

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, 12 October 2022			
	Session 4	Open	
12:00 – 12:30	Update on the RTS,S malaria vaccine roll-out Background Presentation	Ms Eliane Furrer	For information
12:30 – 13:15	Update on malaria elimination and the technical consultation on prevention of re-establishment of malaria Background Presentation	Dr Elkhan Gasimov	For guidance
13:15 – 13:45	Update on the Framework for response to urban malaria Presentation	Dr Abdisalan Noor	
	Session 5	Open	
14:00 – 14:30	Update on rectal artesunate for severe malaria – independent review of evidence and field manual Presentation	Dr Peter Olumese	For guidance
14:30 – 15:00	Update on <i>pfhrp2/3</i> gene deletion issues Background Presentation	Dr Jane Cunningham	
15:00 – 15:30	Update on the spread of <i>An. stephensi</i> in Africa and the WHO response WHO initiative Presentation	Dr Jan Kolaczinski Dr Seth Irish	

Update on the RTS,S/AS01 malaria vaccine roll-out

Malaria Vaccine Implementation Programme, October 2022

1. Background

In October 2021, the World Health Organization (WHO) recommended widespread use of the RTS,S/AS01 (RTS,S) malaria vaccine for children in sub-Saharan Africa and other regions with moderate to high *P. falciparum* malaria transmission (1). The WHO recommendation was informed by data and insights generated by the pilot implementation of the malaria vaccine in routine immunization programmes in selected areas of Ghana, Kenya and Malawi, and other available RTS,S clinical evidence (2).

The Malaria Vaccine Implementation Programme (MVIP) in the three pilot countries will continue through 2023, with continued monitoring of data on safety, impact, coverage achieved and the added benefit of a fourth dose.

WHO and partners are facilitating the next steps for the first malaria vaccine, including the dissemination of pilot experience and evidence to inform country decision-making on vaccine adoption as part of national malaria control strategies.

In July 2022, WHO awarded prequalification to the RTS,S vaccine, which is a mandatory prerequisite for United Nations agencies, such as the United Nations Children's Fund (UNICEF), to procure the vaccine in partnership with Gavi, the Vaccine Alliance, and eligible countries (3).

2. The MVIP

Vaccine implementation performance in the three MVIP countries continues to be generally strong, with no major disruptions, and there is good community acceptance of the vaccine. As of early September 2022, 3.4 million doses of the malaria vaccine had been administered across the three countries, and more than 1.1 million children had received at least one dose of the RTS,S vaccine. Based on administrative data, coverage for the first dose was 74% in Ghana (third dose: 72%), 83% in Kenya (third dose: 71%), and 84% in Malawi (third dose: 72%) in the period between January 2022 and July 2022 (May 2022 for Malawi). This level of uptake continues to meet or exceed expectations for a new vaccine with a novel schedule. Priority actions to maintain and further improve immunization performance, particularly on the uptake of the fourth dose, continue to be taken by the national immunization programmes, supported by partners.

The Ministries of Health of Ghana, Kenya and Malawi have stated their decisions to expand use of the malaria vaccine as rapidly as possible. Each of the countries is planning to expand vaccine implementation into comparator areas of the pilots (i.e. areas that have not yet received the vaccine) in Q4 2022 or Q1 2023, supported by the vaccine doses donated for the MVIP and additional funding provided through a grant from Open Philanthropy to PATH.

All of the pilot countries are currently preparing funding applications to Gavi to continue malaria vaccinations once the MVIP has ended. (See more about Gavi applications for country support below.)

3. Preparation and country support for broader roll-out

Soon after the WHO recommendation for the malaria vaccine, in December 2021, the Gavi Board approved an initial investment of US\$ 155.7 million for the 2022–2025 period to support broader roll-out of the malaria vaccine in Gavi-eligible countries with areas of moderate to high malaria transmission (4). These funds complement an earlier Gavi investment of US\$ 56 million for the malaria vaccine through a “de-risk” agreement with manufacturer GSK and innovative financing partner MedAccess.

In July 2022, Gavi launched the first opportunity for countries to apply for funding to introduce, or further roll-out, the malaria vaccine. The first application deadline on 13 September 2022 is reserved for countries currently piloting the vaccine, for which continuity of the vaccine programme is a priority. The second funding window is open to other eligible endemic countries to apply by January 2023. Countries are encouraged to submit expressions of interest during the first funding window to facilitate planning visibility, including on possible vaccine and technical assistance needs. Gavi and other partners are working with countries to provide orientation and technical assistance to ensure quality planning and country readiness in view of these first two and future application windows. Given an initially constrained vaccine supply, the Gavi application guidelines (5) outline a phased introduction approach in order to target vaccination support to the areas of greatest need, and to expand vaccine use as supply increases to meet demand. This approach is in line with the *Framework for the allocation of limited malaria vaccine supply* (6), which prioritizes the vaccine for children living in areas of greatest need.

Key requirements for the Gavi funding application include national introduction plans that specify the role of the malaria vaccine within comprehensive malaria control strategies, and subnational stratification of the areas of greatest need, based on best available local evidence. Applications will be reviewed by the Gavi Independent Review Committee, and successful applicants will then have a period of implementation planning support before roll-out.

A total of 23 countries in Africa have expressed interest in applying for Gavi support to introduce the malaria vaccine, and 17 intend to submit applications by January 2023. Most of these countries plan to participate in technical assistance workshops to prepare their Gavi applications.

Gavi and WHO are conducting a series of technical workshops to assist countries in decision-making, planning and preparation of Gavi funding applications. The workshops include presentations to review application requirements and background on the malaria vaccine, including panel discussions with MoH from the pilot countries to share lessons learned from the pilot implementation; interactive sessions on data review and assessment to categorize areas of greatest need for phased introduction; and facilitated discussions that lead to initial introduction planning. The first workshop was held in July in Ghana, a second workshop in Ghana in late September, and a third one will take place in Kenya in October.

4. Vaccine supply

UNICEF announced in August that it had secured supply of the GSK-produced RTS,S/AS01, which will enable more countries to start introducing the vaccine. The contract award is for an available malaria vaccine supply of 18 million doses over the next three years at an expected price of €9.30 per dose for 2023–2025 (7, 8). The initial price of the vaccine is influenced by the currently low supply volumes. This critical decision-making information for countries interested in preparing an application for Gavi support is being disseminated through technical assistance workshops and direct interactions with country delegations, in addition to information-sharing efforts by UNICEF and Gavi. WHO is engaging in market shaping activities with Gavi and UNICEF to increase malaria vaccine supply and reduce cost (see below).

High demand for the vaccine was anticipated to outpace supply in the initial few years of roll-out. Steady-state demand for the vaccine is expected to exceed 80 to 100 million doses per year.

Anticipating demand would outstrip supply, WHO coordinated the development of the *Framework for the allocation of limited malaria vaccine supply* (6) in order to guide where limited doses should be allocated in a fair and transparent way, based on ethical principles and the best available evidence. It was developed with guidance from expert advisers, most of whom are from malaria-affected countries in Africa, and inputs from stakeholders during a broad consultation process (including with the Malaria Policy Advisory Group during its meeting in March 2022). The priority principle of the Framework is to allocate the malaria vaccine to the areas of greatest need across countries, that is, to areas where the malaria disease burden in children and the risk of death are highest (category 1 areas as defined by the Framework). A primary implication is that all countries will have to consider a phased approach to vaccine implementation, starting at subnational level in the areas of greatest need, with expansion as supply increases.

The Framework was completed and published in July and made available to countries, stakeholders and partners through a comprehensive dissemination plan. Supply allocation decisions are expected to be made following the conclusion of each Gavi application round. The Framework is intended to be dynamic to support malaria vaccine prioritization decisions at the start of vaccine roll-out and over the coming years as supply ramps up, until supply fully meets demand.

Gavi partners are in the process of developing a market-shaping roadmap that outlines how Gavi wants to see the malaria vaccine market evolve into a healthier state in both the short and long term. Addressing the expected short-term supply constraints is among the highest priority objectives. The potential entrance of a second malaria vaccine to the market in the next few years, as well as expected technology transfer of RTS,S to the Indian manufacturer Bharat Biotech International Limited could increase supply availability and affordability of a malaria vaccine in the medium term. The market-shaping roadmap also addresses key aspects of long-term supply; the need for a competitive, secure and sustainable supplier base (including the ambition for manufacturing in Africa); and the materialization of timely demand, product innovation and malaria vaccine affordability, including through future reductions in weighted average price and the Gavi co-financing policy update. The roadmap is expected to be published by Gavi during the second half of 2022 and the accompanying action plan implemented on an ongoing basis.

5. Candidate malaria vaccines

The most advanced malaria vaccine candidate, now in Phase 3 clinical development, is the R21/Matrix-M, developed at the University of Oxford and currently manufactured by the Serum Institute of India. The results from a Phase 1/2b trial after two years of follow-up in children in Burkina Faso were recently published in the *Lancet* (9). The results from the Phase 3 trials, particularly the results on vaccine safety, efficacy and duration of protection in different malaria transmission settings, will inform future WHO recommendations for this vaccine. A second malaria vaccine could be highly beneficial to malaria control, particularly because it could increase supply to meet the high demand, resulting in greater access and more lives saved.

6. References

1. Malaria vaccine: WHO position paper – March 2022. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/352337>, accessed 18 September 2022).
2. Malaria vaccine implementation programme [website]. Geneva: World Health Organization (<https://www.who.int/initiatives/malaria-vaccine-implementation-programme>, accessed 18 September 2022).

3. Mosquirix product overview [website]. In: WHO – Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control. Geneva: World Health Organization (<https://extranet.who.int/pqweb/content/mosquirix>, accessed 18 September 2022).
4. Gavi Board approves funding to support malaria vaccine roll-out in sub-Saharan Africa [website]. Geneva: Gavi, the Vaccine Alliance; 2021 (<https://www.gavi.org/news/media-room/gavi-board-approves-funding-support-malaria-vaccine-roll-out-sub-saharan-africa>, accessed 18 September 2022).
5. Gavi support guidelines [website]. Geneva: Gavi, the Vaccine Alliance (<https://www.gavi.org/our-support/guidelines>, accessed 18 September 2022).
6. Framework for the allocation of limited malaria vaccine supply. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/m/item/framework-for-allocation-of-limited-malaria-vaccine-supply>, accessed 18 September 2022).
7. Millions more children to benefit from malaria vaccine as UNICEF secures supply [website]. New York: United Nations Children’s Fund; 2022 (<https://www.unicef.org/press-releases/millions-more-children-benefit-malaria-vaccine-unicef-secures-supply>, accessed 18 September 2022).
8. Malaria vaccine: questions and answers on vaccine supply, price and market shaping. Copenhagen: United Nations Children’s Fund Supply Division; 2022 (<https://www.unicef.org/supply/media/13396/file/Malaria-Vaccine-Supply-Price-Market-Questions-Answers-August2022.pdf>, accessed 18 September 2022).
9. Dattoo MS, Natama HM, Somé A, Bellamy D, Traoré O, Rouamba T, et al. Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial. *Lancet Infect Dis*. 2022. doi:10.1016/S1473-3099(22)00442-X.

Contact

For more information, please contact:

Mary Hamel, Malaria Vaccine Team Lead, WHO Headquarters, Immunization, Vaccines & Biologicals,
hamelm@who.int



World Health
Organization

Update on the RTS,S/AS01 malaria vaccine roll-out

Eliane Furrer, WHO/IVB – 12 October 2022

October 2021: WHO recommendation on use of the first malaria vaccine

WHO recommends the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO

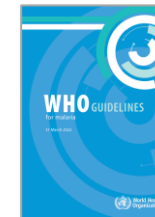
- RTS,S/AS01 malaria vaccine should be provided in a schedule of 4 doses in children from 5 months of age for the reduction of malaria disease and burden.
- Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a 5-dose strategy in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks.
- RTS,S/AS01 introduction should be considered in the context of comprehensive national malaria control plans.

Useful links



WHO malaria vaccine position paper

<https://www.who.int/publications/i/item/who-wer9709-61%E2%80%939380>



WHO Guidelines for malaria
PDF version:

<https://www.who.int/publications/i/item/guidelines-for-malaria>

MAGICapp Online platform:

<https://app.magicapp.org/#/guideline/5701>



Malaria Vaccine Implementation Programme

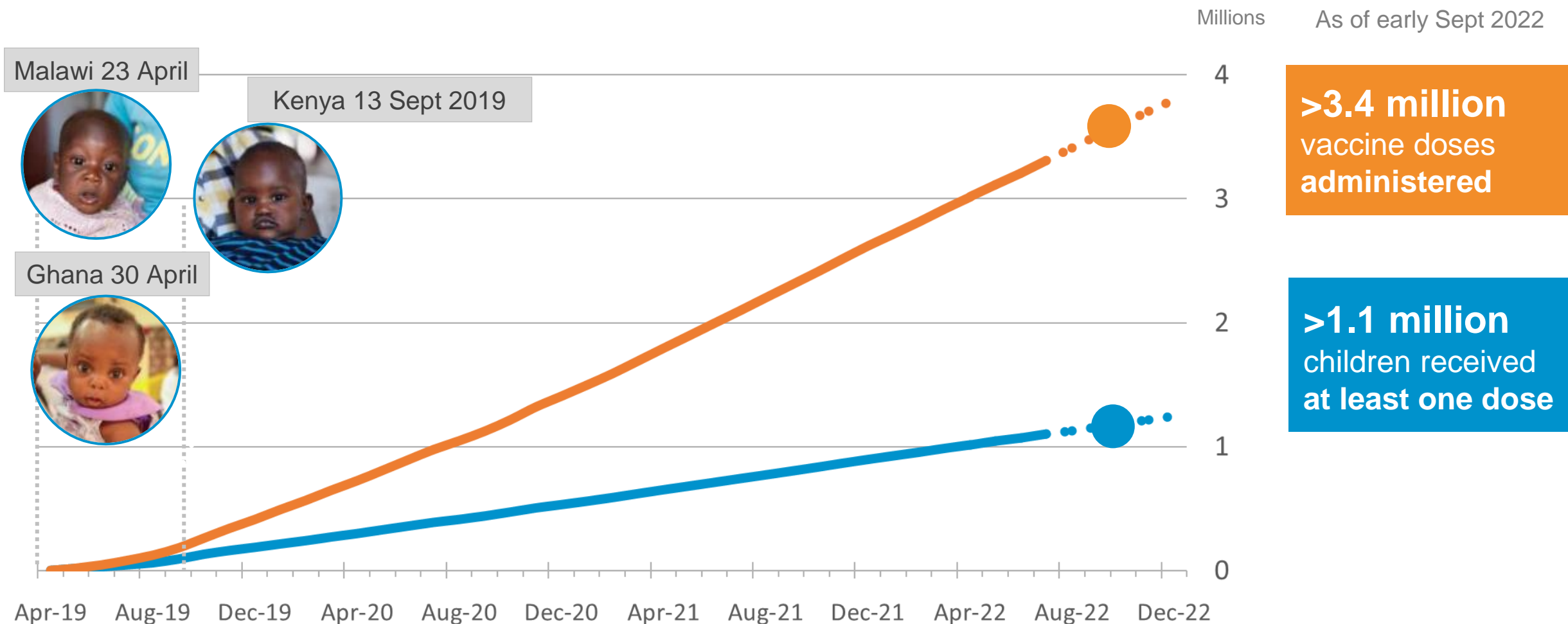
<https://www.who.int/initiatives/malaria-vaccine-implementation-programme>



NITAG Resource center

<https://www.nitag-resource.org/>

The Malaria Vaccine Implementation Programme (MVIP) expected to be completed by Dec 2023



Estimates as of early September 2022 - based on monthly MOH/EPI administrative data reports until July 2022 (for Kenya and Malawi) and May 2022 (for Malawi) and MVIP team projections for subsequent months

Malaria vaccine is becoming part of Gavi, the Vaccine Alliance's portfolio



Included in Gavi support

- Support to Gavi-eligible countries for the introduction of malaria vaccines into national immunisation schedules in areas with moderate to high *P. falciparum* malaria transmission.
- Support covers vaccines and associated safe injection supplies, financial support to facilitate the introduction, and technical assistance.
- Gavi Board in December 2021 approved an initial investment of US\$ 155.7 million for the 2022–2025 period, in addition to US\$ 56 million for a “de-risk” agreement with manufacturer GSK and innovative financing partner MedAccess.

