ listing of quantitative near-patient G6PD tests

WHO Technical Consultation to develop a field manual for case management of P. vivax malaria, 20-21 June 2024 (TBC)



Published soon: PPC of test for detecting the risk of P. vivax relapses

- There are no tests that detect hypnozoites or cryptic/sequestered P. vivax infections
- Methods to detect P. vivax hypnozoite-derived exosomes are in early discovery and serological tests target short-lived (6–9 months) immunological responses to P. vivax blood-stage antigen associated with high likelihood of relapses
- Use case scenarios:
  - 1 - Test to guide radical cure (screen & treat communities in elimination, improve clinical management of P. vivax, screen travelers/migrants)
  - 2 - Population-based screening (stratification of P. vivax transmission, monitoring & evaluation of ongoing elimination programs)
- PPC provided for point-of-care tests and for laboratory-based tests
- >80% sensitivity and >90% specificity to detect a future relapse event



World Health Organization

Thank you
for your attention

World Health Organization

Malaria Policy Advisory Group Meeting

4–5 March 2024, Yaoundé, Cameroon
Background document for Session 7

Update on malaria elimination, including zoonotic malaria

Dr Elkhan Gasimov, Head of Elimination Unit

The World Health Organization's (WHO) *Global technical strategy for malaria 2016–2030* (GTS) *(1)* provides a comprehensive framework to guide malaria-endemic countries in their efforts to accelerate progress towards malaria elimination and attainment of malaria-free status. Adopted by the World Health Assembly in May 2015 and updated in 2021, the GTS targeted the elimination of malaria in at least 10 countries by 2020; it calls for the elimination of malaria in an additional 10 countries by 2025 and at least 15 countries by 2030. In line with the GTS, in 2017, the Global Malaria Programme identified 21 countries, spanning five regions, that could eliminate malaria by 2020 and grouped them under a special initiative that became known as the E-2020 initiative. Funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria, the E-2020 initiative contributed to the achievement of the malaria elimination milestone: 10 countries considered malaria-endemic in 2015 reached at least one year of zero indigenous cases of malaria and maintained that status through 2020. These are Algeria, Azerbaijan, Belize, Cabo Verde, China, El Salvador, the Islamic Republic of Iran, Malaysia, Sri Lanka and Tajikistan. The 2020 milestone related to prevention of re-establishment of malaria transmission was also achieved, as no malaria-free country reported resumption of local transmission.

Building on the foundation and successes of the E-2020 initiative, WHO launched the E-2025 initiative on 1 January 2021 – a three-year continuation effort funded through the Global Fund Strategic Initiative. The 26 countries and territories of the initiative are Belize, Costa Rica, Dominican Republic, Ecuador, French Guiana (France), Guatemala, Honduras, Mexico, Panama and Suriname (WHO Region of the Americas); Malaysia, Republic of Korea and Vanuatu (WHO Western Pacific Region); Islamic Republic of Iran and Saudi Arabia (WHO Eastern Mediterranean Region); Botswana, Cabo Verde, Comoros, Eswatini, Sao Tome and Principe and South Africa (WHO African Region); and Bhutan, Democratic People's Republic of Korea, Nepal, Thailand and Timor-Leste (WHO South-East Asia Region).

The purpose of the E-2025 initiative is to achieve the 2025 GTS elimination milestone by providing increased visibility, both globally and domestically, to countries' efforts to eliminate malaria; specialized technical assistance to identify and resolve technical and operational bottlenecks; opportunities for the exchange of innovative approaches and lessons learned among countries from different regions; guidance to accelerate elimination and the certification process; and support for the development of robust programmes to prevent re-establishment of transmission.

According to the World malaria report 2023 *(2)*, the following countries and areas met the set targets by the end of 2022, using 2019 as the baseline:

- Dominican Republic reached the milestone reduction of > 1000 indigenous cases in 2019 to < 1000 at the end of 2022, moving from 1291 indigenous cases to 320 over this time period.
- French Guiana (France), Nepal and Suriname reached the milestone reduction of 100–999 indigenous cases in 2019 to < 100, bringing their caseloads from 212, 127 and 104 cases to 21, 36 and zero, respectively.
- Saudi Arabia met the objective of moving from 10–99 cases in 2019 to < 10 in 2022, with 38 cases in the baseline year compared to zero cases in 2021 and zero again in 2022.

- Bhutan transitioned from the group of countries with 1–9 cases in 2019 to the group of countries with zero cases in 2022, reporting two indigenous cases in 2019 and achieving malaria elimination in 2022.
- Notably, Saudi Arabia and Suriname, which had 10–99 cases (38) and 100–999 cases (104) in 2019, respectively, reached zero indigenous cases in 2022 (for the second consecutive year for Saudi Arabia).

Note that the true impact of E-2025 will be assessed once 2023 data are available in the World malaria report 2024.

In relation to certification, in 2023, Azerbaijan, Tajikistan *(3)* and Belize *(4)* were declared malaria-free. An independent evaluation mission involving WHO staff from headquarters and the Regional Office for Africa, two members of the Technical Advisory Group on Malaria Elimination and Certification (TAG-MEC) and an ad hoc member was conducted in Cabo Verde from 23 October to 1 November 2023. The TAG-MEC reviewed the findings of the independent certification mission to Cabo Verde at its fifth meeting held in Cairo on 27–28 November 2023, and recommended that Cabo Verde be certified as malaria-free. Following the decision of the WHO Director-General, certification of malaria elimination in Cabo Verde was officially announced on 12 January 2024 *(5)*. With this announcement, Cabo Verde joins the ranks of 43 countries and one territory that have been awarded this certification by WHO. Currently, the Global Malaria Programme is working with several countries to prepare for certification of malaria elimination.

Work continues on the update of *A framework for malaria elimination (6)* and development of global guidance on prevention of re-establishment of malaria transmission. Both documents are expected to be finalized in 2024.

To ensure that the expertise accumulated in countries on achieving elimination of malaria and maintaining malaria-free status is well documented, the Global Malaria Programme initiated development of a series of publications describing the policies and strategies applied by countries that have been certified as malaria-free to contain malaria outbreaks, interrupt transmission of disease and prevent its re-establishment. The Global Malaria Programme has published the stories of Kyrgyzstan *(7)* and Uzbekistan (*8)*, and publication of Sri Lanka's experience is expected shortly.

The "Malaria Elimination" training course on the OpenWHO platform is available in:

- Arabic (https://openwho.org/courses/malaria-elimination-ar),
- English (https://openwho.org/courses/malaria-elimination),
- French (https://openwho.org/courses/elimination-paludisme) and
- Spanish (https://openwho.org/courses/eliminacion-paludismo).

More than 16 000 people have enrolled in the course since its launch in June 2022.

In recent years, *Plasmodium knowlesi* has emerged as a notable concern in malaria cases, especially in the WHO South-East Asia Region countries of Indonesia, Malaysia and Thailand. In 2022, a total of 2768 *P. knowlesi* cases were reported globally, a decrease of 24.2% from 2021 (3651 cases). Indigenous *P. knowlesi* cases also saw a decrease of 26% – from 3629 cases in 2021 to 2682 cases in 2022. Malaysia continues to be the predominant source of *P. knowlesi* cases, contributing 90.5% of the cases in 2022, followed by Thailand and Indonesia, which contributed 3.1% and 0.1%, respectively. In 2022, all the indigenous malaria deaths in Malaysia (nine) and Thailand (one) were attributed to *P. knowlesi*. Malaysia experienced a 30% decline in total *P. knowlesi* cases – from 3575 in 2021 to 2505 in 2022. Most (99.9%) of the *P. knowlesi* cases detected in 2022 were classified as indigenous. The total number of *P. knowlesi* cases rose from five reported cases in 2021 to 87 in 2022 in Indonesia, and from 71 cases in 2021 to 176 in 2022 in Thailand. Although Malaysia reported the highest absolute number of *P. knowlesi* cases, the rate of increase in 2022 was most pronounced in Indonesia and Thailand.

The increase in the burden and transmission of *P. knowlesi* poses unique challenges to malaria elimination; it also has implications for malaria-free certification. Until now, certification has been awarded exclusively to countries where only the four human *Plasmodium* species (*P. falciparum, P. vivax, P. malariae and P. ovale*) were transmitted. Given the context of emerging *P. knowlesi* transmission, WHO has convened its advisory groups to discuss the implications of *P. knowlesi* for certification. If a country is able to eliminate transmission of the four main human species but other species are still being transmitted, certification might be granted if the risk of infection is assessed as negligible. Following discussions on *P. knowlesi* at the fifth TAG-MEC meeting, a TAG-MEC subgroup on *P. knowlesi* was established with the aim of developing a draft of the procedure and requirements for certification of countries that have achieved elimination of the four human *Plasmodium* species but zoonotic malaria continues to be transmitted. The subgroup is also expected to draft guidance on the process and conditions for de-certification of countries where *P. knowlesi* is transmitted.

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8. Towards a malaria-free world: elimination of malaria in Uzbekistan. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/375819, accessed 14 February 2024).