First opportunities to apply

- September: MVIP countries applied to ensure continuation of vaccination following completion of pilots
- January 2023: First window for other eligible countries (and MVIP countries for further expansion requests)

Expression of interest

- As of today, **at least 24 countries have expressed interest** to introduce the malaria vaccine (most aiming to submit application to Gavi at the first opportunity in January)

UNICEF announces contract award that secures supply for further roll-out, August 2022



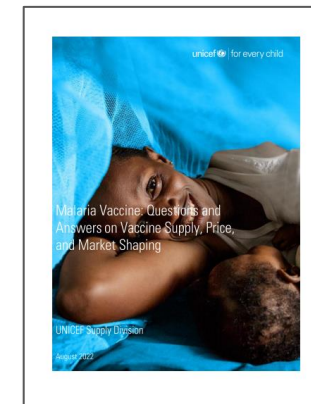
- 18 million doses total from 2023-2025
- Low volumes result in initial high cost: 9.30 Euro/dose
- Supply constraints expected to continue for the next few years. Efforts to increase capacity include:
 - Product transfer from GSK to Bharat Biotech. GSK announcement to double production of AS01 at Kigali Summit (23 June)
 - 2nd malaria vaccine (most advanced is R21/Matrix M in Phase 3 trials)
- To be published shortly: Gavi Alliance market shaping roadmap outlining how the malaria vaccine market should evolve into a healthier state in both the short- and long-term. Increase supply and reduce cost among the key objectives

Useful links



UNICEF news release

<https://www.unicef.org/press-releases/millions-more-children-benefit-malaria-vaccine-unicef-secures-supply>



UNICEF Q&A on malaria vaccines supply, price and market-shaping efforts

<https://www.unicef.org/supply/documents/malaria-vaccine-questions-and-answers-august-2022>

Framework for the allocation of limited malaria vaccine supply

Available on [WHO website](https://www.who.int/)

1 million doses per year
(relevant for countries with large cat. 1 areas)

Governance principles

Transparency

Inclusiveness & participation

Accountability

Ethical principles for allocation

First priority principle: Greatest need

Allocate the vaccine to countries with areas of greatest need, where the malaria disease burden in children and the risk of death are highest

Second priority principle: Maximize health impact

Allocate the vaccine to countries for use in areas where the expected health impact is greatest

Third priority principle: Equity (Equal Respect)

Prioritize countries that commit to fairness and addressing the needs of marginalized individuals and communities in their malaria vaccination programmes

Fourth priority principle: Fair benefit sharing

If everything else is equal, the country with a prior contribution to the vaccine's development should get priority

Additional key considerations



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



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



Minimize risk of vaccine wastage and delayed use of available doses



Allocation should not perpetuate pre-existing structural injustices

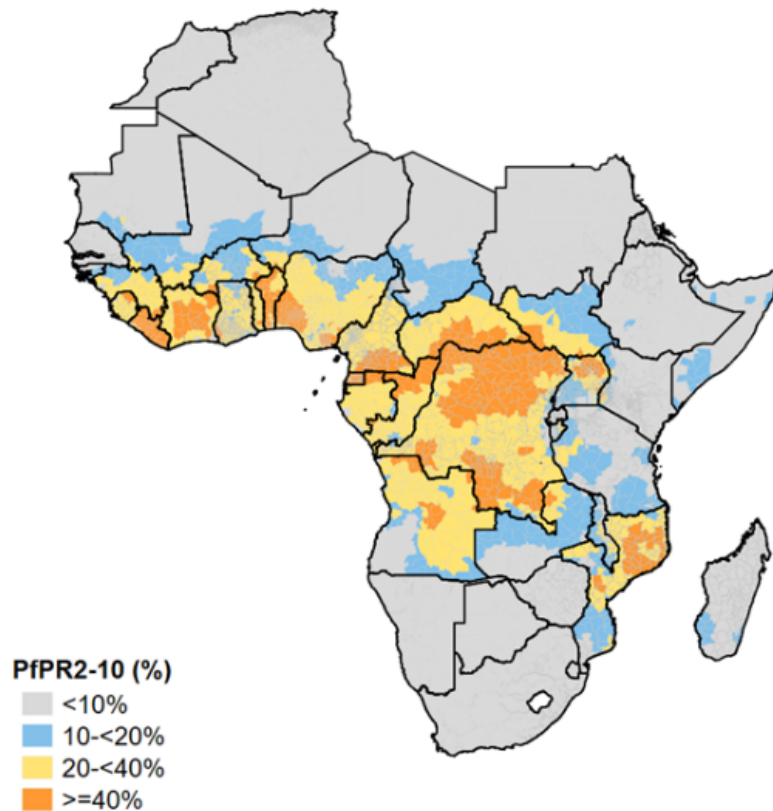
Foundational value: solidarity

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

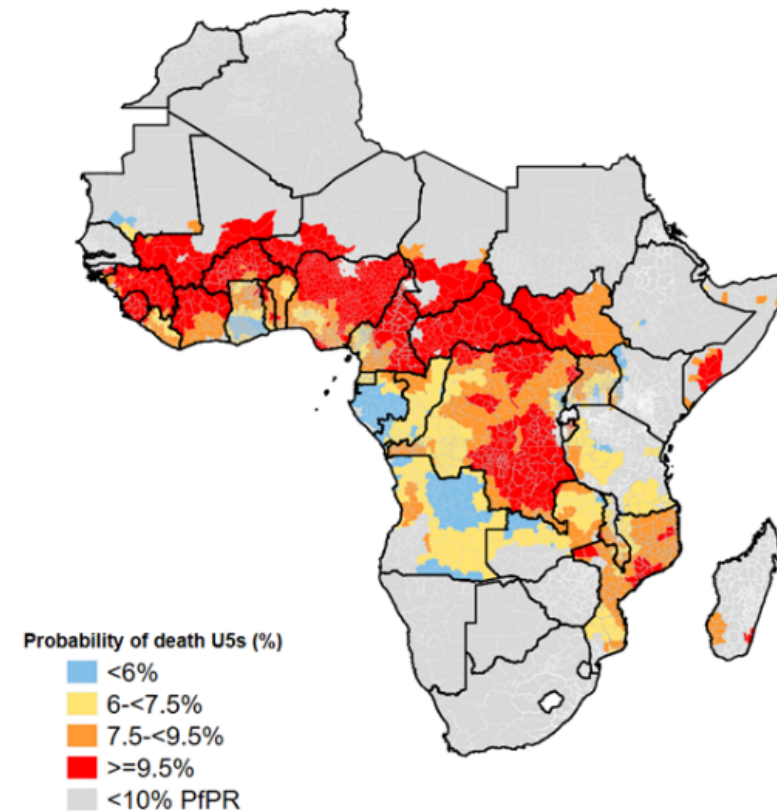
Initially, if there are unmet vaccine requests for greatest need (category 1) areas across multiple countries, no single country should receive more than 20% of the total available supply

Illustration of “need” classification

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

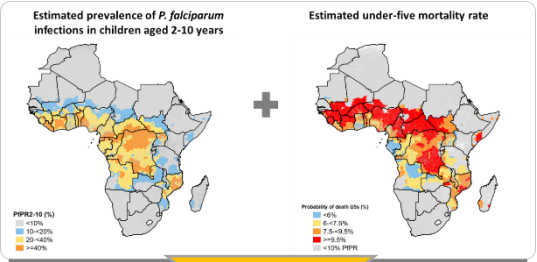


Estimated under-five mortality rate




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

Illustration of “need” classification



























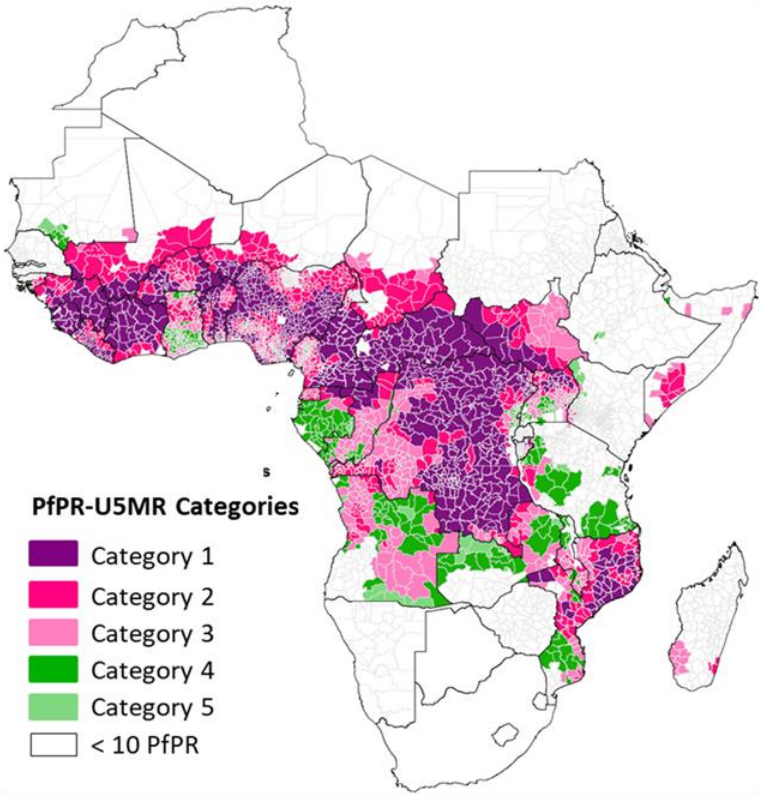
Composite classification of malaria prevalence and all-cause under-five mortality as proxy for “need”

 **Indicative.**
Countries will present their own data

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

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

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



How will the Framework be applied?

 **Indicative*** - Countries invited to review and present their own data

Birth cohort (2023)	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5
Angola	-	86,000	255,000	224,000	351,000
Benin	205,000	102,000	108,000	43,000	-
Burkina Faso	266,000	385,000	163,000	-	-
Burundi	111,000	80,000	100,000	24,000	-
Cameroon	190,000	213,000	318,000	104,000	32,000
Central African Republic	168,000	11,000	-	-	-
Chad	-	376,000	78,000	-	-
Congo	4,000	4,000	48,000	66,000	55,000
Côte d'Ivoire	567,000	328,000	-	-	-
Democratic Republic of the Congo	1,987,000	535,000	641,000	130,000	369,000
Equatorial Guinea	-	20,000	5,000	-	-
Ethiopia	-	-	-	7,000	19,000
Gabon	1,000	5,000	2,000	49,000	1,000
Ghana	10,000	75,000	70,000	247,000	147,000
Guinea	291,000	141,000	17,000	-	77,000
Guinea-Bissau	-	9,000	5,000	3,000	-
Kenya	-	4,000	4,000	11,000	93,000
Liberia	48,000	75,000	49,000	-	-
Madagascar	-	32,000	32,000	12,000	-
Malawi	-	19,000	240,000	136,000	-
Mali	171,000	458,000	11,000	-	-
Mauritania	-	-	3,000	26,000	44,000
Mozambique	337,000	406,000	183,000	77,000	-
Niger	192,000	628,000	100,000	-	-
Nigeria	2,830,000	3,188,000	890,000	301,000	-
Sierra Leone	178,000	-	37,000	-	-
Somalia	-	80,000	30,000	16,000	-
South Sudan	129,000	199,000	164,000	-	-
Togo	61,000	73,000	78,000	-	67,000
Uganda	181,000	192,000	650,000	327,000	243,000
United Republic of Tanzania	-	33,000	77,000	385,000	41,000
Zambia	15,000	33,000	113,000	160,000	88,000
TOTAL	7,942,000	7,790,000	4,471,000	2,348,000	1,627,000

Malaria vaccine - Update to MPAG October 2022

* Additional countries may identify areas of need



- Gavi invites countries to describe the full scope of needs – all categories – in their application, alongside a stratification by categories of need.
- The Framework is expected to be applied **following each Gavi application round** -> to all proposals recommended for approval by Gavi's Independent Review Committee (IRC)
- Firm vaccine allocation decisions will initially be:
 - Limited to category 1** (greatest need) areas.
 - Subject to the “**solidarity cap**” for countries with **large cat 1 areas: 1 million doses per year.**
 - If supply is insufficient to satisfy all category 1 areas from countries with successful applications, the second priority allocation principle (“maximize health impact” – with proxy measure **DTP3 to MCV1 drop out rate**) will be applied to establish the country order of priority

Three multi-country technical assistance workshops in Q3-Q4 2022 to support next steps



- To review Gavi application requirements and support countries to develop quality applications for the malaria vaccine
- To provide background on malaria vaccine and lessons learned from the pilot introductions
- To categorize areas of “need” for malaria vaccine (in alignment with principles of Allocation Framework for limited supply) and define potential phases of vaccine roll-out



Thank you

Susuana Heavenly Joy was the first child in Ghana to be vaccinated with the malaria vaccine in routine immunization as part of the pilot programme. Now three years old, she has received all four doses.



Photo Credit: PATH

We thank the MVIP funders, Gavi, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaaid for their generous support.

Octobre 2021: Recommandation de l'OMS sur l'utilisation du premier vaccin antipaludique



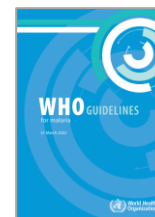
L'OMS recommande d'utiliser le vaccin antipaludique RTS,S/AS01 pour prévenir le paludisme à *P. falciparum* chez les enfants vivant dans les régions où la transmission du paludisme est modérée à élevée, telle que définie par l'OMS.

- Le vaccin antipaludique RTS,S/AS01 doit être administré selon un schéma à 4 doses aux enfants à partir de 5 mois pour réduire la charge de morbidité palustre.
- Les pays pourraient envisager d'administrer le vaccin RTS,S/AS01 de façon saisonnière, avec une stratégie à 5 doses, dans les zones où la transmission du paludisme est fortement saisonnière ou permanente avec des pics saisonniers.
- L'introduction du vaccin RTS,S/AS01 devra être envisagée dans le cadre des plans nationaux complets de lutte antipaludique.

Liens utiles



Note de synthèse :
position de l'OMS à propos du
vaccin antipaludique
<https://www.who.int/publications/i/item/who-wer9709-61%E2%80%939380>



Lignes directrices de l'OMS sur le paludisme
Version PDF :
<https://www.who.int/fr/publications/i/item/guidelines-for-malaria>
Plateforme en ligne MAGiCapp :
<https://app.magicapp.org/#/guideline/5701>



Programme de mise en œuvre du vaccin antipaludique
<https://www.who.int/initiatives/malaria-vaccine-implementation-programme>



Centre de ressources du GTCV
<https://www.nitag-resource.org/>

Technical consultation on prevention of re-establishment of malaria transmission

Concept note

1. Scope and rationale

The *Global technical strategy for malaria 2016–2030* (GTS) (1), endorsed by the World Health Assembly in 2015 and updated in 2021, reiterates the vision of a world free of malaria. The GTS sets four global targets for 2030, with milestones for measuring progress for 2020 and 2025. One of the GTS goals is to prevent the re-establishment of malaria in all countries that are malaria-free.

1.1 Epidemiological consequences of malaria importation: “stickiness” and resurgence

After elimination is achieved, the continued importation of malaria into malaria-free countries or areas might lead to two different epidemiological consequences: elimination is sustained or resurgence occurs. Many countries and regions have been able to maintain a malaria-free status; renewed transmission has not occurred, with only a few sporadic introduced cases. This phenomenon, “anophelism without malaria”, was recognized by early malariologists (2); it means that anophelines that previously transmitted malaria continue to be present, but transmission is not re-established with malaria importation. A review examined 50 malaria elimination programmes that had successfully eliminated malaria and found that only four (8%) had experienced resurgence (3). Every year, approximately 8000 imported cases are detected in Europe and 3000 in China, but transmission has not been re-established.

Several hypotheses have tried to explain the stability (or the “stickiness”) of elimination. Most countries that have achieved elimination probably had lower intrinsic transmission potential, e.g. situated in a temperate zone with a lower level of baseline endemicity. The improvement of health systems to detect and treat cases rapidly, increased urbanization, and social and economic development leading to changes in housing conditions that have reduced contact between humans and mosquitoes have contributed to the achievement of malaria elimination, as well as the stability of elimination. In other words, the methods that have been used intentionally to eliminate malaria, such as malaria-specific interventions, or unintentionally, such as urbanization and deforestation, might have implications for the stability of malaria elimination. In addition, the travel patterns in some malaria-free countries are such that the areas with the highest potential for transmission often have the lowest rates of malaria importation, which reduces the risk of re-establishment (4). Notably, the refractoriness of the local vectors to imported strains of parasites might also contribute to the stability of elimination. For example, the refractoriness of the European malaria vectors that were historically responsible for maintaining the transmission of *Plasmodium vivax* in Europe served to benefit Europe historically by impeding the spread of tropical *P. falciparum* (5). In China, it has been well studied that the most widely distributed vector, *Anopheles sinensis*, cannot transmit *P. falciparum*, which could partly explain the stability of elimination, as the majority of imported malaria cases are caused by *P. falciparum* from the African continent.

At the same time, some countries or regions have experienced renewed malaria transmission after elimination. Singapore experienced an outbreak in April–May 1993, but transmission was interrupted

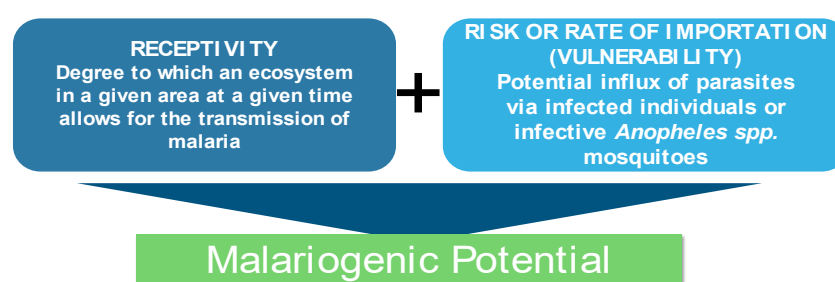
within a few weeks. In 2006, after 44 years of elimination of malaria, Jamaica had an outbreak of *P. falciparum*, with 406 confirmed cases between September 2006 and December 2009, peaking in December 2006 (6). Although most resurgences have been quickly managed and controlled, re-gaining malaria-free status can take a long time. In Mauritius, resurgence occurred two years after the country's malaria-free certification in 1973 and malaria transmission was re-established. The decades-long endemic transmission in Mauritius started from a few imported cases; however, resurgence should also be attributed to reduced case detection, increased breeding sites created by a cyclone and a substantial increase in *An. arabiensis* density due to reduced vector control (7). In recent years, several countries, such as Cabo Verde, Costa Rica and Timor-Leste, reached zero indigenous cases, but transmission re-started soon thereafter. Numerous studies have reported renewed transmission in subnational regions or units.