Malaria Policy Advisory Group meeting
4-5 and 7 March 2024, Yaoundé, Cameroon

Update on malaria elimination, including zoonotic malaria

Dr. Elkhan Gasimov
Head of elimination unit
Global Malaria Program
World Health Organization

World Health Organization

Outline of the presentation

- Malaria in Elimination-2025 countries
- Update on certification of malaria elimination
- Guidance on malaria elimination and prevention of malaria re-establishment
- STOP malaria
- Capacity building and best practicies
- Zoonotic malaria

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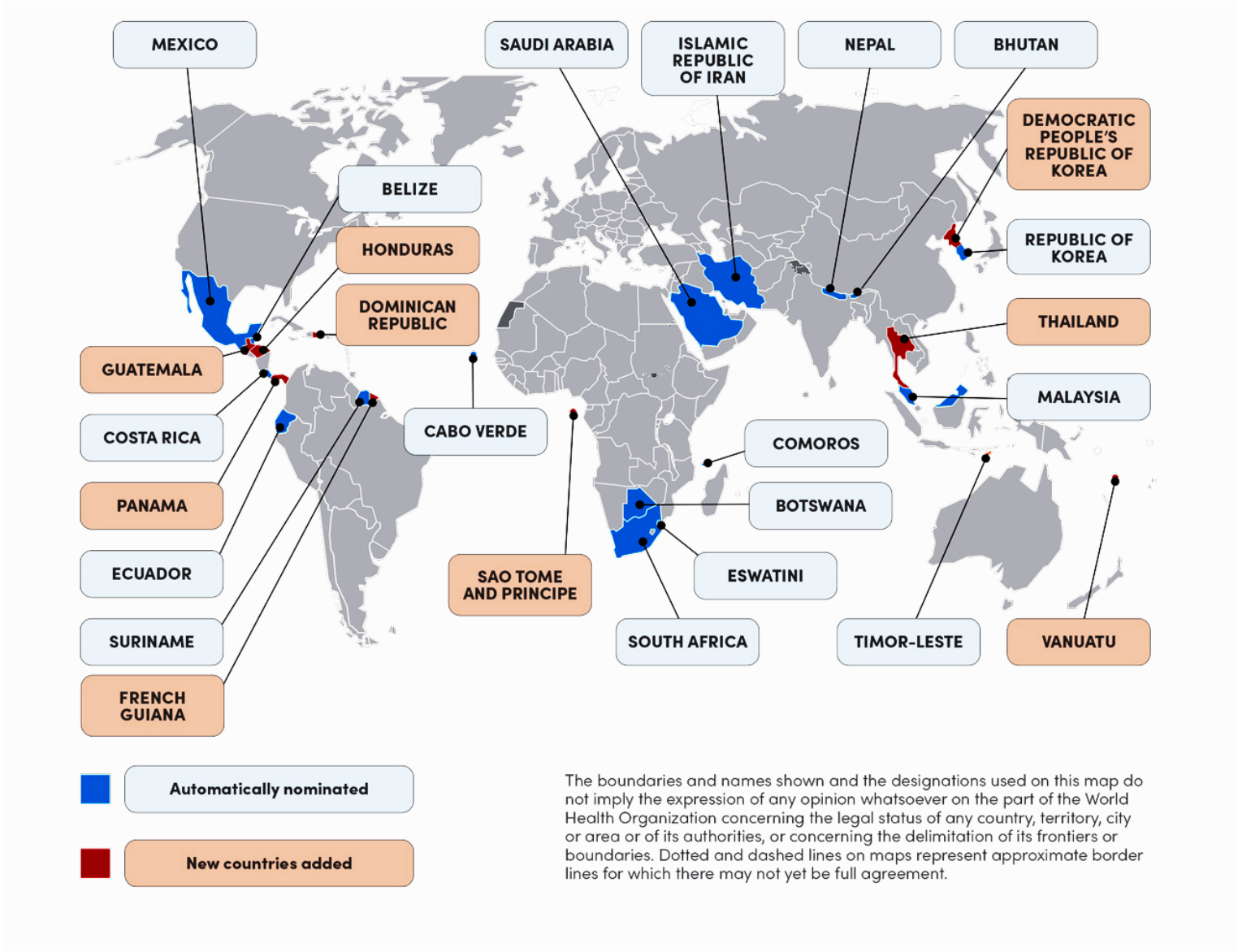
Malaria in Elimination-2025 countries

World Health Organization

Countries and territories selected for the E-2025 initiative



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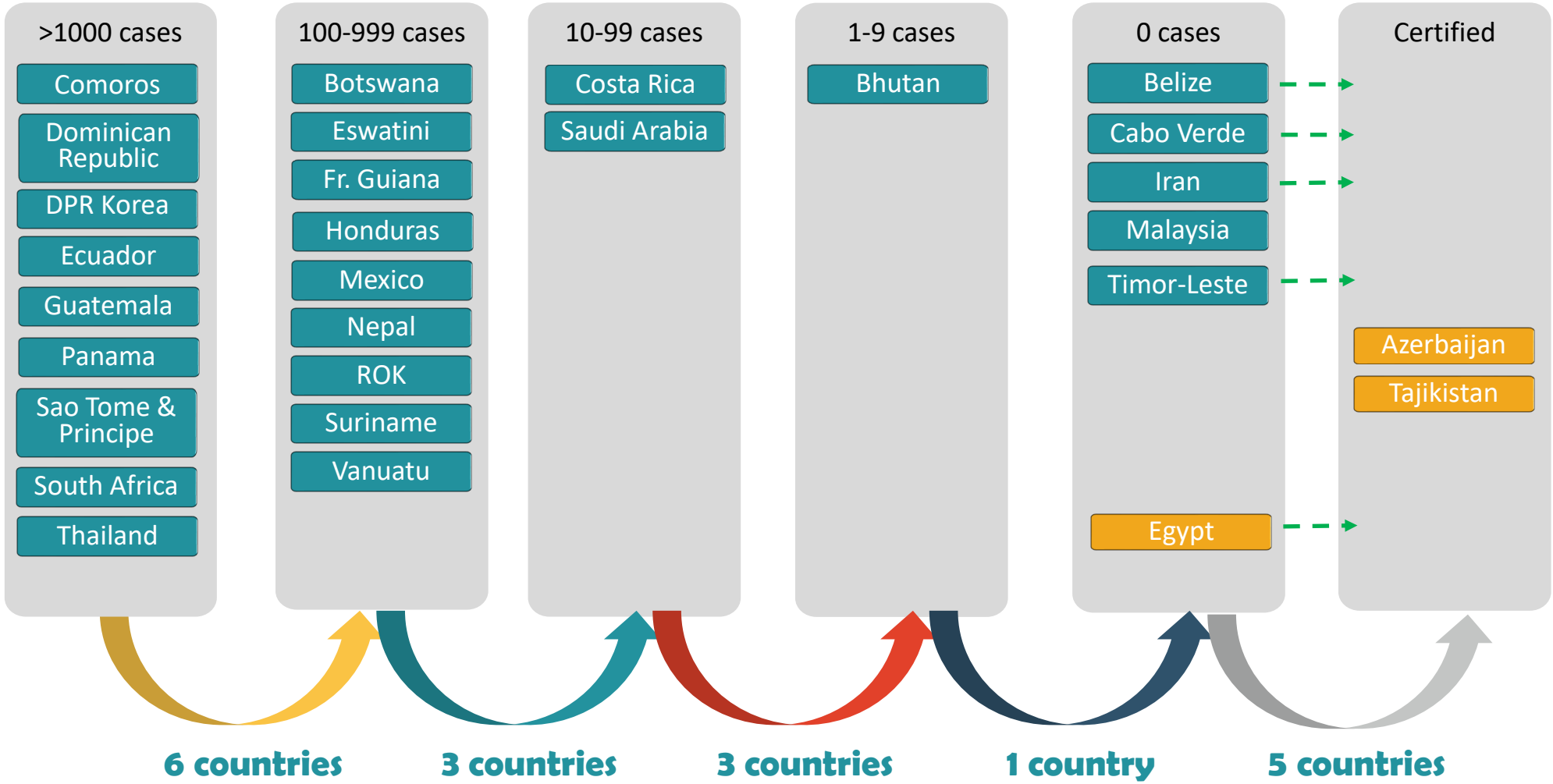
Where we are in 2022