The understanding and analysis of the factors contributing to the stability of elimination and the causes leading to resurgence will inform the practice for prevention of re-establishment.

1.2 The concepts of receptivity, risk of importation and malariogenic potential, their measurement and practical use

The concepts of receptivity and risk of importation (also called vulnerability), as illustrated in Fig. 1, are considered relevant for malaria elimination and prevention of re-establishment, as they provide the basis for malaria risk stratification and tailoring of interventions, including surveillance.

Fig. 1. Concepts of receptivity, risk of importation and malariogenic potential



Proposed during the Global Malaria Eradication Programme, these concepts were initially used to determine the degree and type of vigilance (or disease surveillance) needed to maintain malaria-free status. Use of epidemiological experience, before and after the eradication programme, was recommended for delimiting areas of differential receptivity in order to plan and organize vigilance activities (8). A working group, convened by the WHO Regional Office for Europe, further discussed these concepts and considered receptivity to be a reflection of vectorial capacity. The working group recognized, however, that routine calculation of vectorial capacity for the measurement of receptivity was not feasible in practice (9). Instead, the use of past malaria endemicity, stability of malaria transmission, and the length of transmission season was proposed to measure receptivity. Current WHO guidance, as laid out in *A framework for malaria elimination* (10), recommends that receptivity be derived from the history of malaria, in particular the original endemicity, the vectorial capacity, environmental changes, and the stability of or changes in health system responsiveness. An evidence review group (ERG) was convened in 2018 to review the methods for measuring receptivity and vulnerability reported in the literature, in an attempt to improve the guidance on methods for measuring the components of malariogenic potential and on thresholds relevant for programmatic decisions (11). As part of the ERG, a literature review on malaria receptivity paid particular attention to quantitative measurement using vectorial capacity, reproduction number and other measures. However, the review did not find a standard metric for receptivity that was measurable, easily available and practical (12). For the measurement of vulnerability (importation risk), multiple methods were considered to be useful, but their relevance will be heavily dependent on the local context. It

was concluded that further improvements were needed before the methods discussed would be applicable and informative for programmatic use. The ERG also reviewed the variations in receptivity of *Anopheles* mosquito species (and populations) to exotic *Plasmodium* species (and strains). It was recommended that such parasite–vector infectivity specificity should be adequately acknowledged and that further evaluation should be conducted to support programmatic decisions. For example, the generation and use of vector competence data in China to guide action (e.g. de-prioritization of responses to Africa *P. falciparum* imported cases) may offer a good example that could be applied elsewhere.

Taken together, although the concepts of receptivity and risk of re-establishment are important, it is currently not feasible to measure them quantitatively in practice and they are in fact not used by malaria programmes. In the absence of quantitative measurement of such concepts, the question of “when to stop spraying”, which arose during the Global Malaria Eradication Programme, is not likely to be answered readily. Similarly, it will be difficult to measure whether the search for malaria cases is adequate in the absence of transmission. The experiences and lessons learned along the path from the detection of the last indigenous case to date will be informative for improving the adequacy, efficiency and effectiveness of surveillance and deploying/withdrawing vector control, among other activities.

1.3 Other challenges for prevention of re-establishment and the need for global guidance

After elimination is achieved, some malaria programmes continue with the same approach as during the course of elimination. Others reduce or withdraw activities and interventions, as the achievement of elimination is often used as an excuse or justification to reduce funding and human resources for malaria. Regardless of the risk of re-establishment of transmission, malaria-free countries and areas face challenges such as what technical expertise and activities to maintain and prioritize, and how. These questions are important not only because they are essential to the management of malaria importation and the prevention of resurgence, but also because they provide the rationale for malaria staff to request funding and support from the government after elimination. These questions help programmes to plan, organize and implement integration when they are close to (or have already achieved) malaria elimination. For those malaria programmes that have already integrated with other public health programmes, guidance is needed on improving the efficiency and effectiveness of their interventions, as other diseases are competing with malaria for both human and financial resources.

Although prevention of re-establishment is a goal of the GTS, global guidance on the prevention of re-establishment is scant, with the last global meeting on prevention of re-introduction having been convened in 1967 (13). Some regions have published guidance on prevention of re-introduction, as progress on malaria elimination was more advanced (14,15). Globally, 100 countries are entirely free of malaria. Of the 92 malaria-endemic countries, 47 report fewer than 10 000 malaria cases, which means that parts of their territories are free of transmission. From 2000 to 2020, the number of countries reporting fewer than 100 cases has increased from six to 26. Therefore, many malaria programmes are working or will be working on prevention of re-establishment. Unlike the countries that achieved malaria elimination during the Global Malaria Eradication Programme, many of the countries that have eliminated malaria in the very recent past and those in the last mile of elimination are situated in tropical zones; therefore, they have higher receptivity and higher risk of re-establishment. There is therefore a greater need to provide guidance on prevention of re-establishment. Over the last few decades, the wealth of knowledge on prevention of re-establishment of transmission has been expanding as elimination gathers speed. The current coronavirus disease (COVID-19) pandemic has presented unprecedented challenges for public health systems, but has also offered opportunities to reflect and improve preparedness and the capacity for dealing with emergencies, which is very relevant to the subject of prevention of malaria transmission. Therefore, WHO has decided to convene a technical consultation on prevention of re-establishment to review

the evidence, practices, experiences and lessons learned across the globe, and to develop guidance to inform current efforts to maintain malaria-free status in countries and regions.

2. General objective

Review and update current WHO guidance on prevention of re-establishment to support countries' efforts to maintain malaria-free status at national and subnational levels.

3. Specific objectives

The technical consultation meeting will review available data and evidence, practices, experiences and lessons learned in preventing the re-establishment of transmission in malaria-free countries or areas in order to achieve the following objectives:

- Provide guidance on how to improve the efficiency, effectiveness and sustainability of detection of malaria cases, including outbreak detection and response.
- Provide guidance to maintain quality-assured diagnosis and case management.
- Provide guidance on integrating malaria activities into general health services and sustaining a malaria-free status through the process of building a resilient health system.
- Provide guidance on mitigating receptivity and risk of importation, and methods to monitor changes in receptivity, risk of importation and risk of re-establishment in order to inform a suitable mix of interventions.
- Provide guidance on leveraging multisectoral collaboration for the prevention of re-establishment of transmission.
- Define research priorities to inform the practice of preventing re-establishment of transmission.

4. Methods of work

The technical consultation will include a series of activities broken down into five events, as detailed in Table 1.

Table 1. List of planned activities and timeline

EVENT		OBJECTIVE	TIMELINE
1	Working group meeting #1	Discuss and consolidate the workplan, define roles and responsibilities	November 2022
2	Officially launch the technical consultation on prevention of re-establishment during the fourth Global Forum of malaria-eliminating countries	<ul style="list-style-type: none"> • Launch the technical consultation • Review and discuss two case studies: China and El Salvador • Discuss challenges to prevention of re-establishment: perspectives from national malaria programme managers (Algeria, Cabo Verde, Paraguay, Timor-Leste) 	December 2022
3	Virtual meetings to review case studies and updates on WHO policies and recommendations on health systems	3-1 Greece, Oman and Paraguay 3-2 Tajikistan, Uzbekistan plus one presentation on health systems (primary health care)	January–February 2023

		3-3 Mauritius, Sri Lanka plus one presentation on health systems (resilience)	
4	Physical meeting tentatively in Tbilisi, Georgia	Evidence review meeting	March 2023
5	Working group meeting #2 virtual: consolidate writing	Discuss an advanced draft	August 2023
6	Publish the product of the technical consultation		December 2023

5. Evidence to be reviewed at the meeting in Tbilisi, Georgia

1. Literature and grey literature review on prevention of re-establishment (commission ISGlobal), including:
 - literature and grey literature on factors that contribute to the resurgence of malaria after elimination is achieved
 - literature and grey literature on factors that might contribute to the stability of malaria elimination in malaria-free countries
 - literature and grey literature on the risk of malaria re-establishment in Europe, including during and before the Global Malaria Elimination Programme
 - WHO meeting reports on prevention of re-introduction (including the ERG on malariogenic potential and the commissioned review on receptivity, vulnerability and infectivity)
2. Studies on the risk of re-establishment of transmission in recently certified countries (in chronological order by certification date): United Arab Emirates, Armenia, Morocco, Kyrgyzstan, Turkmenistan, Maldives, Sri Lanka, Uzbekistan, Paraguay, Algeria, Argentina, El Salvador, China
3. Country case studies, including:
 - synthesized case studies from country presentations: China, El Salvador, Georgia, Greece, Mauritius, Oman, Paraguay, Sri Lanka and Tajikistan
 - 10 available case studies on malaria elimination published by WHO in 2012 (Bhutan, Cabo Verde, Malaysia, Mauritius, Philippines, the island of Reunion (France), Sri Lanka, Tunisia, Türkiye and Turkmenistan)

6. Outcomes

1. Global framework for prevention of re-establishment of transmission
2. Published case studies on the prevention of re-establishment in the selected malaria-free countries: Greece, Paraguay and Tajikistan (outline in Annex 1)

7. Proposed participants

Experts in the following areas:

1. Selected members of the WHO Technical Advisory Group on Malaria Elimination and Certification
2. Independent experts on malaria epidemiology, entomology and disease surveillance

3. Experts on health system, warning and alert system, emergency preparedness and response
4. National programme managers

8. References

1. Global technical strategy for malaria 2016–2030, 2021 update. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/342995>, accessed 5 August 2022).
2. Hackett LW. Malaria in Europe, an ecological study. Oxford: Oxford University Press, H. Milford; 1937.
3. Feachem RGA, Phillips AA, Targett GA, Snow RW. Call to action: priorities for malaria elimination. *Lancet*. 2010;376:1517–21. doi:10.1016/S0140-6736(10)61500-0.
4. Dharmawardena P, Premaratne R, Wickremasinghe R, Mendis K, Fernando D. Epidemiological profile of imported malaria cases in the prevention of reestablishment phase in Sri Lanka. *Pathog Glob Health*. 2022;116(1):38–46. doi:10.1080/20477724.2021.1951556.
5. Bruce-Chwatt LJ, de Zulueta J. The rise and fall of malaria in Europe: a historico-epidemiological study. Oxford: Oxford University Press; 1980.
6. Webster-Kerr K, Figueroa JP, Weir PL, Lewis-Bell K, Baker E, Horner-Bryce J, et al. Success in controlling a major outbreak of malaria because of *Plasmodium falciparum* in Jamaica. *Trop Med Int Health*. 2011;16(3):298–306. doi:10.1111/j.1365-3156.2010.02700.x.
7. Tatarsky A, Aboobakar S, Cohen JM, Gopee N, Bheecarry A, Moonasar D, et al. Preventing the reintroduction of malaria in Mauritius: a programmatic and financial assessment. *PLoS One*. 2011;6(9):e23832. doi:10.1371/journal.pone.0023832.
8. WHO Technical Report Series 324, WHO Expert Committee on Malaria, 12th report Geneva, World Health Organization, 1966 (<https://apps.who.int/iris/handle/10665/39822>, assessed 27 September 2022)
9. Receptivity to malaria and other parasitic diseases: report on a WHO working group, Izmir, 11–15 September 1978. Copenhagen: World Health Organization Regional Office for Europe; 1978 (<https://apps.who.int/iris/handle/10665/204466>, accessed 18 September 2022).
10. A framework for malaria elimination. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/254761>, accessed 18 September 2022).
11. Meeting report of the WHO Evidence Review Group on the assessment of malariogenic potential to inform elimination strategies and plans to prevent re-establishment of malaria, 2–4 October 2018, Geneva, Switzerland. Geneva: World Health Organization; 2019 (<https://www.who.int/publications/m/item/WHO-CDS-GMP-MPAC-2019.05>, accessed 18 September 2022).
12. Yukich JO, Lindblade K, Kolaczinski J. Receptivity to malaria: meaning and measurement. *Malar J*. 2022;21:145. doi:10.1186/s12936-022-04155-0.

13. Prevention of the re-Introduction of malaria: a report of a WHO meeting held in Washington, D.C. from 14 to 18 November 1966. Geneva: World Health Organization; 1967 (<https://apps.who.int/iris/handle/10665/40670>, accessed 18 September 2022).
14. Guidelines on prevention of the reintroduction of malaria. Cairo: World Health Organization Office of the Eastern Mediterranean; 2007 (<https://apps.who.int/iris/handle/10665/119851>, accessed 18 September 2022).
15. Ejov M, Davidyants V, Zvantsov A. Regional framework for prevention of malaria reintroduction and certification of malaria elimination 2014–2020. Copenhagen: World Health Organization Regional Office for Europe; 2014 (<https://apps.who.int/iris/handle/10665/344589>, accessed 18 September 2022).

Annex 1. Outline of case studies (to be further defined)

1. Background
 - 1.1. Brief history of malaria
 - 1.2. Vectors, *Plasmodium* species transmitted
 - 1.3. Key interventions to achieve elimination: time to achieve elimination, major interventions used
 - 1.4. Any important aspects that contribute to elimination (urbanization, deforestation, others)
2. Health system (with a focus on malaria)
 - 2.1. Primary health care system: the collaboration between primary health care and the malaria programme
 - 2.2. Public health system: the surveillance and response system in peripheral areas to address the risk of re-establishment of malaria transmission
 - 2.3. Financing
3. Surveillance
 - 3.1. Suspected case definition
 - 3.2. Passive case detection
 - 3.3. Active case detection
 - 3.4. Cases detected
 - 3.5. Strategies to improve the efficiency of case detection
 - 3.6. Guidance and strategies to increase vigilance where applicable
 - 3.7. Case/outbreak investigation and response: integrated with other diseases? emergency response or not? why?
 - 3.8. Data analysis: annual surveillance data review?
 - 3.9. Monitoring and evaluation: maintain vigilance?
4. Risk of re-establishment of transmission
 - 4.1. Practices to stratify risk of re-establishment of transmission in malaria-free countries
 - 4.2. Monitoring the receptivity and risk of importation
 - 4.2.1. Who monitors? What methods are used to monitor? How does collected information/data lead to actions?
 - 4.2.2. Entomological surveillance
 - 4.3. Experiences and lessons learned on withdrawal of vector control: when/how (case studies: programme data)
 - 4.3.1. Time to start large-scale vector control
 - 4.3.2. Time to withdraw vector control
 - 4.3.3. Change in health system strength (indicators?)
 - 4.3.4. Social and economic development (indicators?)
 - 4.3.5. Other significant changes in environments (forestation/deforestation)

- 4.4. Other approaches to reduce receptivity
- 4.5. Other approaches to mitigate the risk of importation
- 5. Maintaining quality-assured diagnosis and case management
 - 5.1. Current practices in malaria-free countries (methods for diagnosis, drugs supply, referral system for severe case management, etc.)
 - 5.2. Challenges
 - 5.3. Cost-effectiveness
- 6. Integrating malaria activities into broader public health services
 - 6.1. Description of changes in the national malaria programme structure over time
 - 6.2. The decision-making process (how/when to integrate)
 - 6.3. Practices, experiences and lessons of integration
- 7. Role of multisectoral collaboration in prevention of re-establishment
 - 7.1. Improving surveillance
 - 7.2. Vector control
 - 7.3. Travellers' health
 - 7.4. Others
- 8. Cross-border collaboration (if relevant)
- 9. Outbreak response preparedness
- 10. Integration with other vector-borne disease programmes/general health system
- 11. Financial support

Update on malaria elimination and the technical consultation on prevention of re-establishment of malaria

Dr Elkhan Gasimov

Head, Elimination Unit

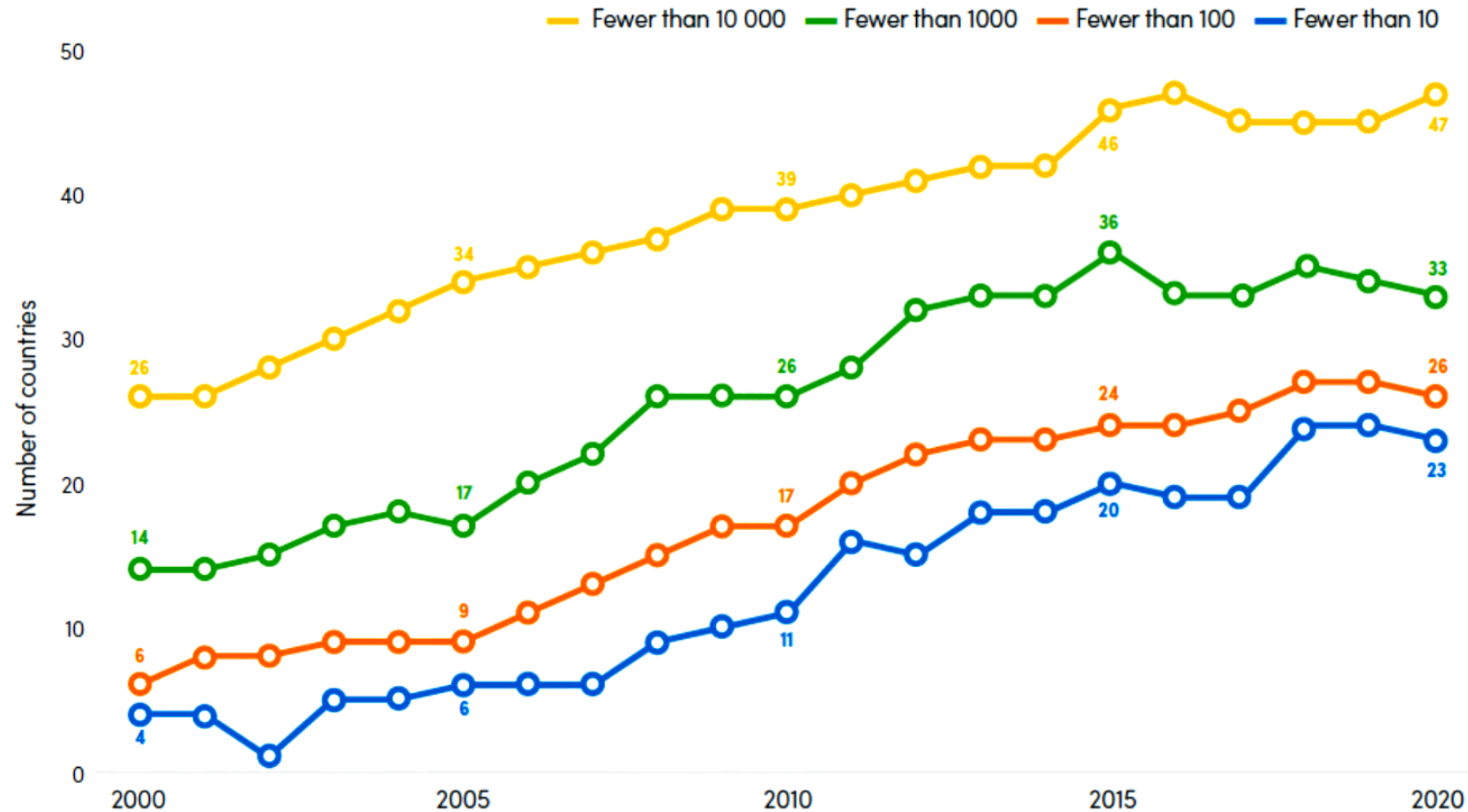
Global Malaria Programme

12 October 2022

Background



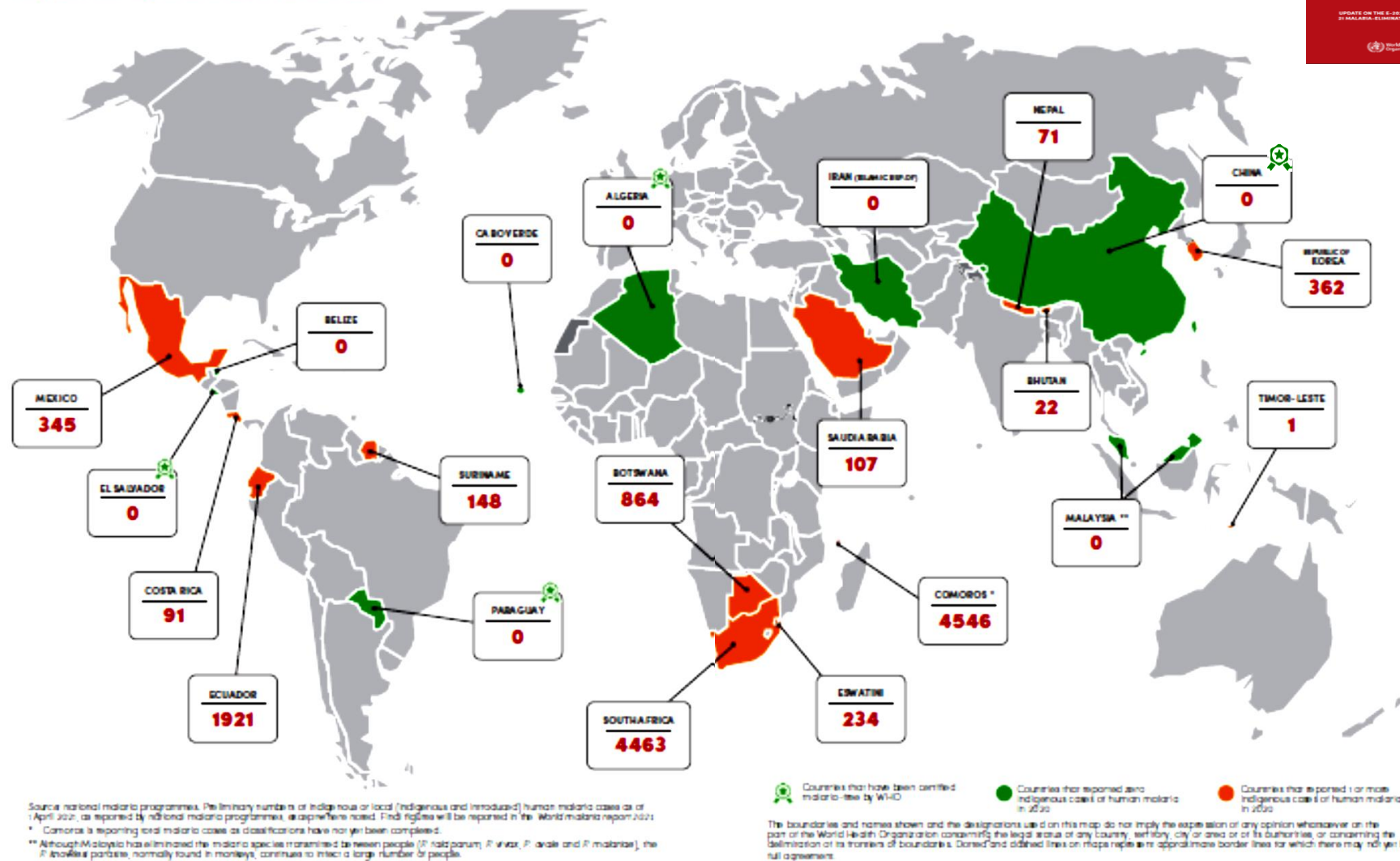
Number of countries that were malaria endemic in 2000 and had fewer than 10, 100, 1000 and 10 000 indigenous malaria cases between 2000 and 2020 *Sources: NMP reports and WHO estimates.*



NMP: national malaria programme; WHO: World Health Organization.

E-2020 countries

Snapshot of indigenous malaria cases in 2020



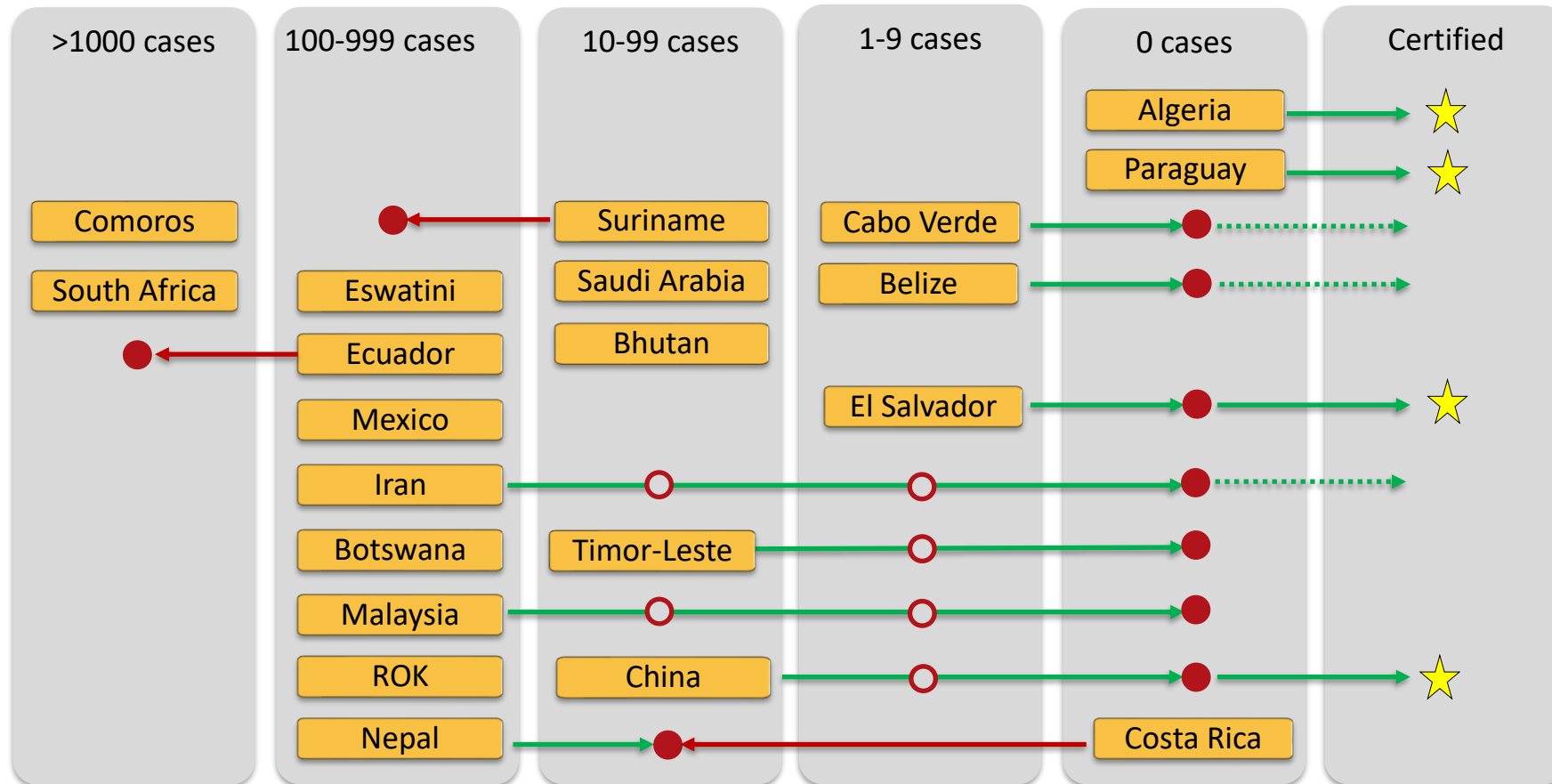
8 Drawing is an artistic estimation. Final report of the E-2020 initiative

Drawing is an artistic estimation. Final report of the E-2020 initiative 9

E-2020 Initiative outcomes



Health outcomes by end of 2020 compared to 2015 baseline

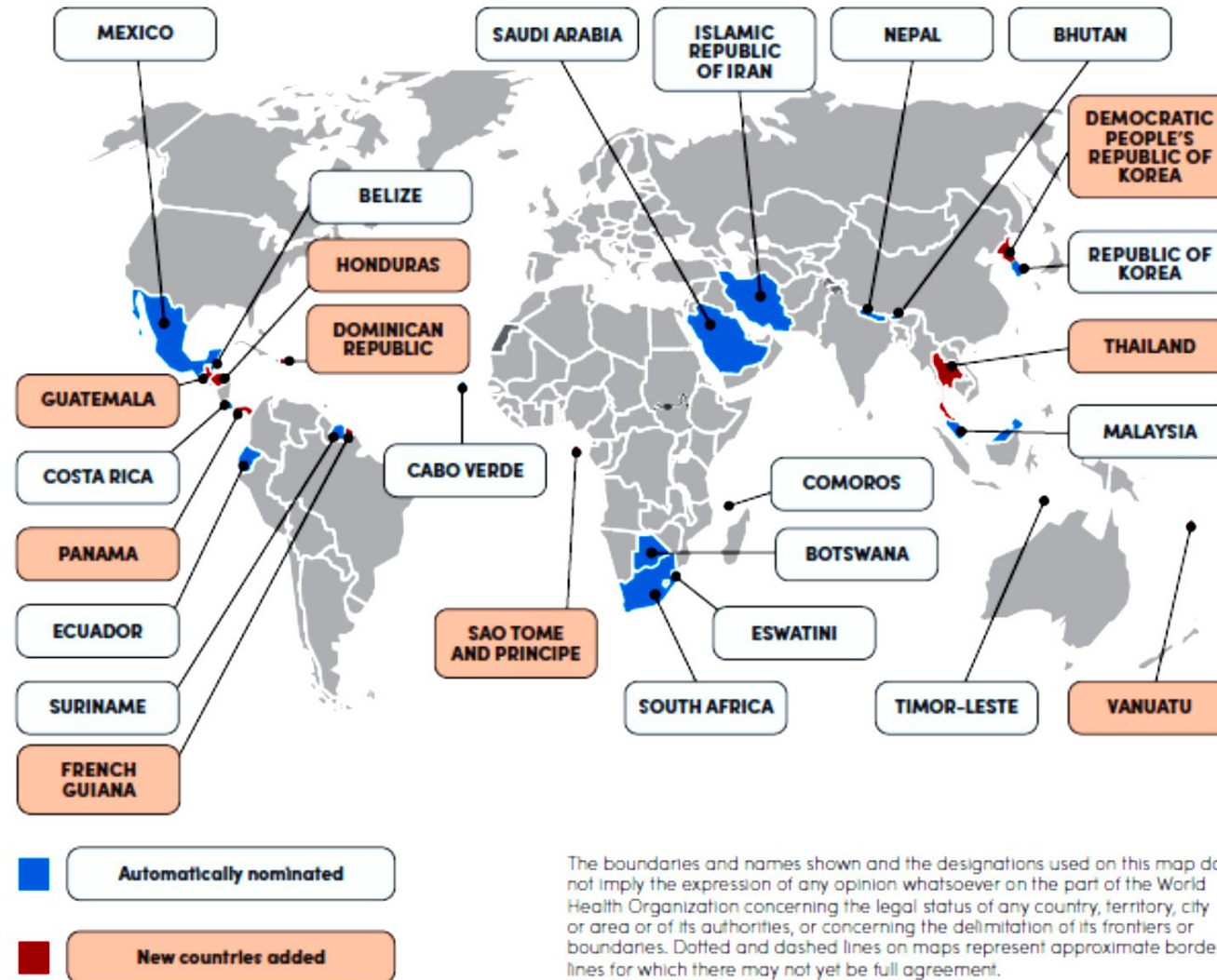


E-2020 countries endemic for malaria in 2015 that achieved 0 indigenous cases by the end of 2020:

- ✓ Algeria
- ✓ Belize
- ✓ Cabo Verde
- ✓ China
- ✓ El Salvador
- ✓ Iran
- ✓ Malaysia
- ✓ Timor-Leste

Countries and territories selected for the E-2025 initiative

2025



E-2025 Initiative: Objectives



Obj. 1: Accelerate the elimination of indigenous malaria transmission in E-2025 countries

At least one year of zero indigenous cases by 2025 in 10 countries that had indigenous malaria cases in 2015 and had not reached 0 indigenous cases by the end of 2020

Obj. 2: Certify countries as malaria-free after three years of zero indigenous transmission

At least 5 countries that meet the criteria and request certification are certified

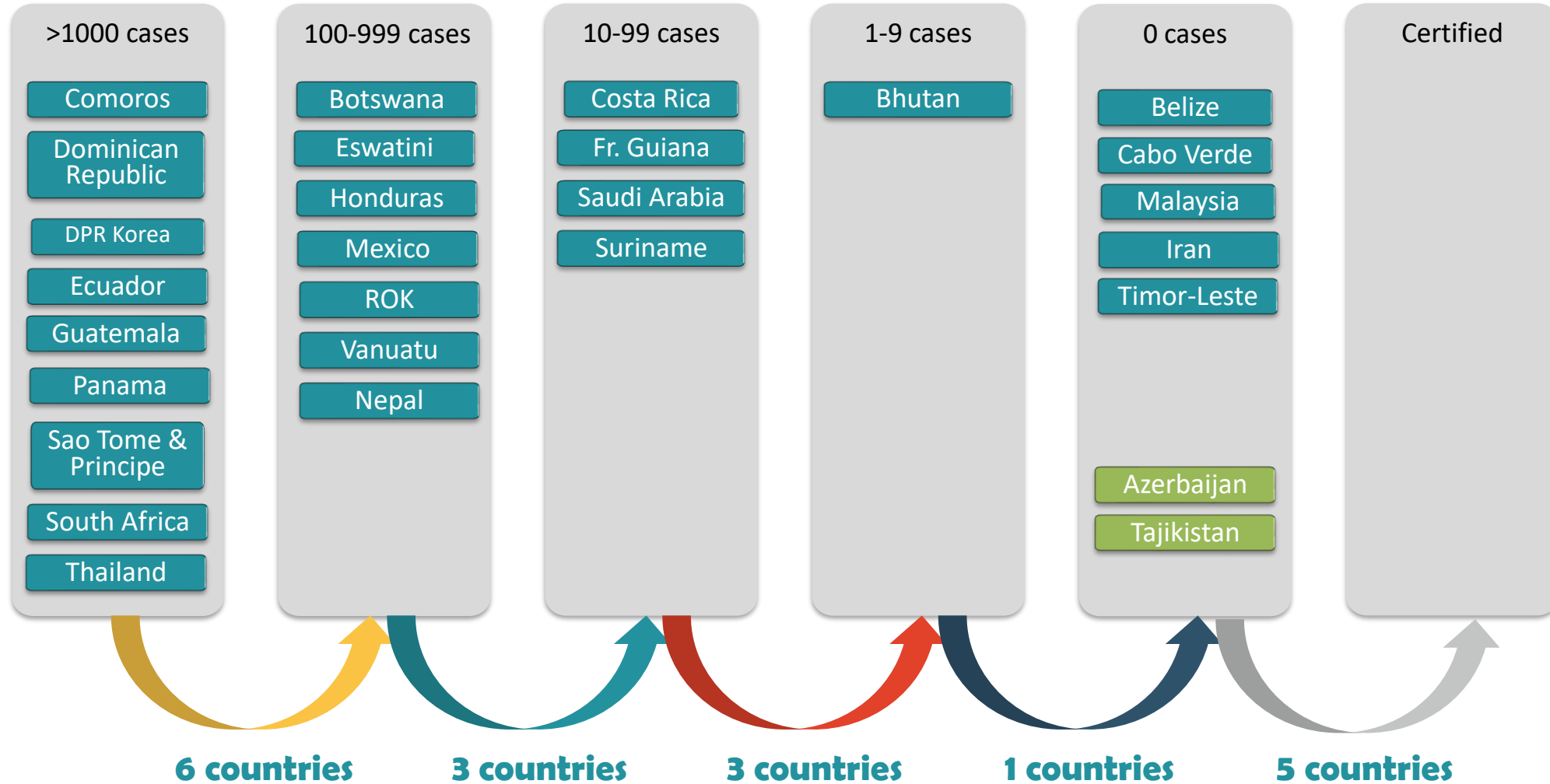
Obj. 3: Support malaria-free countries to prevent re-establishment