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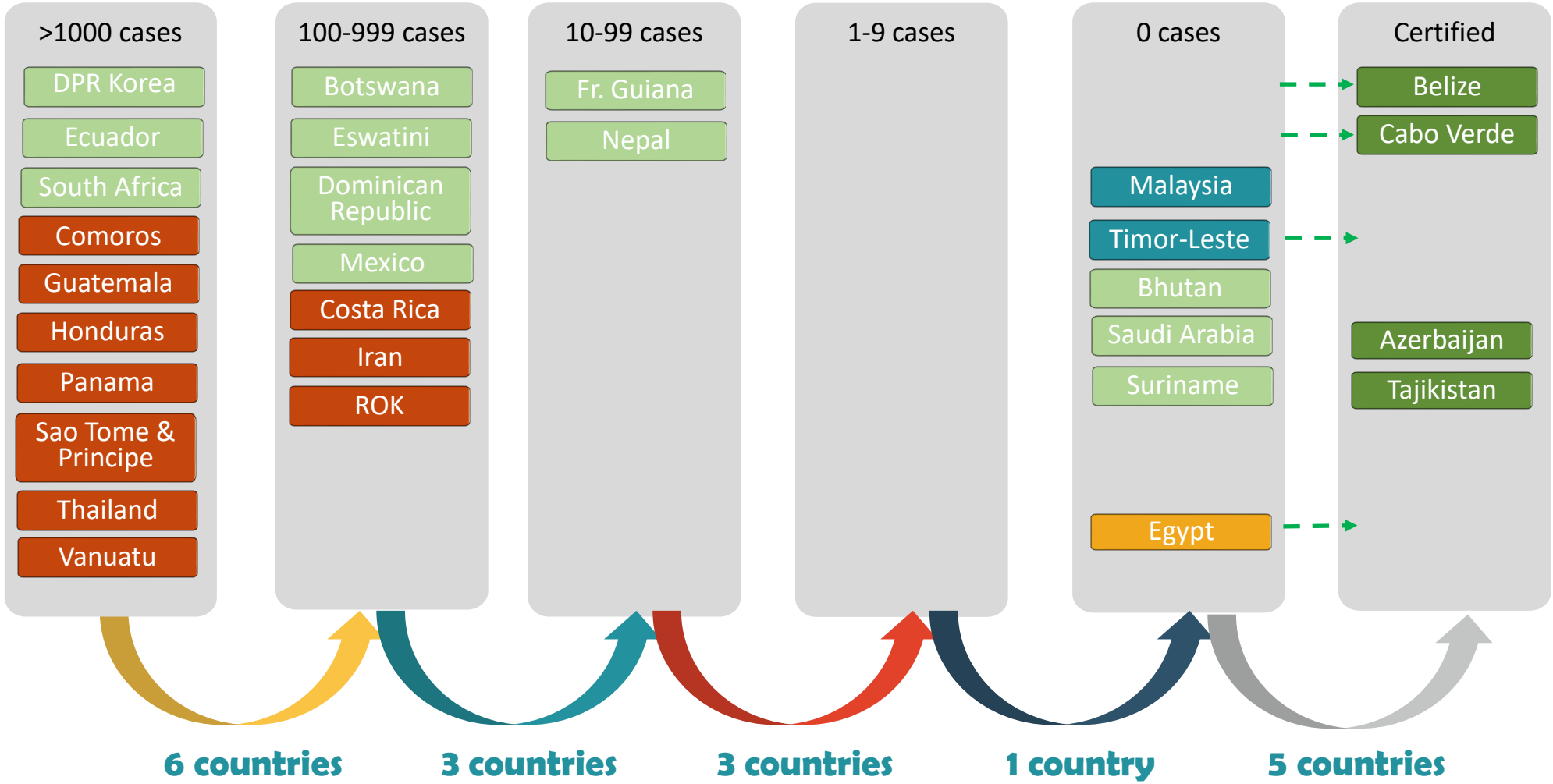
Where we are in 2022



World Health Organization

Country	2015	2016	2017	2018	2019	2020	2021	2022
Belize	9	4	7	3	0	0	0	0
Bhutan	34	15	11	6	2	22	9	0
Botswana	284	659	1,847	534	169	884	703	397
Cabo Verde	7	49	423	2	0	0	0	0
Comoros	1,884	1,467	3,896	15,613	17,599	4,546	10,537	20,675
Costa Rica	0	4	12	70	95	90	189	406
Democratic People's Republic of Korea	7,022	5,033	4,603	3,698	1,869	1,819	2,357	2,136
Dominican Republic	631	690	341	433	1,291	826	284	320
Ecuador	618	1,191	1,275	1,653	1,803	1,934	2,175	1,348
Eswatini	318	250	440	686	235	233	505	214
French Guinana	374	217	554	546	212	140	143	21
Guatemala	5,538	5,000	4,121	3,018	2,069	1,058	1,273	1,856
Honduras	3,555	4,094	1,273	632	330	815	1,550	3,534
Iran (Islamic Republic of)	167	81	57	0	0	0	0	1,439
Malaysia	242	266	85	0	0	0	0	0
Mexico	517	551	736	803	618	356	242	167
Nepal	591	507	623	493	127	73	32	36
Panama	546	769	649	684	1,756	1,946	4,354	7,103
Republic of Korea	627	602	436	501	485	356	274	382
Sao Tome and Principe	2,056	2,238	2,239	2,937	2,732	1,933	2,719	3,970
Saudi Arabia	83	272	177	61	38	83	0	0
South Africa	4,959	4,323	23,381	9,540	3,096	4,463	2,958	2,043
Suriname	81	78	137	37	104	156	22	0
Thailand	14,265	12,076	7,416	5,110	4,065	3,123	2,426	6,262
Timor-Leste	80	81	16	0	0	3	0	0
Vanuatu	571	2,243	1,227	632	567	493	312	1,102

Update on certification of malaria elimination

World Health Organization

Certification of malaria elimination

- 43 countries and 1 territory have been certified malaria-free
- 61 countries listed in supplementary list

World Health Organization

Certification of malaria elimination

11 COUNTRIES	15 COUNTRIES and 1 TERRITORY	0	7 COUNTRIES	10 COUNTRIES
1955–1969	1970–1987	1988–2006	2007–2017	2018–2024
• Bulgaria • Cyprus • Dominica • Grenada • Hungary • Jamaica • Poland • Romania • Saint Lucia • Spain • Trinidad and Tobago	• Australia • Bosnia-Herzegovina • Brunei Darussalam • Croatia • Cuba • Italy • La Réunion (France) • Mauritius • Montenegro • Netherlands • North Macedonia, • Portugal • Serbia • Singapore • Slovenia • United States of America		• Armenia • Kyrgyzstan • Maldives • Morocco • Sri Lanka • Turkmenistan • United Arab Emirates	• Algeria • Argentina • Azerbaijan • Belize • Cabo Verde • China • El Salvador • Paraguay • Tajikistan • Uzbekistan

World Health Organization

- 43 countries and 1 territory have been certified malaria-free
- 61 countries listed in supplementary list

Certification plans

Egypt

- Official request is received in September 2023
- Independent evaluation mission **10-17 April 2024**

Timor-Leste

- Official request is received in September 2023
- Certification is planned in 2024

Georgia

- Official request is expected in February 2024
- Certification is planned in 2024

Turkey

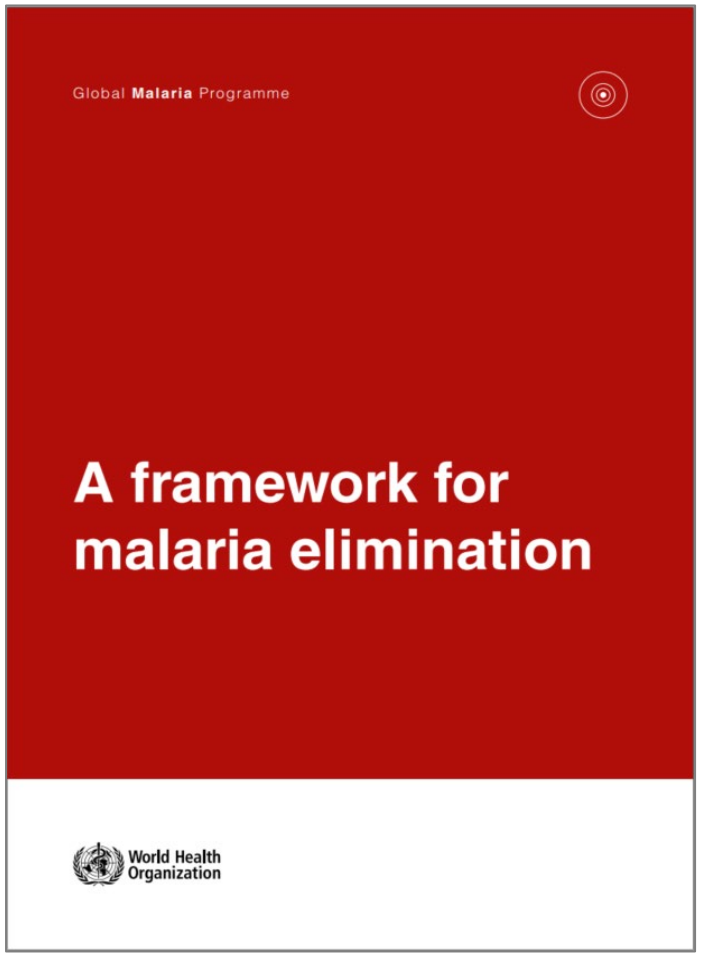
- Initiated process for preparing for certification in May 2023
- Official request is expected in 2024