Re-establishment of malaria transmission is prevented in all malaria-free countries

E-2025 Initiative: expected outcomes by 2023



Health outcomes by end of 2023 compared to 2019 baseline



Country	2015	2016	2017	2018	2019	2020
Belize	9	4	7	3	0	0
Bhutan	34	15	11	6	2	22
Botswana	284	659	1 847	534	169	884
Cabo Verde	7	48	423	2	0	0
Comoros	1 884	1 467	3 896	15 613	17 599	4 546
Costa Rica	0	4	12	70	95	90
Democratic People's Republic of Korea	7 022	5 033	4 603	3 698	1 869	1 819
Dominican Republic	631	690	340	433	1 291	826
Ecuador	618	1 191	1 275	1 653	1 803	1 934
Eswatini	318	250	440	686	239	233
Guatemala	5 538	5 000	4 121	3 018	2 069	1 058
Honduras	3 555	4 094	1 266	632	330	815
Iran (Islamic Republic of)	167	81	57	0	0	0
Malaysia	242	266	85	0	0	0
Mexico	517	551	736	803	618	356
Nepal	591	507	623	493	127	73
Panama	546	769	649	684	1 580	2 190
Republic of Korea	627	602	436	501	485	356
Sao Tome and Principe	2 056	2 238	2 239	2 937	2 732	1 933
Saudi Arabia	83	272	177	61	38	83
South Africa	4 959	4 323	23 381	9 540	3 096	4 463
Suriname	81	76	19	29	95	147
Thailand	8 022	7428	5 694	4 077	3 198	3 009
Timor-Leste	80	81	16	0	0	3
Vanuatu	571	2252	1 227	632	567	493





- In 2022 both committees had come to an end of their tenure;
- GMP has taken a consultative process to determine the most optimal way forward taking the experiences and lessons learned over the last few years.
- WHO transformation: the establishment of the Science Division and the Department of Quality Assurance for Norms and Standards (2019)
- ToR: Combining the functions of MECP and MEOC
 - All functions of the former MECP
 - Some functions of MEOC

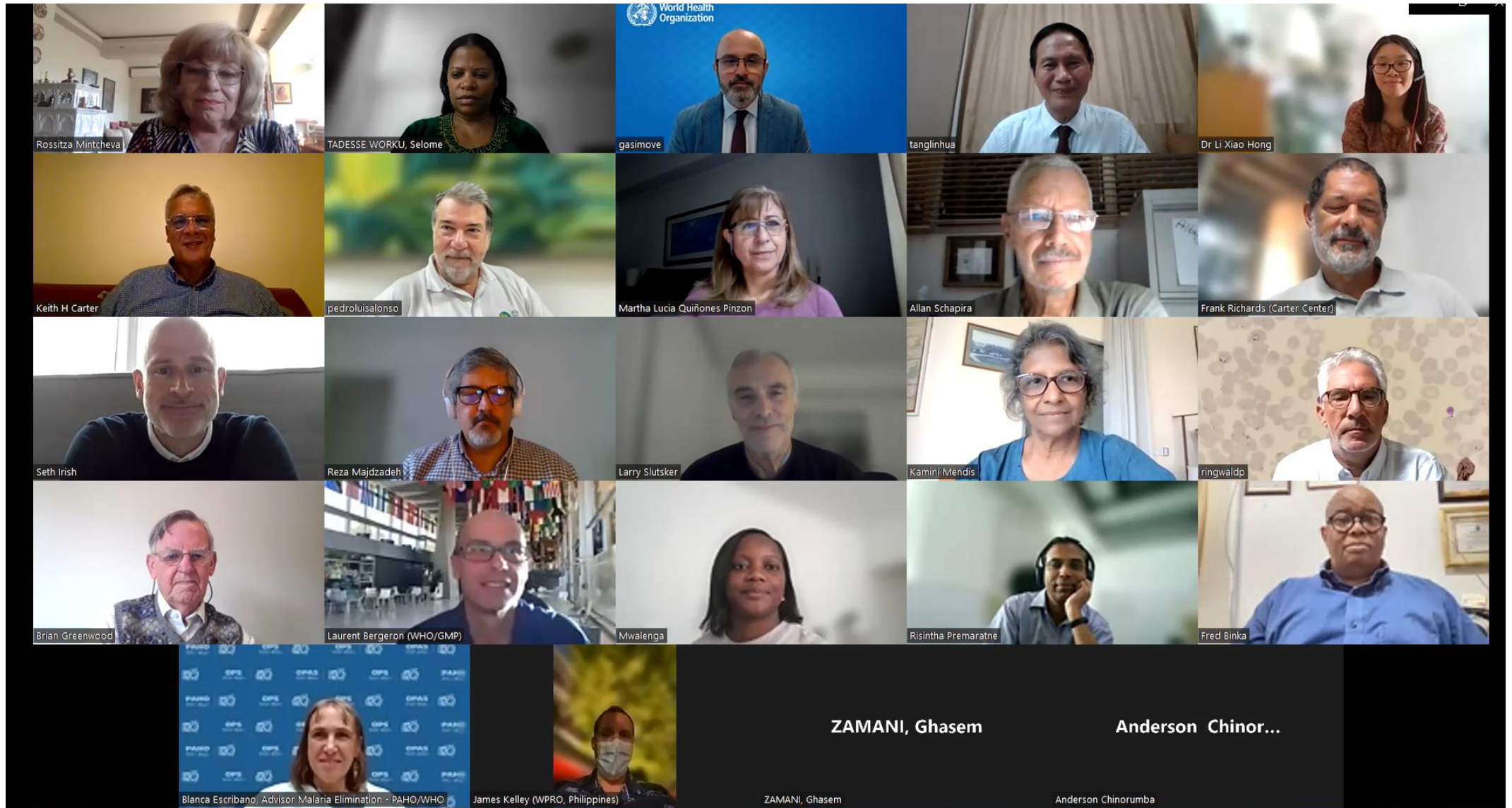


1. Provide independent evaluation and advise WHO whether a country could be certified as malaria free based on WHO criteria or certification should be postponed.
2. Review the data from countries that are certified malaria free on an annual basis and advise WHO whether a country should be de certified based on the WHO criteria.
3. Provide support to WHO to resolve bottlenecks for malaria elimination at country, regional and global levels.
4. Provide advice to WHO on areas where new or improved policy recommendations or implementation guidance may be required from WHO.
5. Provide other support and advice to WHO in the field of malaria elimination and prevention of re-establishment of transmission.



- **Pedro Alonso**
- **Fred Binka**
- **Keith Carter**
- **Brian Greenwood (chair)**
- **Anatoly Kondrashin**
- **Reza Majdzadeh**
- **Kamini Mendis**
- **Rossitza Mintcheva**
- **Martha Quinones**
- **Frank Richards (vice-chair)**
- **Allan Shapira**
- **Leonardo Simao**
- **Larry Slutsker**
- **Linhua Tang**

1st Meeting of TAG-MEC: 13-14 September 2022



Certification of malaria elimination



11 COUNTRIES	15 COUNTRIES and 1 TERRITORY	0	7 COUNTRIES	6 COUNTRIES
1955–1969	1970–1987	1988–2006	2007–2017	2018-2021
<ul style="list-style-type: none"> • Bulgaria • Cyprus • Dominica • Grenada • Hungary • Jamaica • Poland • Romania • Saint Lucia • Spain • Trinidad and Tobago 	<ul style="list-style-type: none"> • Australia • Bosnia-Herzegovina • Brunei Darussalam • Croatia • Cuba • Italy • La Réunion (France) • Mauritius • Montenegro • Netherlands • North Macedonia, • Portugal • Serbia • Singapore • Slovenia • United States of America 		<ul style="list-style-type: none"> • Armenia • Kyrgyzstan • Maldives • Morocco • Sri Lanka • Turkmenistan • United Arab Emirates 	<ul style="list-style-type: none"> • Algeria • Argentina • China • El Salvador • Paraguay • Uzbekistan

- 40 countries and territories have been certified malaria-free.
- 61 countries listed in supplementary list.



- In 2021-2022 five countries formally applied to WHO to initiate certification process: Azerbaijan, Belize, Cabo Verde, Iran (Islamic Republic of), Tajikistan

Azerbaijan: 3 to 14 October 2022

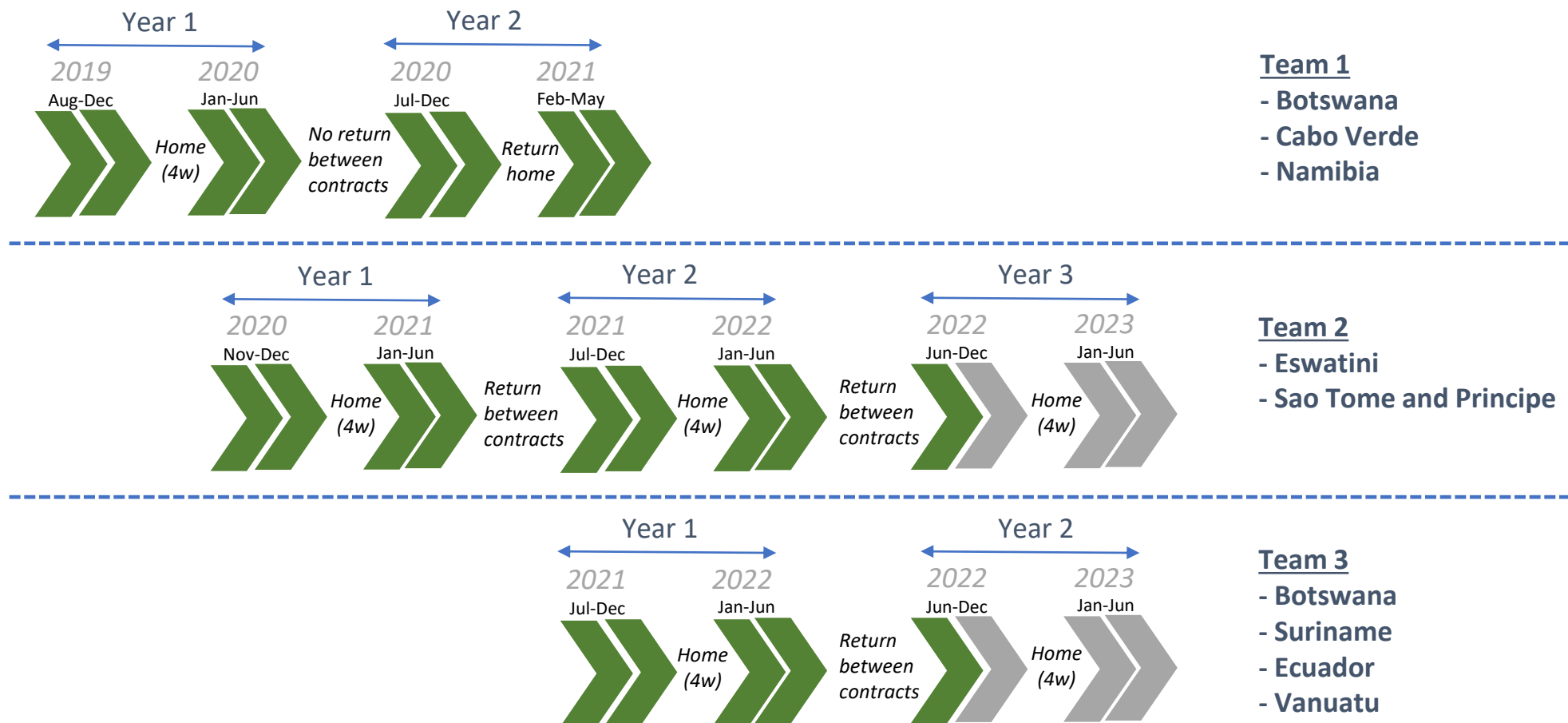


Tajikistan: 17 to 26 October 2022





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



STOP-malaria level of effort / Cost incurred (*August 2019-July 2022*)



Country of deployment	Number of months in-country
Botswana	28
Cabo Verde	18
Ecuador	6.5
Eswatini	15.5
Namibia	18
Sao Tome and Principe	15.5
Suriname	9
Vanuatu	1
TOTAL	111.5

Year	US\$
2019	57k
2020	255k
2021	325k
2022 (Jan-Jul)	201k
Total	838k
Consultant years (11 months)	~10
Annual costs	~83.8k



Output 1: To conduct an impact assessment and effectiveness evaluation of STOP malaria activities

- Deliverable: Report on functional evaluation of STOP consultants' support to countries and in-depth evaluation of consultants compared to country needs and expectations. The report will focus on impact and effectiveness.

Output 2: To identify alternative scenarios for support to malaria elimination at subnational level and estimate related costs

- Deliverables: a) three proposed alternatives to STOP-malaria as it stands today; and on b) estimated costs and theoretical efficiency and sustainability of each proposed alternative

Output 3: To make a cost-benefit comparison of the STOP-malaria programme with these alternatives, and to estimate their theoretical efficiency and sustainability

- Deliverables: a) Written analysis on the cost-benefit comparison between STOP malaria and other proposed alternatives.

New guidelines on elimination



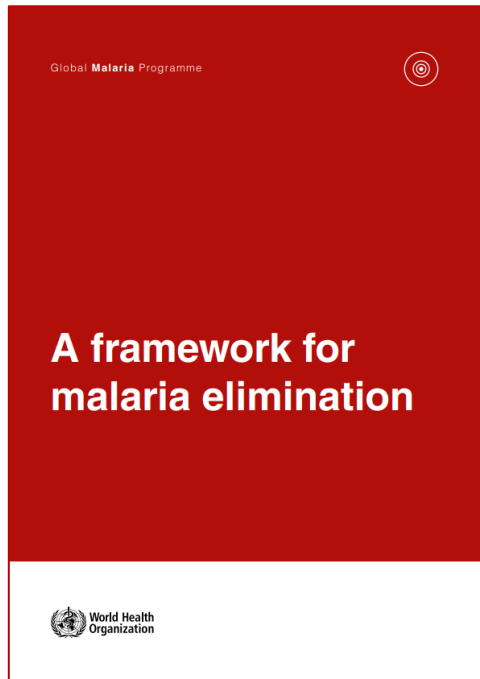
Technical area	Strength & evidence	For/against	Recommendation	New/update
Elimination	Conditional, very low-certainty	For	Targeted drug administration to reduce transmission in low/very low transmission	New
Elimination	Conditional, moderate certainty	Against	Mass testing and treatment to reduce malaria transmission	New
Elimination	Conditional, very low-certainty	Against	Testing and treatment of people at increased risk to reduce transmission	New
Elimination	Conditional, low-certainty	For	Reactive drug administration to people near malaria cases to reduce transmission	New
Elimination	Conditional, very low-certainty	For	Testing and treatment of people near malaria cases to reduce transmission	New
Elimination	Conditional, very low-certainty	For	Reactive indoor residual spraying near malaria cases to reduce transmission	New
Elimination	Conditional, very low-certainty	Against	Routine test and treatment of people at points of entry to reduce importation	New
Elimination	Conditional, very low-certainty	For	Testing and treatment of groups from endemic areas to reduce importation	New