World Health Organization

Guidance on malaria elimination and prevention of malaria re-establishment

World Health Organization

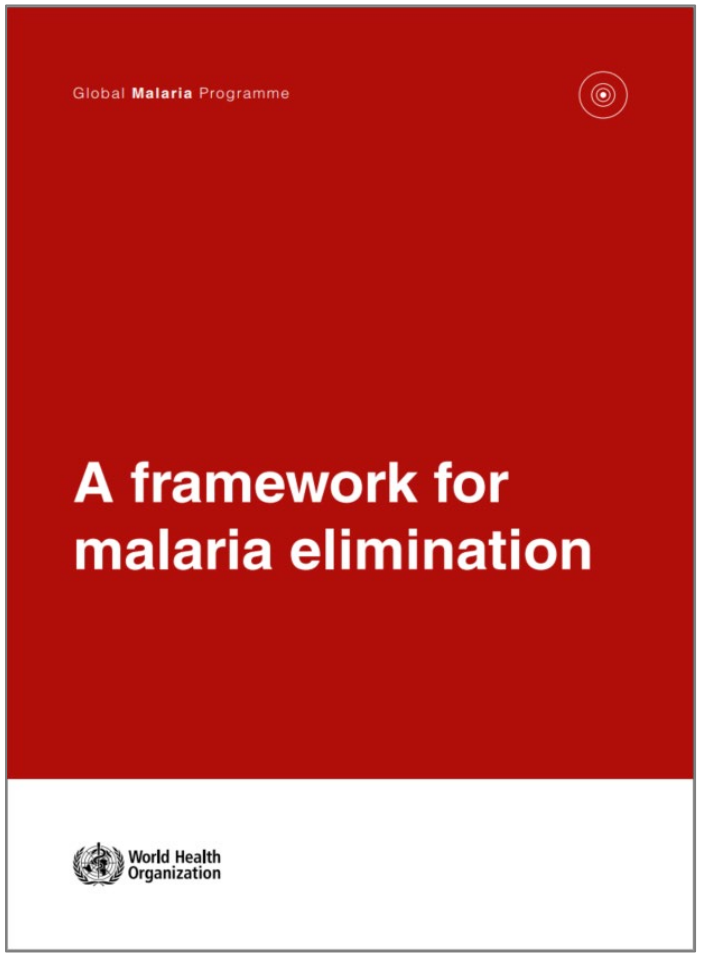
Guidance



- The guidance for malaria elimination was developed in 2017
- Since 2017 several updates were done to key WHO recommendations and several documents were published:
  - Malaria surveillance, monitoring & evaluation: a reference manual was published in 2018 / under revision now
  - Guidelines on ***Interventions in the final phase of elimination and prevention of re-establishment*** were published in 2022
  - Preparing for Certification of Malaria Elimination, 2nd edition is published in 2022
  - Global guidance on PoR is under development
- GMP is reviewing the Framework to align it with the update WHO guidelines /guidance

World Health Organization

Guidance: A framework for malaria elimination



New sections

- Accelerating transmission reduction
- Management and Planning challenges in elimination
- Cross-border collaboration
- Risk communication
- Integrating gender, equity and human rights considerations in malaria elimination

To be removed

- *Certification of malaria elimination will be reduced to overview and reference*
- *PoR section will be reduced to overview and reference*

World Health Organization

Malaria Elimination Audit Tool

Review of MEAT

7. Process of consensus building to determine scores	1	2	3	4	5 (n/a)
8. Use of the recommendations section on critical elements	1	2	3	4	5 (n/a)
9. Was the MEAT used in program reviews? If yes, Easiness of adapting the MEAT into the program review process	1	2	3	4	5 (n/a)

Applicability at Sub national level					
Was the MEAT used at sub national level?? Circle 1=Yes 2=No.				**1 Y**	**2 N**
For each step below, circle 1 if Hard, circle 2 if Moderate, circle 3 if Easy, circle 4 if Very Easy, circle 5 if not sure or if non applicable					
1. Easiness of adapting the MEAT to sub national level	1	2	3	4	5 (n/a)
2. Applicability of domains and critical elements to sub national level	1	2	3	4	5 (n/a)
3. Easiness of collecting required audit evidence at sub national level	1	2	3	4	5 (n/a)
4. Availability of expertise to use the MEAT tool at sub national level	1	2	3	4	5 (n/a)

1. **Streamlining the tool**: The MEAT is very heavy and require huge amounts of financial and human resources to be conducted. The tool should be therefore streamlined to allow for it to be used easily, with little resources at all levels.
2. **Updating scoring system:** A new scoring system should be developed that identify and separate major and minor nonconformities by putting different score weighting for the two.
3. **Digitalizing MEAT:** There is need to provide the MEAT in digital form to allow for faster assessments with less expertise and ease of generation of performance and follow up at all levels.
4. **Adding missing domains:** The tool does not comprehensively cover the domains of Community mobilization/advocacy and social mobilization and Health Financing.

World Health Organization

Currently guidance on PoR is scant

GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

World Health Organization

Workplan for development of the PoR guidance: Launch

	EVENT	OBJECTIVE	TIMELINE
1	Officially launch the technical consultation on prevention of re-establishment during the fourth Global Forum of malaria-eliminating countries	• Launch the technical consultation • Review and discuss two case studies: China and El Salvador • Discuss challenges to prevention of re-establishment	24-26 Jan 2023

World Health Organization

Workplan for development of the PoR guidance: Evidence review

ISGlobal Barcelona Institute for Global Health

Literature and grey literature review on prevention of re-establishment, including on factors that contribute to the resurgence of malaria after elimination is achieved and that might contribute to the stability of malaria elimination in malaria-free countries

IRD Institut de Recherche pour le Développement FRANCE
French National Research Institute for Sustainable Development

Review on the refractoriness to *Plasmodium* infections in *Anopheles* species/strains and biological factors that could result in refractoriness.

University of Essex

Scoping review on health system strategies for preventing the re-establishment of malaria

World Health Organization

Workplan for development of the PoR guidance: Virtual meetings

	EVENT	OBJECTIVE	TIMELINE
2	Virtual meetings to review case studies and updates on WHO policies and recommendations on health systems	Greece and Paraguay Sri Lanka, Oman, Mauritius Tajikistan, Uzbekistan, Georgia	21-23 Feb 2023

World Health Organization

Workplan for development of the PoR guidance: Review meeting

	EVENT	OBJECTIVE	TIMELINE
3	Evidence review in Tbilisi, Georgia	Evidence review meeting	29-30 Mar 2023

World Health Organization

Workplan for development of the PoR guidance

- Consultation with the Regional Advisors
- Review at the TAG-MEC (27-28 Nov)
- Finalization of the document

	EVENT	OBJECTIVE	TIMELINE
4	Publish the product of the technical consultation		Q4 2024

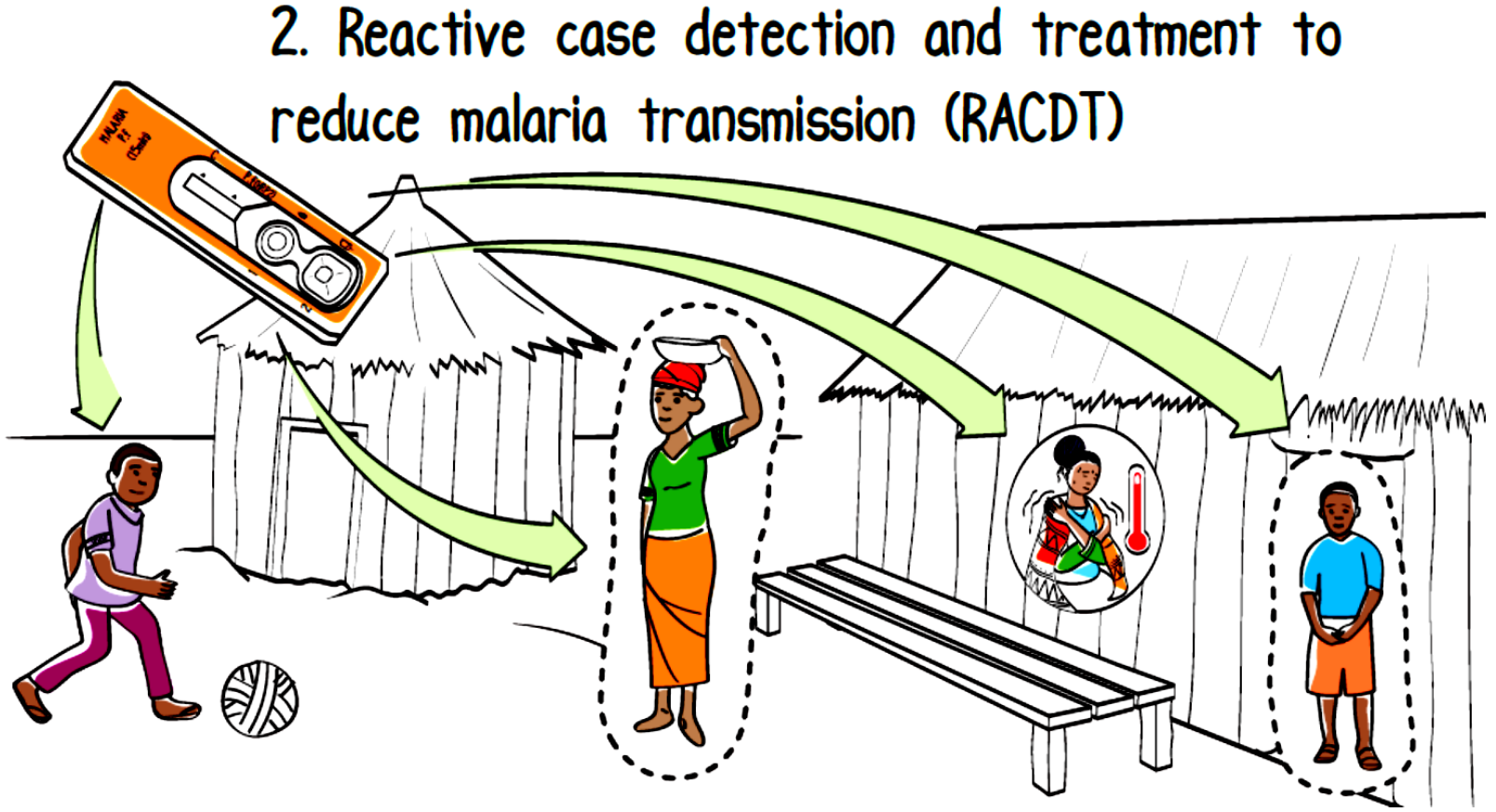
World Health Organization

Video on reactive strategies

and a number of other countries were close to achieving this goal.