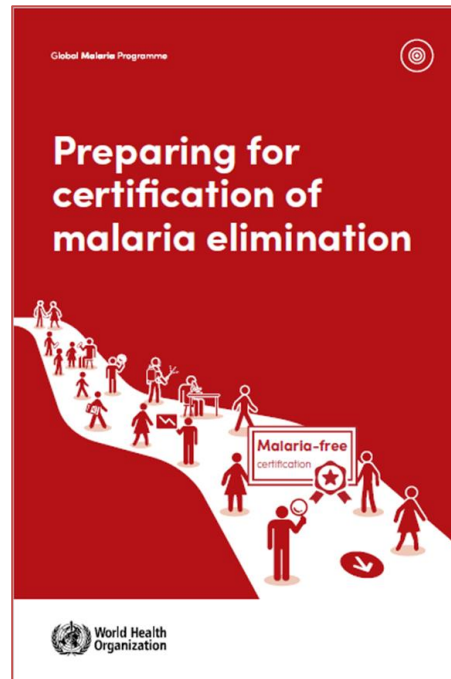
Tools for malaria elimination



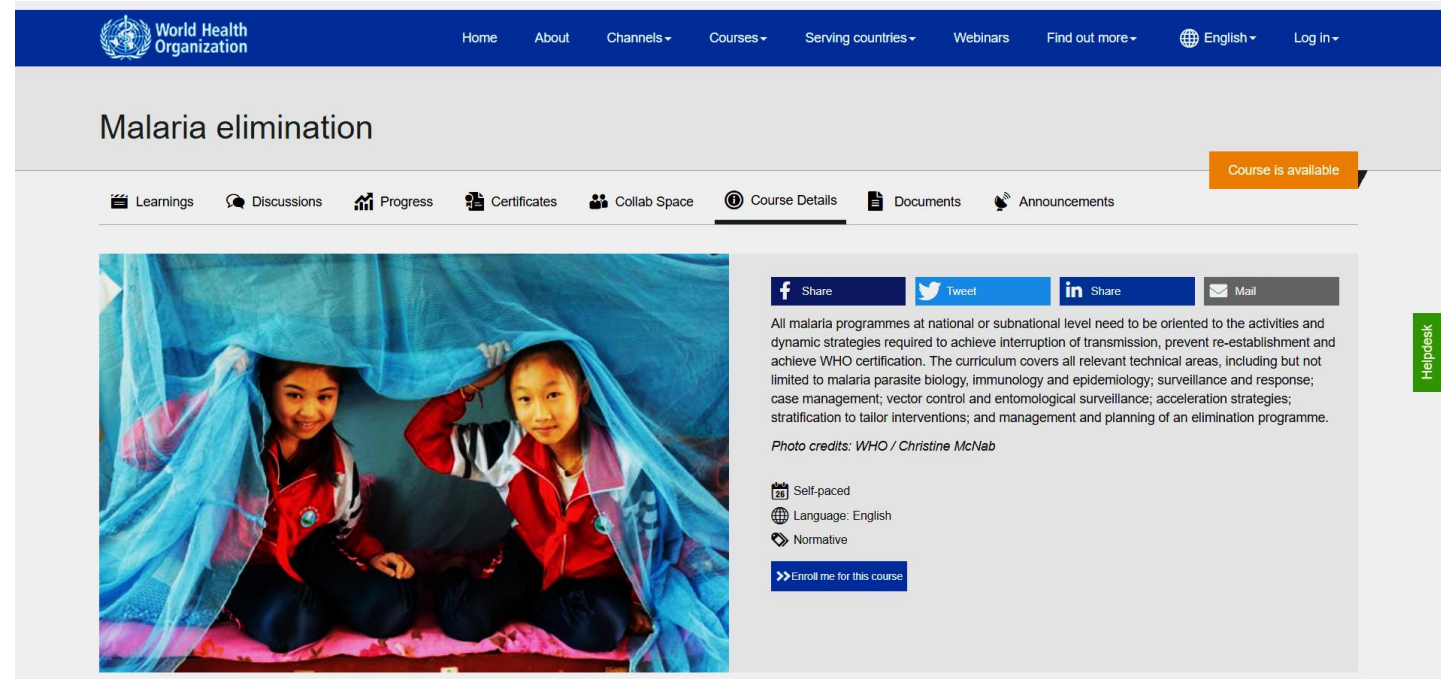
2017



2020



2022



<https://openwho.org/courses/malaria-elimination>

More than 8 200 enrollments



- **24 – 26 January 2023, Cape Town, South Africa**
- **Theme:** Accelerate elimination to achieve GTS milestones
- The **purpose** of the 4th Global Forum is to convene E-2025 countries and territories to highlight achievements, report on their progress, understand and overcome bottlenecks and challenges, share lessons learned and discuss WHO guidance and strategies
- ***Session 3: Prevention of re-establishment***
 - Lessons learnt from El-Salvador and China
 - Panel discussions: Malaysia and Cabo Verde; Paraguay and Algeria; Timor-Leste and Vanuatu



Technical consultation on prevention of re-establishment of malaria transmission to *review and update current WHO guidance on prevention of re-establishment to support countries' efforts at maintaining malaria-free status at national and sub-national levels.*

Technical consultation on PoR: Workplan



EVENT	OBJECTIVE	TIMELINE
1 Working group meeting #1	Discuss and consolidate the workplan, define roles and responsibilities	Nov 2022
2 Officially launch the technical consultation on prevention of re-establishment during the fourth Global Forum of malaria-eliminating countries	<ul style="list-style-type: none"> • Launch the technical consultation • Review and discuss two case studies: China and El Salvador • Discuss challenges to prevention of re-establishment 	Jan 2023
3 Virtual meetings to review case studies and updates on WHO policies and recommendations on health systems	3-1 Greece, Oman and Paraguay 3-2 Tajikistan, Uzbekistan plus one presentation on health systems (primary health care) 3-3 Mauritius, Sri Lanka plus one presentation on health systems (resilience)	Feb 2023
4 Physical meeting tentatively in Tbilisi, Georgia	Evidence review meeting	Mar 2023
5 Working group meeting #2 virtual: consolidate writing	Discuss an advanced draft	Aug 2023
6 Publish the product of the technical consultation		Dec 2023

Thank you!

Global Framework for Response to Malaria in Urban Areas



Abdisalan M Noor (WHO)
Graham Alabaster (UN Habitat)

Global **Malaria** Programme



World Health
Organization

WHO Framework for Response to Malaria in Urban Areas

Aim of the framework

- To guide countries, globally, to develop policies, strategies and plans that are system-wide and multi-sectoral to effectively respond to malaria in urban areas.
- To identify important knowledge gaps and define research priorities in the response to malaria in urban areas.

Who is the target audience?

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

Technical Consultation
launched on 22nd
September by



**Hon. Yvonne Aki-Sawyerr,
Mayor of Freetown, Sierra
Leone**



**Dr Pedro Alonso, Former
Director, GMP, WHO**

WHO Framework for Response to Malaria in Urban Areas

Themes

Prevention interventions & delivery

Health care delivery

Urban governance, policies and planning

Multisectoral response
(focusing on private and community sectors)

Surveillance, mapping and analysis

- Over 120 participants, about 30 consultations, 33 presentations across all thematic groups
- *Draft Framework* submitted to Malaria Policy Advisory Group for discussion in March 2022
- Framework targets urban leadership, national programmes, implementation partners.
- Goes beyond officially approved WHO recommendation and advocates a holistic approach to the malaria problem, centered on urban leadership.
- Promotes a targeted approach to efficiently target malaria resources
- Framework to be launched on 31st October at the World Cities Day convened by UN HABITAT

Content of the Framework

Executive summary

- ☐ Rationale
- ☐ Target audience
- ☐ Malaria in urban areas
- ☐ Control and elimination of malaria in urban areas
- ☐ Role of stakeholders
- ☐ Resource mobilization
- ☐ What success looks like
- ☐ Challenges and opportunities

Content of the Framework

Background

- ❑ Global malaria context
- ❑ Defining urban areas – the urbanicity continuum and typologies
- ❑ Malaria and urbanization – ecology and epidemiology

Vision

Vision

A world where towns and cities are free from malaria and other mosquito-transmitted diseases.

Aim

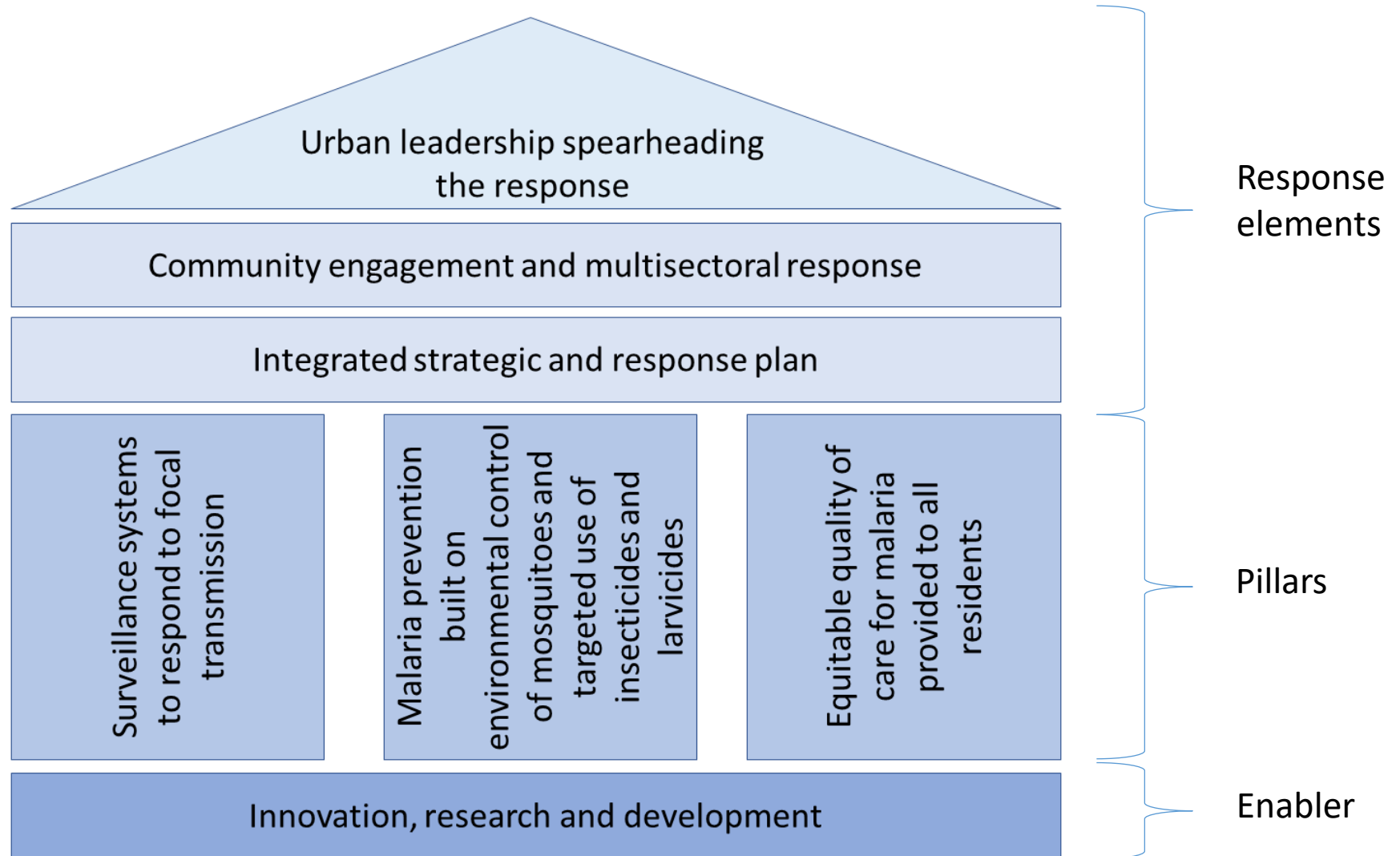
Reduce the transmission and burden of malaria, and eventually eliminate the disease through effective, locally adapted and sustainable control measures for urban areas.

Focus

This framework offers guidance to implementing effective interventions that contribute to malaria elimination, to improve the lives of millions of citizens of towns and cities in malaria-endemic countries

Vision

Building blocks

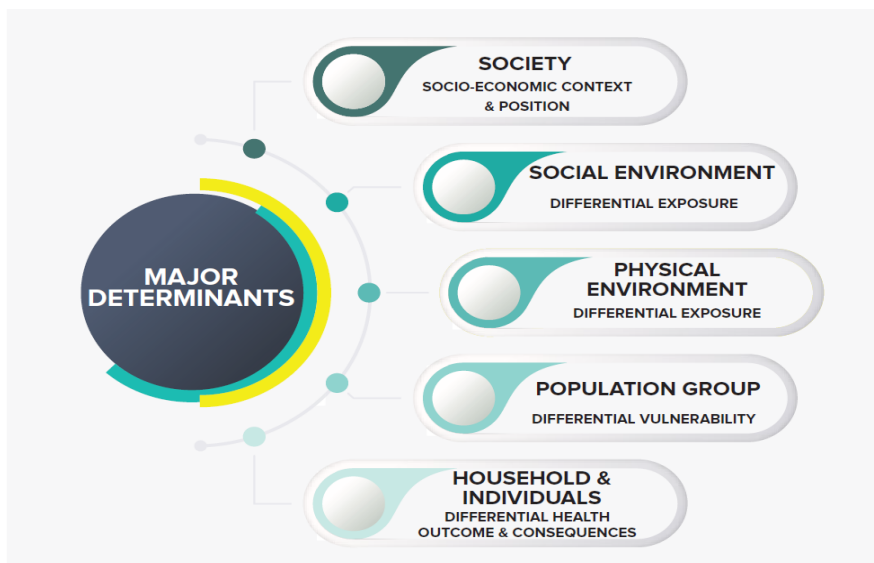


Urban leadership and the malaria response

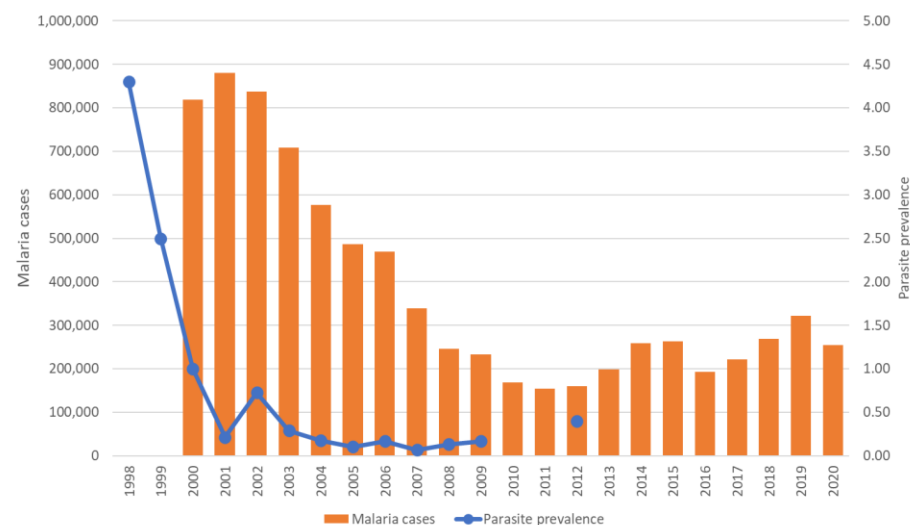
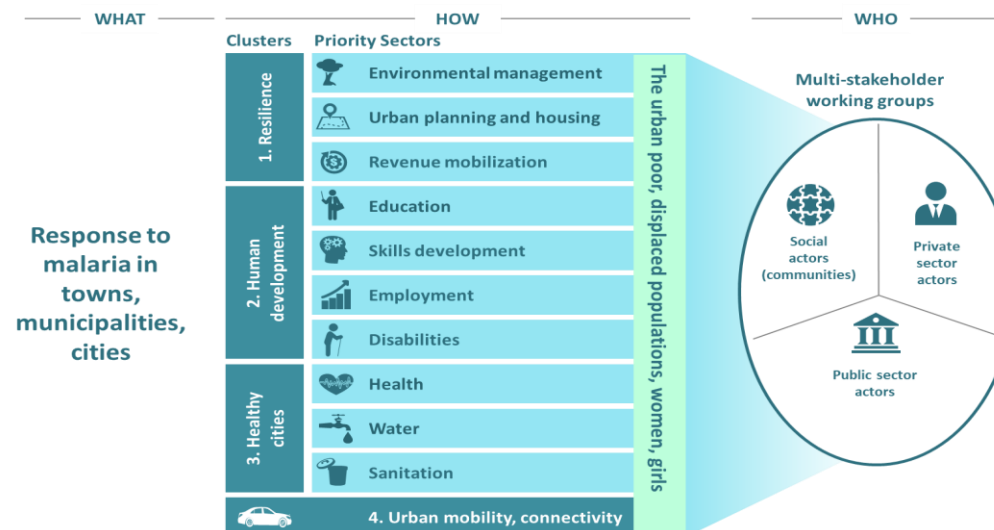
- ❑ Role of urban leadership and governance
- ❑ Benefiting from alignment with international goals
- ❑ Integration with sustainable city growth and the One Health approach
- ❑ Mobilizing resources for urban malaria control

Multisectoral and community engagement

Comprehensive Multisectoral Action Framework for malaria (RBM and UNDP)