World Health Organization

Video on reactive strategies



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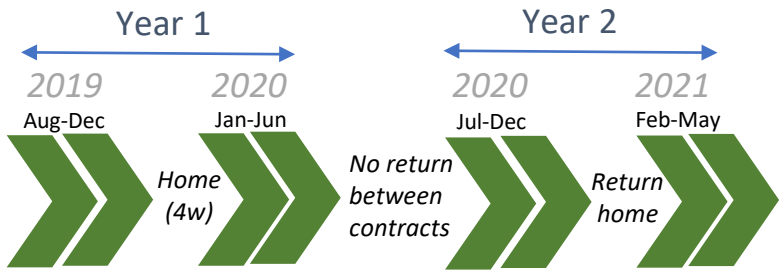
STOP malaria

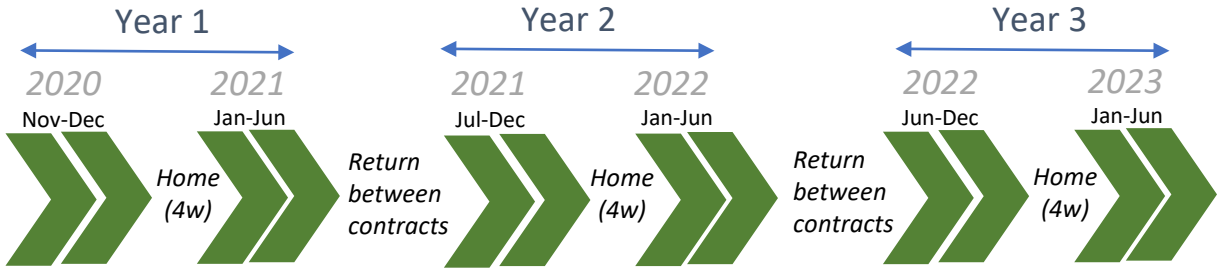
World Health Organization

STOP-malaria initiative has been stopped

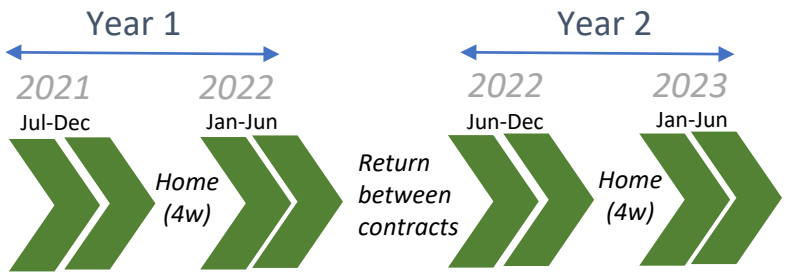
- **Launched in 2019**
- **Programme goal: Strengthen subnational technical and operational capacity to eliminate the last foci of malaria transmission**



Team 1
- Botswana
- Cabo Verde
- Namibia



Team 2
- Eswatini (resigned in Feb 2023)
- Sao Tome and Principe



Team 3
- Botswana
- Suriname (Aug 2021 – Jul 2022)
- Ecuador
- Vanuatu

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STOP-malaria: cost incurred (August 2019-June 2023)

Country of deployment	Number of months in-country
Botswana	37
Cabo Verde	18
Ecuador	16
Eswatini	22
Namibia	18
Sao Tome and Principe	26
Suriname	9
Vanuatu	8
TOTAL	154 (~14 years)

Year	US$
2019	57k
2020	255k
2021	325k
2022	375k
2023 (Jan-Jun)	171k
Total	1,183k
Consultant years (11 months)	~14
Annual costs	~84.5k

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STOP-malaria: Impact assessment / alternative models

Objectives

- to undertake an impact /cost effectiveness assessment of the STOP malaria programme
- to identify alternative scenarios for support to malaria elimination at subnational level and estimate related costs
- to make a cost-benefit comparison of the STOP-malaria programme with these alternatives, as well as to estimate their theoretical efficiency and sustainability.

Factors that could improve cost-effectiveness of STOP-malaria

- Best timing is when indigenous cases are fewer than 1000
- Adapted strategic and normative environment
- Country tailored support
- Specific evaluation framework
- Whole country coverage
- Capacity transfer and sustainability

Alternative options considered

1. One international volunteer for 11 months
2. Two national consultants at provincial level
3. Five district level SSAs
4. Training of 10–15 district officers

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STOP-malaria: Impact assessment / alternative models

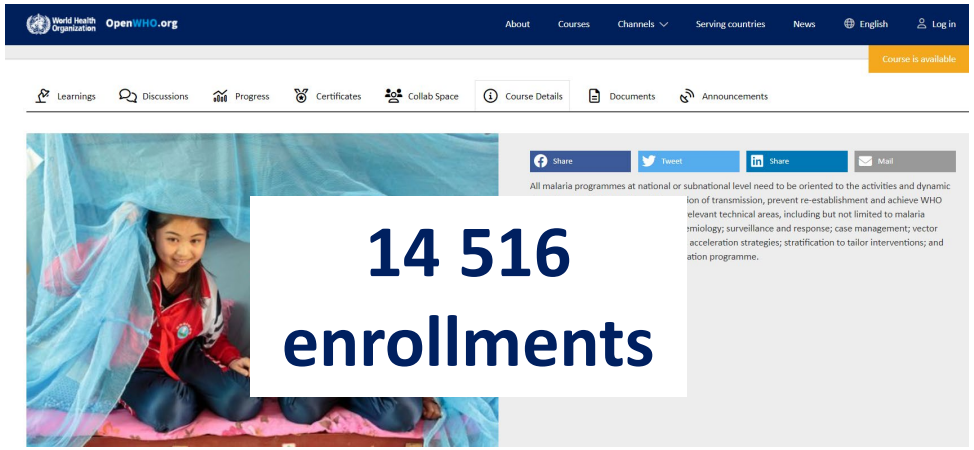
	STOP model	One international consultant for 11 months	Two national consultants at provincial level	Five district level SSAs	Training of 10–15 district officers
Staffing					
International	1 x 22m	1 x 11m	-	-	1 x 2m
National consultant	-	-	2 x 11m	-	-
SSA	-	-	-	5 x 12m	-
District officers	-	-	-	-	10-15
Cost					
Annual budget (US$)	84,500	90,000	84,600	96,000	90,000
Baseline situation					
National level capacity*	--	Inadequate	Inadequate	Adequate	Inadequate
District human resources	--	Inadequate	Adequate	Inadequate	Adequate
Country size	Variable	Small	Large	Small	Large
Expected effectiveness					
Covered districts	1-20	4-6	6-30	5	10-15
Country coverage	+ to +++	++	+++	++	+++
Impact at district level	+ to +++	+++	+++	+++	+++
Sustainability	+	++	++	+++	+++

Organization

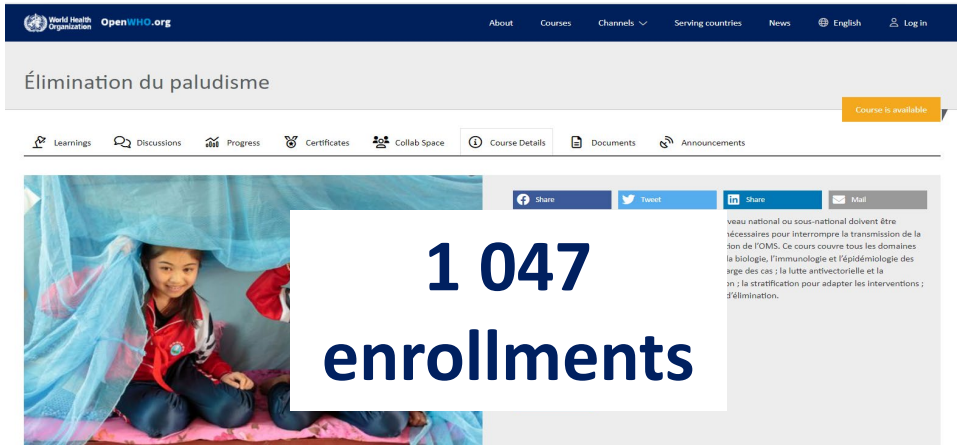
Capacity building and best practices

World Health Organization

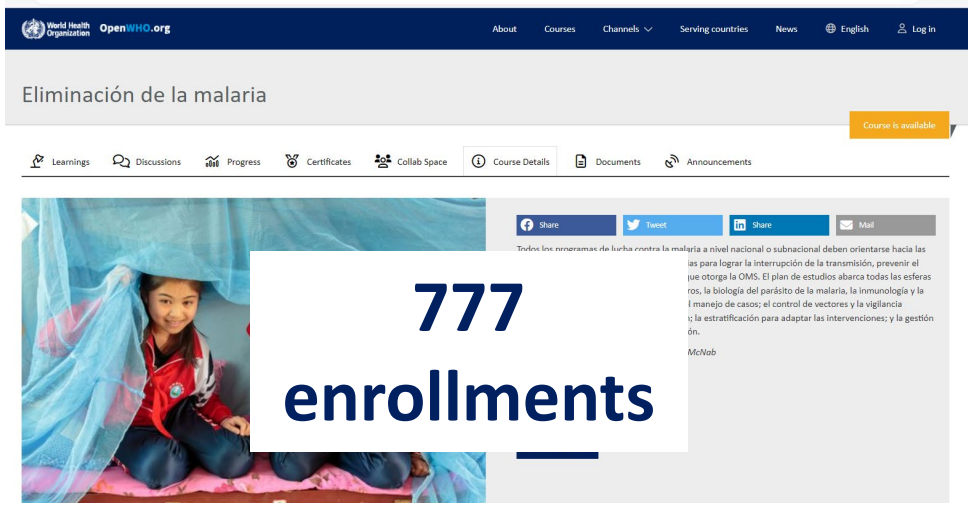
Malaria elimination course



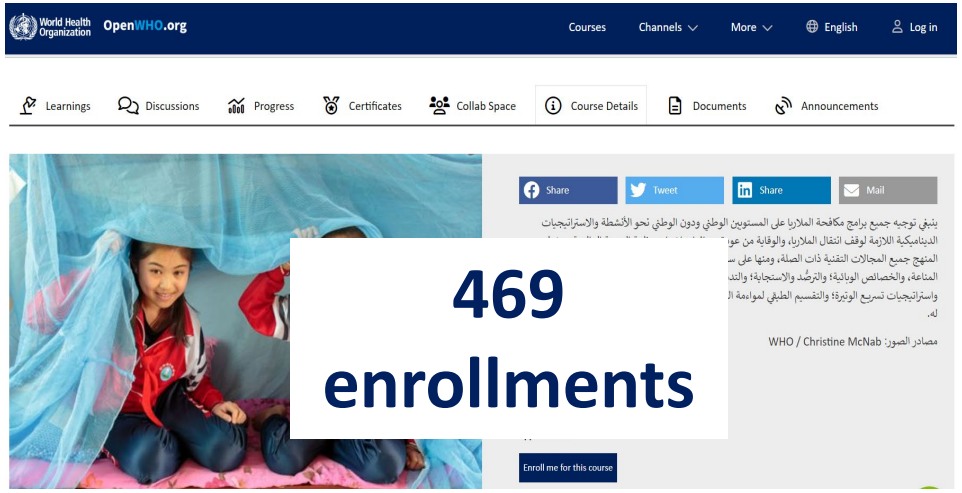
English



French



Spanish



Arabic

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Strengthening capacity of E-2025 AFRO countries on malaria elimination

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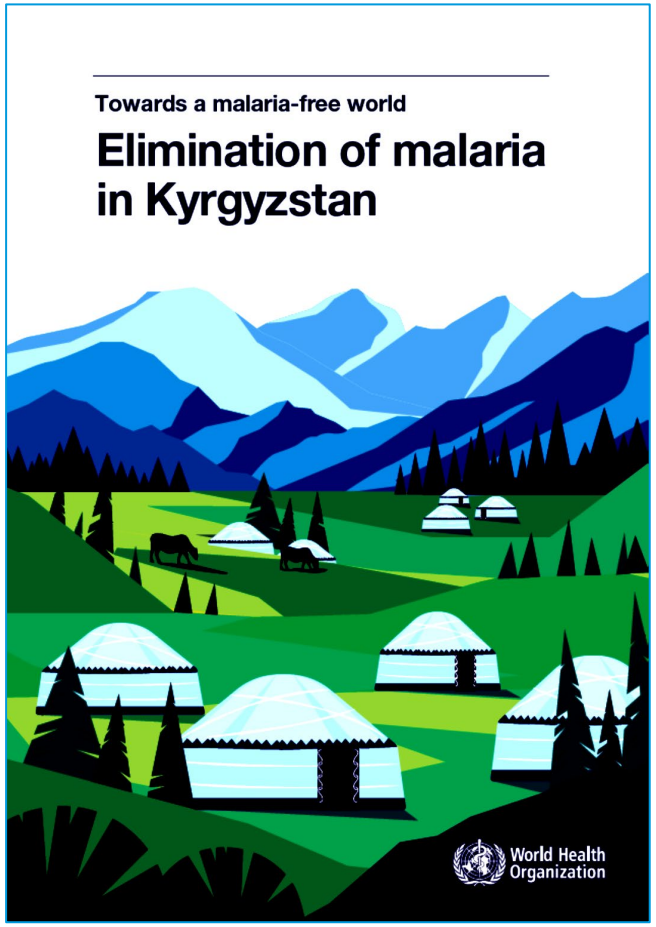
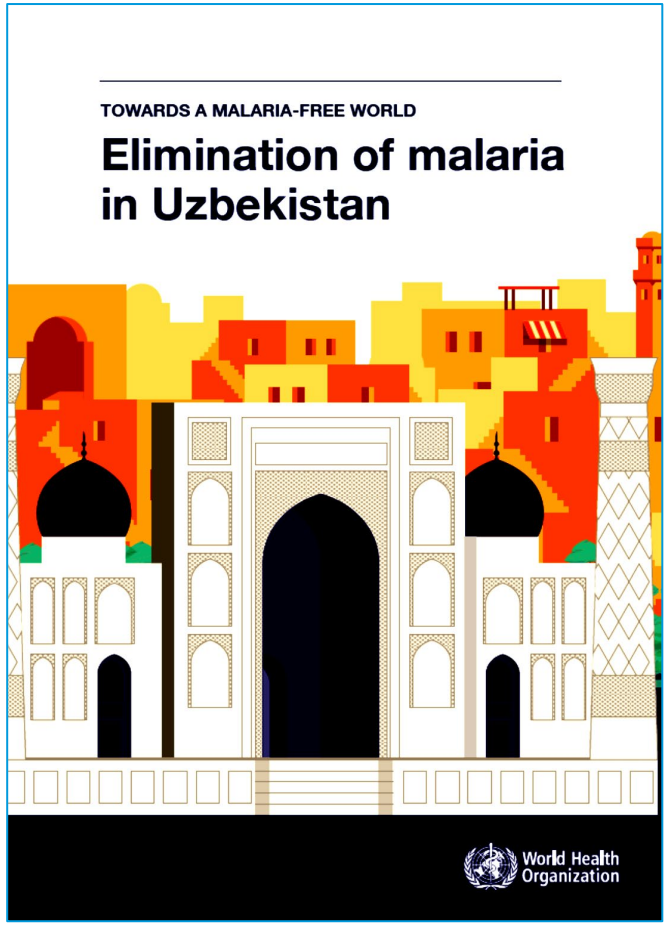
TOWARDS A MALARIA FREE-WORLD series



https://www.who.int/publications/i/item/9789240080836



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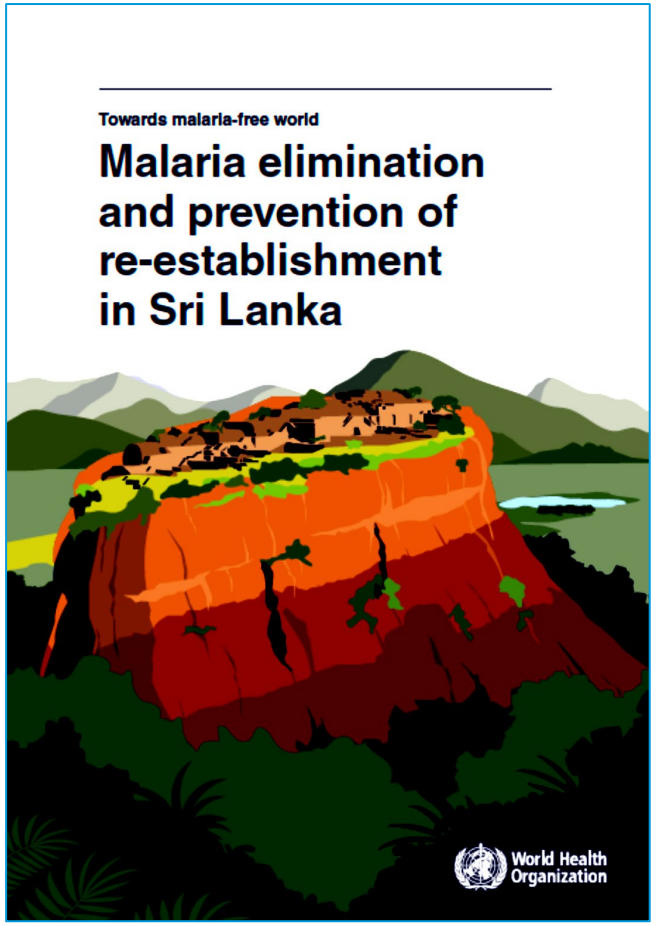