Adaptation of the Transform Freetown Agenda



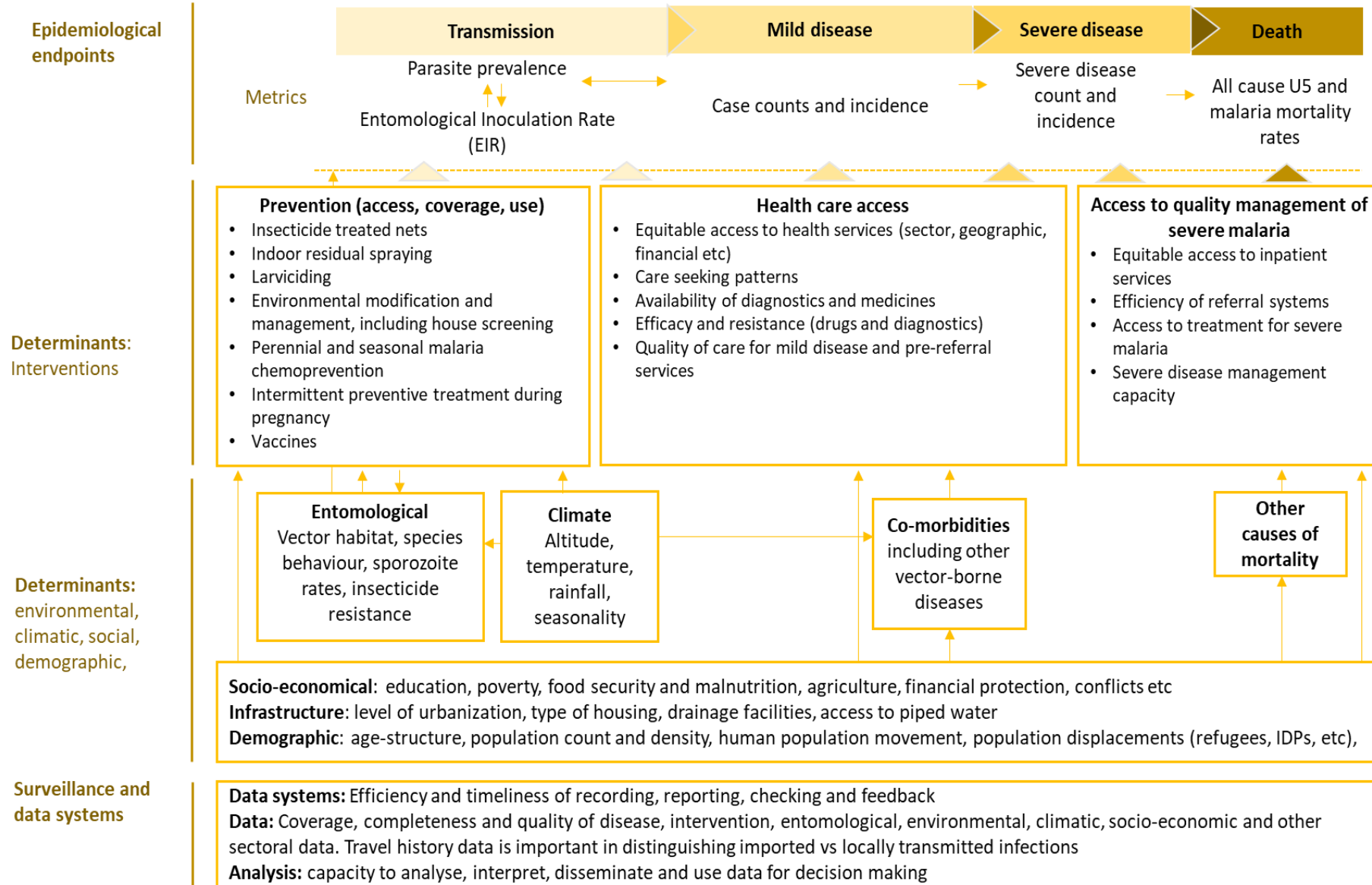
Case Study of the Khartoum Malaria Free Initiative

Multisectoral and community engagement

Community engagement is “a process of continuous relationship-building in which those affected are central to decision-making”. Local communities play a major role in, and are key to the success and sustainability of urban malaria control and elimination. Urban leadership has a critical role to play in the coordination of communities at different levels.

- ❑ not what gets done. But how things get done and by whom;
- ❑ the quality of relationships between stakeholders;
- ❑ the patterns of interaction over time;
- ❑ the strength of connection between different parts of the health system; and
- ❑ the link between staff experience, patient experience and outcomes of interest.

Surveillance



Focus on integration, digitalization, competencies and case-based surveillance with travel history as an ambition across all urban settings

Preventing malaria in urban areas

Box 3. Approaches and interventions to prevent malaria in urban areas

Environmental management

- Improved drainage
- Improved water storage or installation of piped water
- Improved sanitation and waste management
- Improved housing with screens
- Urban agriculture without surface water pooling
- Filling of swamp areas and other stagnant water sources
- Other construction activities that eliminate potential breeding sites

Chemical and microbial control

- Larviciding guided by appropriate ground surveillance of potential larval habitats
- ITNs and IRS in pockets of moderate and high transmission
- Reactive IRS for outbreak response

Chemoprevention

In pockets of moderate and high *P. falciparum* transmission:

- Depending on seasonality, perennial or seasonal chemoprevention where there is a clear indication of severe disease in children under the age of 5 years
- Intermittent preventive treatment in pregnancy
- In some settings, targeted reactive drug administration

Vaccine

In pockets of moderate and high *P. falciparum* transmission, use of the RTS,S malaria vaccine to protect children under the age of 5 years. Other vaccines in development may also be applicable to urban settings.

Behavioural change

- Social and behavioural change messages to increase public awareness of malaria and the public's participation in the response, including appropriate use of preventive and case management interventions
- Messages targeting industry and corporations to ensure their engagement and support of the response to malaria in urban areas

Delivering quality care in urban areas

Quality domain	Implications for malaria care
Effective	Appropriate knowledge and skills of health workforce in delivering preventive and curative services in urban settings. Adherence to best-practice treatment guidance and protocols. Optimal training and supportive supervision.
Safe	Ensuring safety when preventive and clinical care is provided. Existence of appropriate safety protocols and standards.
People centred	Close engagement with communities to develop locally contextualized and people-centred strategies, and foster community ownership of interventions. Special attention paid to being accountable to the urban poor, whose voices are often not heard.
Timely	Responding to urgent population needs in a timely manner, including potentially large numbers of malaria cases imported to urban areas.
Equitable	Improving access and providing quality services, irrespective of socioeconomic status or urban community, thereby ensuring access by poor and marginalized groups, which suffer the greatest malaria burden.
Efficient	Efficient use of scarce resources – training of community health workers in assessment and treatment of uncomplicated malaria.
Integrated	Integrated management of malaria and other health services (e.g. pneumonia; maternal, newborn and child health; HIV), moving towards integrated health services.

- a motivated health workforce that is supported to provide quality care;
- accessible and adequately equipped health facilities;
- safe and appropriately designed interventions, devices and technologies;
- information systems that support continuous monitoring and response;
- financing mechanisms that enhance quality of care; and
- patients and communities that demand a high quality of care.

Delivering quality care in urban areas

Box 4. Provision of prompt, high-quality diagnosis and effective treatment

Diagnosis

- Rapid diagnostic tests available in all primary healthcare facilities, including in the private sector where access remains limited
- Quality microscopy available at relevant levels of the health system, especially in inpatient facilities, including in the private sector or for confirmatory purposes in elimination settings

Treatment

- First- and second-line treatment available at all appropriate levels of health service facilities
- Appropriate management of severe malaria cases in all inpatient facilities

Delivery

- Strong public health system with adequate and motivated health workforce
- Universal health coverage – all residents have access to quality, affordable care
- Strong engagement of the private sector to provide quality, affordable care
- Exploration of delivery of quality service through community health workers and the private sector to serve marginalized and/or underserved populations in urban areas
- Investigation of the presence of substandard and counterfeit products, and implementation of legal codes to mitigate these risks

Developing an urban malaria response plan

- A targeted plan that responds to the usually high levels of malaria transmission heterogeneity in urban areas;
- linking policy planning, budgeting and response at the national and local urban government levels to ensure resource mobilization across multiple sectors, including funds earmarked for infrastructure development;
- intersectoral collaboration between the municipality's malaria control unit, national malaria programmes, other sections in the local health department, other municipal departments e.t.c
- inclusion of, and engagement with, all parts of the local community to ensure their support and involvement;
- targeted social and behavioural change communication; and
- ongoing research to generate innovative solutions to respond to malaria in urban settings.

India case study
presented

Developing an urban malaria response plan

Step 1: Pre-planning

Step 2: Situation analysis

Step 3: Tailoring malaria interventions to clusters of transmission within urban settings - microstratification

Step 4: Developing the response plan

Developing an urban malaria response plan

Microstratification

Step 1: Granular mapping of malaria risk and its determinants

Step 2: Define appropriate interventions and approaches – adaptations of WHO recommendations

Step 3: Project the impact of intervention and strategy combinations

Step 4: Prioritize choices within limited resources

Step 5: Establish appropriate platforms for monitoring the response and evaluate impact

Innovations, research and development

Several areas identified:

- ☐ Epidemiology
- ☐ Entomology
- ☐ Social and economic determinants
- ☐ Intervention efficacy
- ☐ Multisectoral approaches
- ☐ Advances in mapping and modeling
- ☐ Climate change
- ☐ Legislation

Update on rectal artesunate as pre-referral treatment of severe malaria

Malaria Policy Advisory Group (MPAG) Virtual Meeting

11-13 October 2022



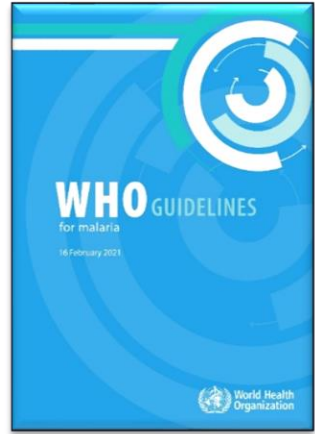
Dr. Peter OLUMESE, Global Malaria Programme, WHO, Geneva, Switzerland

Global **Malaria** Programme



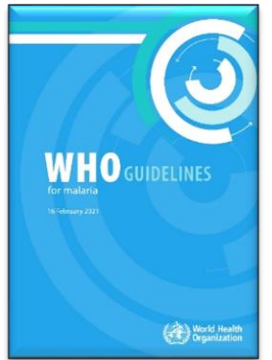
Treatment of Severe malaria

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



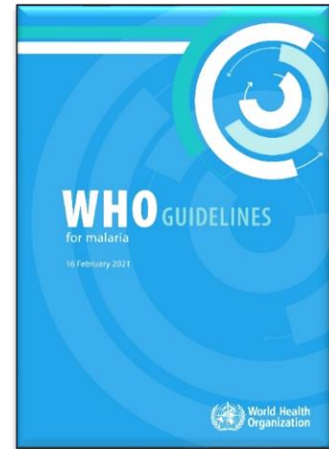
Treatment of Severe malaria (MTG 2015)

- 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



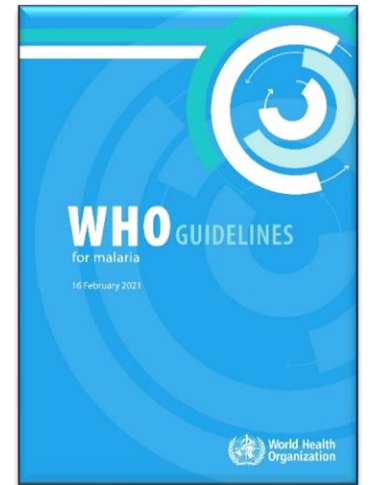
Treatment of Severe malaria (2015)

- 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.



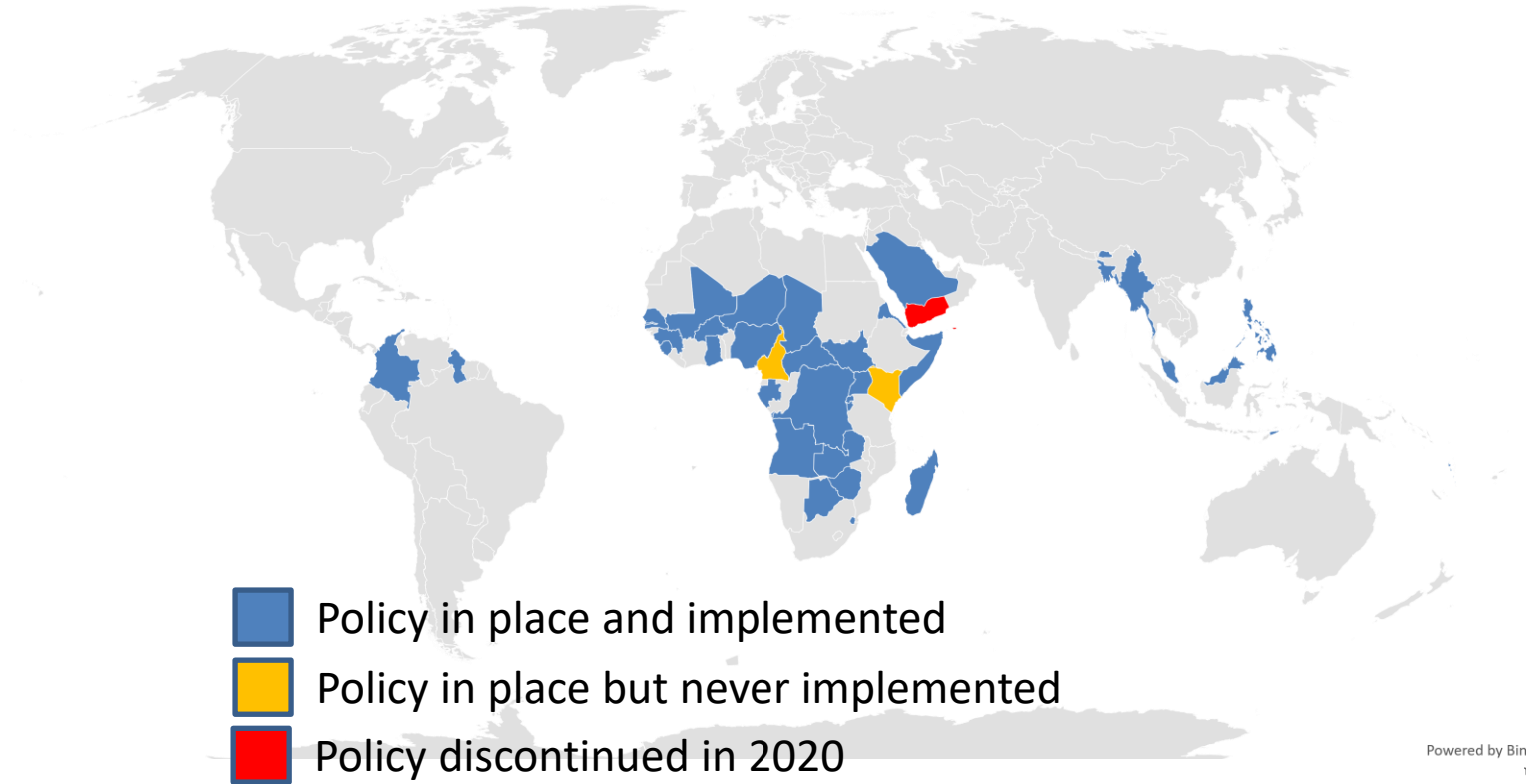
Treatment of Severe malaria (2015)

- 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

Countries with policy of pre-referral treatment of severe malaria in children in 2020
with quinine, artemether IM or rectal artesunate



- 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

Background

- The MPAG advise to WHO GMP:
 - to advise countries that have not yet introduced the intervention to await further guidance before adopting and deploying RAS;
 - to notify countries that have adopted RAS about the risk of negative effects if the WHO recommendation cannot be fully implemented, including the referral for complete treatment and ensuring the quality of care throughout, and
 - to conduct an evidence, review and develop guidance for the conditions under which this tool can be implemented safely and effectively

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>,



The use of rectal artesunate as a pre-referral treatment for severe *P. falciparum* malaria

JANUARY 2022

INFORMATION NOTE

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:
 - Firstly, a remote meeting on 20-21 September 2022 to review in detail all pre-reads by the independent experts and prepare specific follow-up questions to the study teams including the STPH. (DONE)
 - In-person meeting
 - 18 – 19 October 2022 in Geneva

Objective of the 1st meeting (20-21 Septemeber)

The specific objective of the meeting was:

- to intimate the panel with the currently available evidence, and
- in-depth review of the evidence and generate questions or areas for further clarifications directed to the respective study teams and /or Principal investigators of the studies.
- 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

- **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

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.

Expected outcome / product

- An implementation guidance manual to support countries in the safe and effective deployment to pre-referral treatment including rectal artesunate.
 - Timelines – February 2023
- A draft of the implementation guide will be presented to MPAG at the next available opportunity

Update on *Plasmodium falciparum* histidine-rich protein 2/3 gene deletion issues

Global Malaria Programme, October 2022

1. Introduction

Accurate, timely diagnosis of malaria is critical to case management and is a key element in national and global malaria control and strategies for elimination. Rapid diagnostic tests (RDTs) detecting histidine-rich protein 2 (HRP2) have transformed the malaria diagnostic approach over the past 15 years, greatly facilitating access to diagnostic testing prior to treatment and surveillance efforts. Over 400 million tests are sold annually, and 24 RDTs from eight manufacturers are now prequalified by the World Health Organization (WHO). However, this precious tool is now under threat due to the emergence, and in some cases dominance, of *Plasmodium falciparum* parasites with HRP 2/3 (*pfhrp2/3*) gene deletions that result in false= negative RDT results. Since the discovery of *pfhrp2/3* deletions among clinical isolates in Peru in 2008, WHO, partners and research groups have been at the forefront of addressing this issue, both in the laboratory and in the field. In 2014, WHO co-authored the first report to promote the accurate investigation and reporting of *pfhrp2/3* deletions (1). The WHO malaria RDT product testing programme, which ran for a decade, made annual calls to test developers to invest in alternatives to HRP2-based diagnostics in order to reduce the reliance on these products. However, despite repeat attempts, only one Pf-specific lactose dehydrogenase (pf-LDH)-based RDT has ever met the minimum performance requirements for the detection of *P. falciparum*. In 2022, three pf-LDH-based products are in the WHO prequalification pipeline and another company has promising pf-LDH products in clinical trials. In 2019, a global response plan was released, laying out a core set of actions for WHO, scientists, ministries of health, implementing partners and manufacturers (2). In 2021, the Malaria Policy Advisory Group (MPAG) released a statement to address the high prevalence of *pfhrp2/3* deletions in the Horn of Africa and beyond (3). This background document summarizes the current status of the proposed actions laid out in the response plan and planned activities for the coming months. The Secretariat seeks guidance from MPAG members on the relevance of the proposed plan and any gaps.