World Health Organization

Zoonotic malaria

World Health Organization

Zoonotic malaria: Background

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

WORLD HEALTH ORGANIZATION

TECHNICAL REPORT SERIES

No. 205

EXPERT COMMITTEE ON MALARIA

Eighth Report

WORLD HEALTH ORGANIZATION

PALAIS DES NATIONS

GENEVA

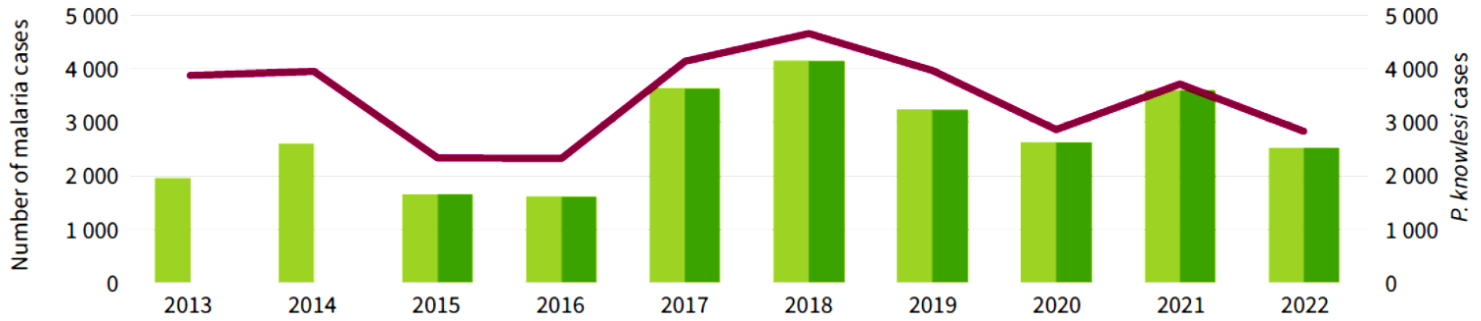
1961

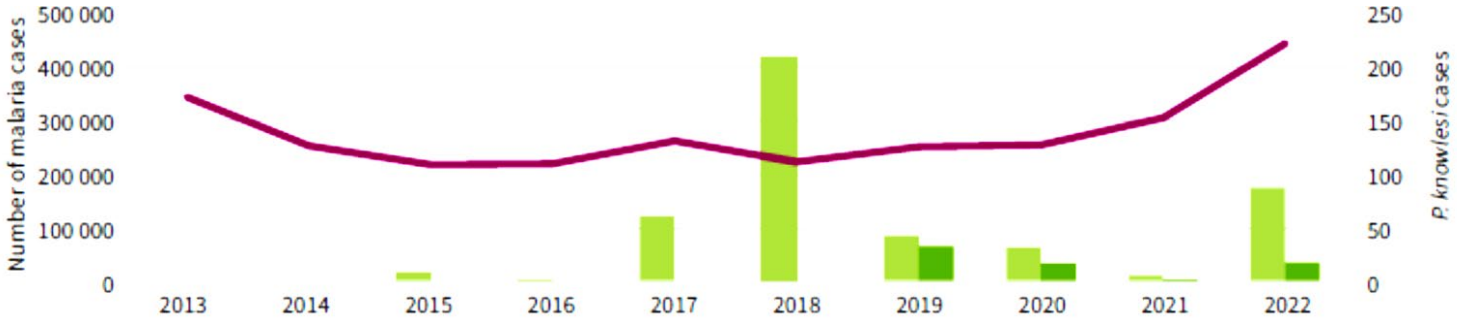
World Health Organization

The true significance of simian malaria in relation to man will become apparent when the eradication of human malaria has been accomplished in such areas of the world as Malaya, Borneo, Indonesia, the Philippines, Taiwan, Central and West Africa.

P. knowlesi

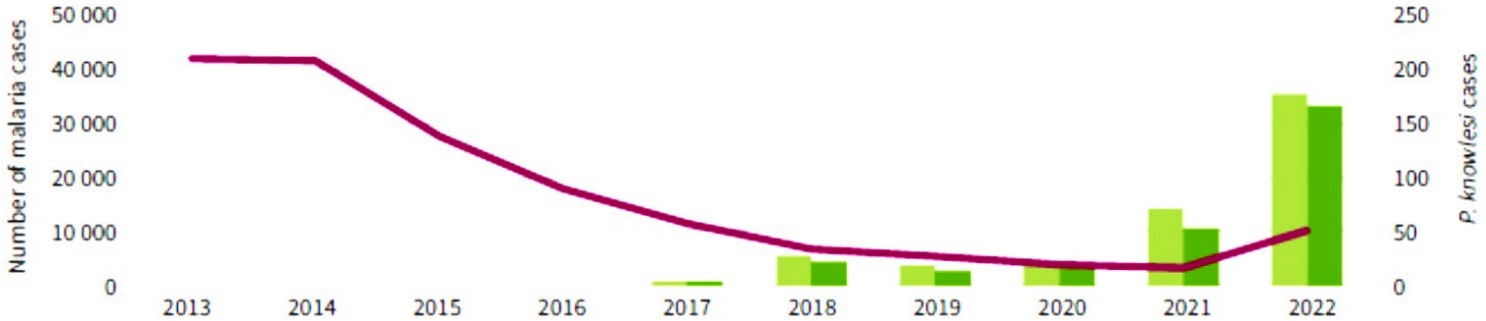
Malaysia





Indonesia

Thailand



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Total malaria cases | *P. knowlesi* malaria cases | *P. knowlesi* indigenous malaria cases

P. knowlesi: imported cases

Year of acquisition	Country of presentation	Presumed area of acquisition
2006	Sweden	Sarawak, Malaysia
2007	Finland	Rural areas around Kuala Lumpur + South Ipoh + Langkawi, Peninsular Malaysia
2008	USA	Island of Palawan, Philippines
2008/2009	Spain	Bangkok, Thailand; Banda Aceh + Pulau Weh, Indonesia; Kuala Lumpur, Malaysia; Hanoi, Vietnam
2009	Netherlands	Sarawak, Malaysia
2010	Australia	Kalimantan, Indonesia
2010	New Zealand	Borneo Malaysia
2010	France	Ranong and Island of Ko Phayam, Thailand
2011	Netherlands	Borneo Malaysia
2012	Japan	Temengor Perak, Peninsular Malaysia
2013	Germany	Ranong, Thailand
2013	Germany	Khoa Sok, Thailand
2013	Germany	Island of Mecleod, Myanmar; Island Koh Ra + Khao Lak + Phuket, Thailand
2014	Scotland	Borneo Malaysia
NA	Germany	Island of Ko Chang + Krabi, Thailand
NA	Turkey	Myitkyina, Myanmar
2016	Sri Lanka	Pulada Johor, Peninsular Malaysia
2016	Italy	Island of Palawan + Siquijor + Bohol, Philippines
2016/2017	Germany	Chiang Mai + Bangkok + Ranong city + Island of Little Koh Chang, Thailand
2017/2018*	Japan	Island of Palawan, Philippines
2018	Poland	Sumatera, Indonesia

WHO's work on *Pk*: Informal consultation on the public health importance of *Plasmodium knowlesi*

Kuching, Sarawak, Malaysia, 22- 24 February 2011

"There has been some concern that the presence of human cases of *P. knowlesi* will have a negative impact on both countries that have already been declared malaria-free and for those countries moving towards elimination. *P. knowlesi* is a zoonosis so it is not included in the current WHO definition or guidelines on elimination. If in the future human-to-human transmission is demonstrated in nature this may change."

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WHO's work on *Pk*: Evidence Review Group on *P. knowlesi*

- 2016 - WHO's MPAG established an Evidence Review Group to analyze the problem of *P. knowlesi*. In March 2017, the ERG submitted its report to MPAG

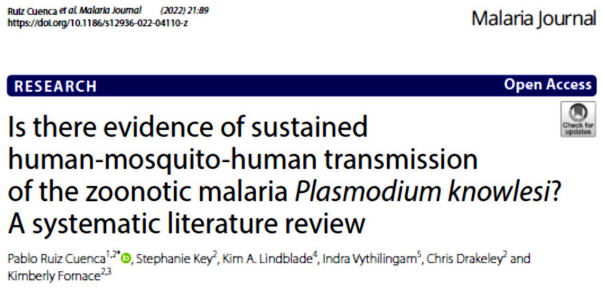
- **MPAC conclusions:** MPAC noted with concern the increase of *P. knowlesi* cases in Malaysia, potentially linked to a change in land use and the plausibility (though not definitively demonstrated) of human-vector-human transmission. If human-vector-human transmission is demonstrated in Malaysia, *P. knowlesi* would need to be considered a human malaria infection and elimination of *P. knowlesi* may be necessary for certification of malaria-free status. (https://www.who.int/publications/i/item/WHO-HTM-GMP-MPAC-2017.8)

World Health Organization

WHO's work on *Pk*: expert consultation on *Plasmodium knowlesi* malaria to guide malaria elimination strategies

- 2017 - A WHO expert consultation on *Plasmodium knowlesi* malaria to guide malaria elimination strategies
  - "Thus, human *P. knowlesi* appears still to be largely a zoonosis. There is a need for research that is more directed at establishing human-to-human transmission. It should be noted that transmission dynamics are likely to change with time, if the incidence of human *P. knowlesi* increases. It was also noted that human-to-human transmission of *P. knowlesi*, if it exists, has implications on the definition of malaria elimination and to WHO's requirements in certifying countries as malaria-free.

WHO's work on Pk



Ruiz Cuenca et al. Malaria Journal (2022) 21:89
https://doi.org/10.1186/s12936-022-04110-z

Malaria Journal

RESEARCH Open Access

Is there evidence of sustained human-mosquito-human transmission of the zoonotic malaria *Plasmodium knowlesi*? A systematic literature review

Pablo Ruiz Cuenca[1,2*], Stephanie Key[2], Kim A. Lindblade[4], Indra Vythilingam[5], Chris Drakeley[2] and Kimberly Fornace[2,3]

"… the evidence synthesis demonstrates that sustained human-mosquito-human transmission chains are indeed possible, but currently available evidence indicates that, if these transmission events are occurring, they might be rare."

Conclusion	Evidence
Experimental human-mosquito-human transmission has been demonstrated in laboratory settings	High consistency, limited evidence
Spatio-temporal clusters of human cases have been found which may be consistent with human-mosquito-human transmission, but no quantitative analyses have been performed to confirm this	Medium consistency, limited evidence
Distribution of known natural hosts and vectors for *P. knowlesi* correlates with areas where human cases have been reported	High consistency, robust evidence
The lack of *P. knowlesi* cases in malaria endemic areas is most likely due to detection bias and misdiagnosis	High consistency, robust evidence
Models suggest human-mosquito-human transmission is unlikely but still plausible within observed parameters	High consistency, medium evidence
Models suggest reproductive rates are highly sensitive to contact patterns between simian hosts, vectors and people as well as vector biting preferences and likely to be highly affected by land use change	High consistency, medium evidence
Mixed infections with *P. knowlesi* and human malaria species have been reported in both humans and known natural vectors across various countries in South-East Asia	High consistency, medium evidence
P. knowlesi parasites can adapt to exclusive human red blood cell culture, invading and multiplying successfully for multiple generations	High consistency, medium evidence
Multiple invasion pathways have been identified, with a range of specific proteins aiding cell invasion. This shows there are no molecular barriers to invasion of human erythrocytes other than the requirement of Duffy antigens	High consistency, robust evidence

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WHO's work on *Pk*: 10th meeting Malaria Elimination Certification Panel, 03 March 2023

- For countries where transmission of the four "human" Plasmodium species has been interrupted but *P. knowlesi* cases continue to occur, certification should depend on a careful assessment of the risks.

- When countries are reporting hundreds or thousands of *P. knowlesi* cases, certification of malaria-free status should be postponed.

- An arbitrary low threshold could be applied, e.g., 10 or fewer cases per year, below which a country can be potentially certified as having eliminated malaria, as the risk of zoonotic transmission might be considered "negligible".

World Health Organization

WHO's work on Pk: MPAG meeting, 23–24 March 2022

- MPAG acknowledged that this is a complex issue and one that presents unique challenges as countries near elimination.
- It is well established that *P. knowlesi* is a zoonotic infection that can infect humans and lead to disease, including severe disease and death. Elimination of the parasite in the zoonotic host seems unlikely and therefore the MECP is suggesting setting criteria for negligible risk.
- There are several knowledge gaps that prevent the establishment of a universal and quantitative criterion for *P. knowlesi* transmission, including detailed knowledge of vector behaviour and vectorial capacity and the extent of human transmission chains.
- MPAG agreed that the concept of negligible risk suggested by the MECP may be the most practical way forward given the current situation. The assessment of the risk, which should include careful epidemiological and other investigations, should be conducted on a case-by-case basis.

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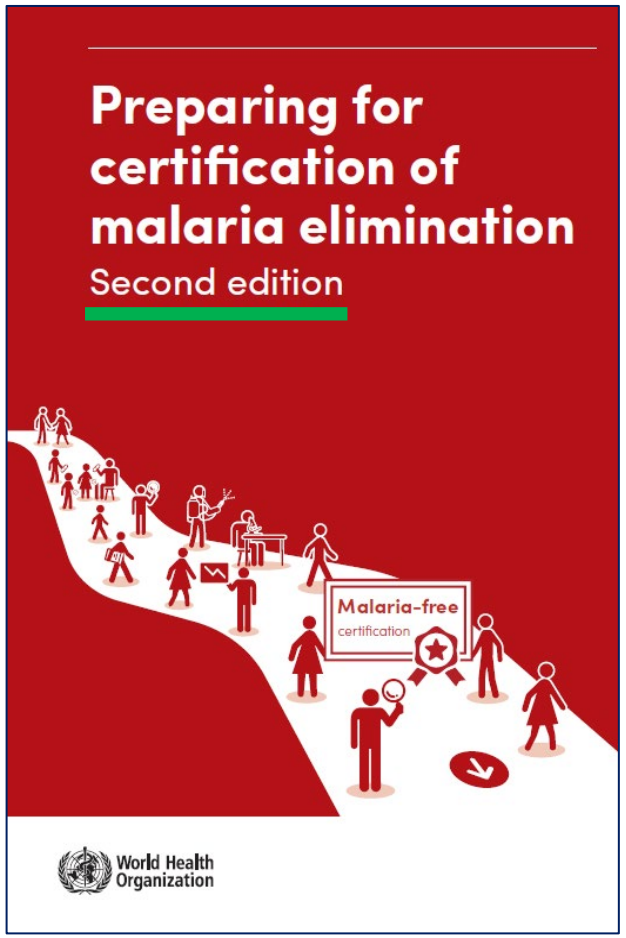
WHO's work on Pk: Updating certification manual



Certification of malaria elimination by WHO requires the elimination of the four main human parasite species: *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Certification might be granted to countries where cases of other Plasmodium species are reported if the risk to humans is assessed negligible.

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WHO's work on Pk: Scoping mission to Malaysia, 23-28 July 2023

Conclusions

- Malaysia already has established an excellent Pk control programme with strong surveillance; data represents the real situation.
- Data and information presented are compatible with the hypothesis that transmission of Pk in Sabah is largely zoonotic
- It must be recognized that given the large volume of Pk case Pk in humans over the past decades, there is a risk that Pk may become human-to-human transmitted, posing a huge threat to Southeast Asia and globally
- Thus, *P. knowlesi* malaria is a major public health problem, which could become more serious, especially if human-to-human transmission takes off. It is therefore a priority to reduce the transmission to humans as rapidly and as much as is possible.
- Outdoor residual spraying (ORS) has been evaluated through a controlled trial and appears to be associated with a reduction in the number of Pk cases in selected localities. However, in WHO's opinion, the evidence is not strong enough
- There are very good efforts at identifying alternative Pk control methods but to date, efforts have not resulted in sufficient reduction of transmission

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WHO's work on Pk: Scoping mission to Malaysia, 23-28 July 2023

Joint Working Group

1. Hold quarterly situational updates on zoonotic malaria and exchange information, at least once per year face-to-face
2. Regularly review current zoonotic malaria control strategies, for example ORS, based on new tools and knowledge and propose adjustments as needed
3. Discussion on criteria for certification of malaria elimination in the presence of zoonotic malaria
4. Establish research questions as part of zoonotic malaria research framework, including budgets and required expertise
5. Commission reviews on priority areas to answer gaps in knowledge
6. Conduct international level advocacy for global knowledge and advancement of funding opportunities, including communication packages both within and beyond the health sector
7. Assist selected institution on the preparation of an application to become WHO Collaborating Center (WHO-CC)

WHO CC on zoonotic malaria

- Development of a kit for rapid diagnosis of Pk at point of care
- Development of diagnostic tool for outbreak investigation
- Genetic factors for severity of Pk malaria
- Factors responsible for zoonotic malaria prevalence on the east side of Crocker range
- Determine plasmodium species in human and non-human primates
- Pk in healthy people, vectors and pet monkeys
- Detection of natural products against malaria
- Community engagement and education

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WHO's work on Pk: TAG-MEC subgroup on zoonotic malaria

Members

- Pedro Alonso
- Brian Greenwood
- Kamini Mendis
- Allan Schapiro
- Larry Slutsker
- Martha Quiñones

- Draft of the procedure and requirements for certification of countries that have achieved elimination of the four plasmodium species (*P. falciparum*, *Pv, Pm* and *Po*), while zoonotic malaria remains transmitted.
- Draft guidance on the process and conditions for decertification of countries where Pk is transmitted.

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Thank you

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