The response plan laid out four objectives, as detailed in the following sections.

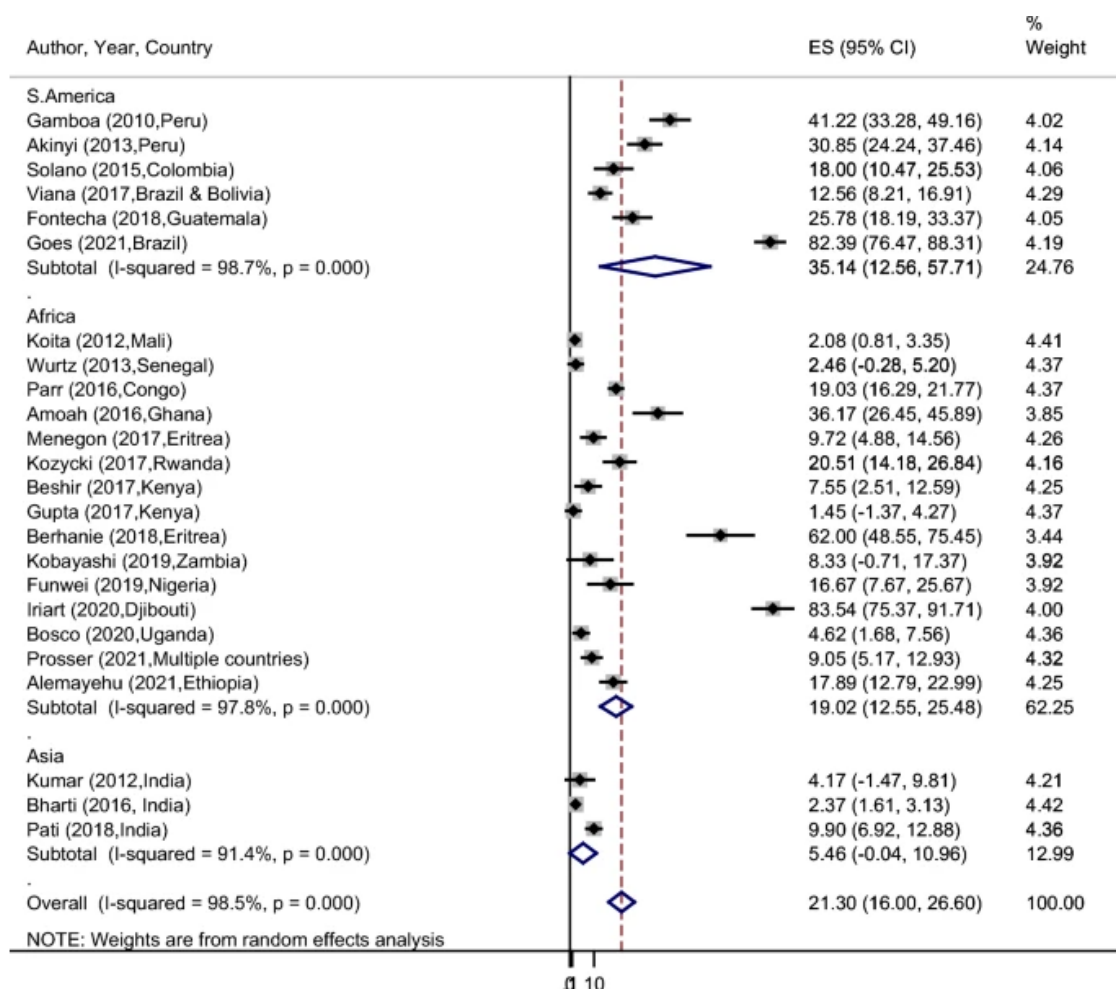
2. Objective 1

Define the frequency and distribution of diagnostically relevant mutations in circulating *P. falciparum* strains.

Progress: In 2020, WHO published a systematic review (4) of the frequency and distribution of *pfhrp2/3* deletions based on published reports, and have been continuously updating the WHO Malaria Threats Map (5) since 2017. More recent systematic reviews (6) have also been published, highlighting the growing interest in this field. The majority of data on *pfhrp2/3* deletions have come from Africa, including from travellers returning from these countries (Angola, Congo, Djibouti, Ethiopia, Eritrea, Eswatini, Ghana, Kenya, Madagascar, Mali, Mozambique, Nigeria, Rwanda, Senegal, South Sudan, Sudan, Uganda and Zambia), followed by South America (the Plurinational State of Bolivia, Brazil, Colombia, French Guiana and Peru) and India. There is significant heterogeneity in the

results, which is likely attributable to epidemiological differences, as well as study design differences, e.g. symptomatic vs asymptomatic, sample selection, and so on (Fig. 1). Data from surveillance activities have led to policy change in RDTs in several countries in South America and in Africa (Djibouti, Ethiopia and Eritrea). To encourage the generation of data that would be comparable and able to drive policy, survey protocol templates (7) have been developed with an emphasis on screening for discordant samples (HRP2 RDT negative/pf-LDH RDT or microscopy positive), which would give cause to suspect *pfhrp2/3* deletions and are clinically relevant as they result in negative HRP2 RDT results. In some studies, 80–90% of discordant samples were confirmed to have *pfhrp2* deletions. Alternative explanations for discordance include the misidentification of species through microscopy, the presence of low-density infections, or potentially operator or administrative error. High-throughput antigen screening methods using dried blood spots have also emerged (8). These methods have shown good correlation with *pfhrp2/3* genotyping and facilitate fieldwork. Multiplex quantitative polymerase chain reaction (qPCR) protocols have also been developed, which greatly reduce turnaround times. These advances were summarized in a peer review manuscript co-authored by WHO in 2022 (9) and will be the source for updates to protocol templates in 2023. A number of countries are currently conducting or are in the late stages of planning surveys, having received funds through grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria, and in some cases grants from Bill & Melinda Gates Foundation to support the building or expansion of malaria molecular surveillance. To this end, baseline national or regional data are anticipated from several countries in 2023.

Fig. 1. Forest plot representing subgroup analysis of pooled *pfhrp2* gene deletions by continent



Source: reproduced from Zeleke et al.(6)

A geographically diverse international reference laboratory network (eight members) was established to support efficient and high-quality genotyping of *pfhrp2/3* through tripartite legal agreements (WHO/laboratory in endemic country/ministry of health) put in place to safeguard the interests of the survey country and to ensure timely access to data. All of the laboratories participate in the WHO malaria nucleic acid amplification test external quality assurance scheme, which includes *pfhrp2*- and *pfhrp3*-deleted samples in the panels.

Plan:

- A dashboard for tracking planned and ongoing surveys has been piloted and will be launched in September 2022. In Q1 2023, this dashboard will be visually integrated into the Malaria Threats Map (5). Critical study characteristics will be featured, including target areas, design and timelines. This will facilitate the identification of priority countries for surveillance and resource allocation, as well as RDT demand forecasting. It is also envisioned that representative data or a funded surveillance plan for *pfhrp2/3* deletions could become a requirement for continued procurement of HRP2-based RDTs, particularly in higher risk areas.
- An erratum needs to be published in the surveillance master protocol templates due to error in the sample size estimates, which did not include the design effect and therefore underestimated requirements. This will be accompanied by an information note to guide countries who have already completed or have ongoing studies on how to revise their analysis by aggregating data from transmission zones.
- The surveillance master protocol templates (with and without biobanking) need to be updated to incorporate the revised sample size estimates and laboratory methods, and expand on the impact of multiplicity of infection and seasonality on estimates of *pfhrp2/3* prevalence.
- Templates need to be developed for sentinel surveillance following baseline or regional surveys.
- With the expansion of capacity, expertise and interest in this field, it is anticipated that the international reference laboratory network will grow. Network exchanges could also support the validation of new methods.
- Continued technical support should be provided to implementing partners, research groups and countries planning and executing *pfhrp2/3* deletion surveillance activities.

3. Objective 2

Provide concrete guidance to countries on malaria diagnosis and treatment in settings where such mutations are found to be frequent.

Progress: Step-wise guidance is provided in the response plan document, and technical support has been provided on a case-by-case basis to several countries and to partners through the RDT Procurement Task Force.

Plan: Update the *pfhrp2/3* response plan to incorporate lessons learned from countries that have changed their policy. Review recent literature and surveillance data to compare the performance/sensitivity of HRP2 and pf-LDH RDTs in order to inform “switch criteria” and track research on the evolution and spread of *pfhrp2/3* deletions in parasite populations.

4. Objective 3

Identify gaps in knowledge on the genesis and spread of strains with *pfhrp2* and/or *pfhrp3* deletions and the actions required to develop new, accurate tests for malaria based on alternative target antigens.

Progress: Several research groups have conducted genetic analysis to better understand the evolution of *pfhrp2* and *pfhrp3* deletions. Data from a large survey in Ethiopia suggest that there has been a recent selective sweep, indicative of strong evolutionary pressure favouring *pfhrp2*-deleted *P. falciparum* parasites (10). By contrast, parasite populations with *pfhrp3* deletions expanded in the more distant past and potentially arose independently multiple times. This understanding is based on low extended haplotype homozygosity statistics surrounding *pfhrp3*, multiple deletion profile patterns, the high overall frequency of *pfhrp3*-deleted parasites and their presence in older samples. In this context, recent strong selection favouring parasites with *pfhrp2* deletions has probably occurred due to the “test-track-treat” policies that rely on HRP2-based RDTs, which have enabled parasites with deletions of one or both genes to escape treatment. In Eritrea, a follow-up survey two years after a switch from HRP2-based RDTs revealed reduced prevalence of *pfhrp2/3* deletions and increased genetic diversity of parasites with the expansion of parasite genotypes, indicating HRP2-RDT use to be the driving force behind *pfhrp2/3* deletions (11). In Peru, where RDTs are not a widely used tool, the increasing trend of dual gene-deleted parasites over the years correlated with a clonal expansion of a single parasite haplotype that carried dual deletions. This indicates that the driving force behind this trend was a rapid expansion of a new strain replacing old strains (Valdivia et al., unpublished findings, 2021).

Pooled neutral microsatellite marker data analysis of *pfhrp2/3*-deleted parasites from multiple countries in South America and Africa points to de novo gene deletions and expansion of these deleted *P. falciparum* populations in the Horn of Africa, rather than importation of deleted parasites from other areas of the world (12). Specifically in the Horn of Africa, the presence of close background lineages in neutral microsatellite data for *pfhrp2*- and *pfhrp3*-deleted parasites from Djibouti and Ethiopia points to an expansion of common gene-deleted populations that exist in these adjacent countries. Eritrea parasite lineages from both wild-type and deleted *P. falciparum* appear to be differentiated from the Ethiopia/Djibouti lines, suggesting separate *pfhrp2/3* deletion events in unique *P. falciparum* strains and a more distant common ancestor.

New tests with alternative antigens alone or in combination with HRP2 are available, but not yet WHO-prequalified. Some are currently undergoing clinical trials. Nevertheless, there is little incentive for those manufacturers currently manufacturing HRP2-only RDTs to diversify, given the low profit margins. Assuming that new pf-LDH products are prequalified, the market would be limited to two suppliers, posing potential supply risk and leading to higher prices. New incentives and/or licensing of pf-LDH antibodies and/or other technologies need to be explored to ensure that some suppliers can stay in the market as the global community gradually shifts away from exclusively HRP2-based RDTs.

Plan:

- Encourage research groups to continue conducting parasite genomic studies to further understand the mechanisms, origin, driving forces and fitness of gene-deleted parasites.
- Conduct kelch 13 sequencing for mutations among *pfhrp2* and dual-deleted parasites, as recent unpublished data from Eritrea suggest an increased prevalence of kelch 13 mutation (R622I) in dual-deleted *pfhrp2/3* parasites. This will be done in samples from the Somaliland region of Somalia and Yemen in 2022.

- Work with the Clinton Health Access Initiative and other members of the RDT Procurement Task Force, as well as a small group of mathematical modellers to develop a risk-based transition plan and forecast for pf-LDH-based RDTs over the next five years.

5. Objective 4

Coordinate advocacy and communication with donors, policy-makers, test developers, research agencies, technical partners and disease control programmes to assist in planning.

Progress: There is heightened awareness of this problem in both the research and public health communities. Accordingly, there has been a steady increase in the number of reports of surveys/studies interrogating samples for *pfhrp2/3* deletions and reporting results, along with high levels of participation in webinars and forums featuring the problem of *pfhrp2/3* deletions. Screening for deletions has piggybacked on other surveys, e.g. therapeutic efficacy studies. The need for surveillance has been incorporated into Global Fund guidance to grantees. Grants from Bill & Melinda Gates Foundation to build and expand malaria molecular surveillance and data from surveillance efforts have supported policy change in at least three countries over the past five years and informed the continued use of HRP2-based RDTs in others. RapiGen has heeded WHO's advice to concentrate efforts on pf-LDH-based RDTs and to pursue WHO prequalification. Donors have sponsored some manufacturers to improve their pf-LDH RDTs (Bill & Melinda Gates Foundation–Abbott) and public–private partnerships such as the Foundation for Innovative New Diagnostics and PATH are supporting evaluations of these new RDTs.

Plan: As new pf-LDH RDTs become WHO-prequalified in the next 1–2 years, the case for periodic surveillance versus a switch to pf-LDH RDTs will need to be developed and debated among various stakeholders. In the interim, the dashboard of planned and ongoing studies should assist in ensuring that unmet surveillance needs are met promptly and duplication of efforts is minimized.

6. References

1. Cheng Q, Gatton ML, Barnwell J, Chiodini P, McCarthy J, Bell D, et al. *Plasmodium falciparum* parasites lacking histidine-rich protein 2 and 3: a review and recommendations for accurate reporting. *Malar J*. 2014;13:283. doi:10.1186/1475-2875-13-283.
2. Response plan to *pfhrp2* gene deletions. Geneva: World Health Organization; 2019 (WHO/CDS/GMP/2019.02; <https://apps.who.int/iris/handle/10665/325528>, accessed 18 September 2022).
3. Statement by the Malaria Policy Advisory Group on the urgent need to address the high prevalence of *pfhrp2/3* gene deletions in the Horn of Africa and beyond [website]. In: News. Geneva: World Health Organization; 2021 (<https://www.who.int/news/item/28-05-2021-statement-by-the-malaria-policy-advisory-group-on-the-urgent-need-to-address-the-high-prevalence-of-pfhrp2-3-gene-deletions-in-the-horn-of-africa-and-beyond>, accessed 18 September 2022).
4. Thomson R, Parr JB, Cheng Q, Chenet S, Perkins M, Cunningham J. Prevalence of *Plasmodium falciparum* lacking histidine-rich proteins 2 and 3: a systematic review. *Bull World Health Organ*. 2020;98:558–68. doi:10.2471/BLT.20.250621.
5. Malaria Threats Map [website]. Geneva: World Health Organization (<https://apps.who.int/malaria/maps/threats/>, accessed 18 September 2022).

6. Zeleke AJ, Hailu A, Bayih AG, Kefale M, Amare AT, Tegegne Y, et al. *Plasmodium falciparum* histidine-rich protein 2 and 3 genes deletion in global settings (2010–2021): a systematic review and meta-analysis. *Malar J.* 2022;21:26. doi:10.1186/s12936-022-04051-7.
7. Surveillance template protocol for *pfhrp2/pfhrp3* gene deletions. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/331196>, accessed 18 September 2022).
8. Plucinski MM, Herman C, Jones S, Dimbu R, Fortes F, Ljolje D, et al. Screening for *Pfhrp2/3*-deleted *Plasmodium falciparum*, non-*falciparum*, and low-density malaria infections by multiplex antigen assay. *J Infect Dis.* 2019;219:437–47. doi:10.1093/infdis/jiy525.
9. Beshir KB, Parr JB, Cunningham J, Cheng Q, Rogier E. Screening strategies and laboratory assays to support *Plasmodium falciparum* histidine-rich protein deletion surveillance: where we are at and what is needed. *Malar J.* 2022;21:201. doi:10.1186/s12936-022-04226-2.
10. Feleke SM, Reichert EN, Mohammed H, Brhane BG, Mekete K, Mamo H, et al. *Plasmodium falciparum* is evolving to escape malaria rapid diagnostic tests in Ethiopia. *Nat Microbiol.* 2021;6:1289–99. doi:10.1038/s41564-021-00962-4.
11. Mihreteab S, Anderson K, Pasay C, Smith D, Gatton ML, Cunningham J, et al. Epidemiology of mutant *Plasmodium falciparum* parasites lacking histidine-rich protein 2/3 genes in Eritrea 2 years after switching from HRP2-based RDTs. *Sci Rep.* 2021;11:21082. doi:10.1038/s41598-021-00714-8.
12. Rogier E, McCaffery JN, Mohamed MA, Herman C, Nace D, Daniels R, Lucchi N, Jones S, Goldman I, Aidoo M, Cheng Q, Kemenang EA, Udhayakumar V, Cunningham J. *Plasmodium falciparum* *pfhrp2* and *pfhrp3* Gene Deletions and Relatedness to Other Global Isolates, Djibouti, 2019–2020. *Emerg Infect Dis.* 2022 Oct;28(10):2043–2050. doi: 10.3201/eid2810.220695. PMID: 36148905

Response to *Pfhrp2* deletions

11-13 October, 2022, MPAG



Jane Cunningham, Medical Officer

WHO Global Malaria Programme

cunninghamj@who.int

Global **Malaria** Programme

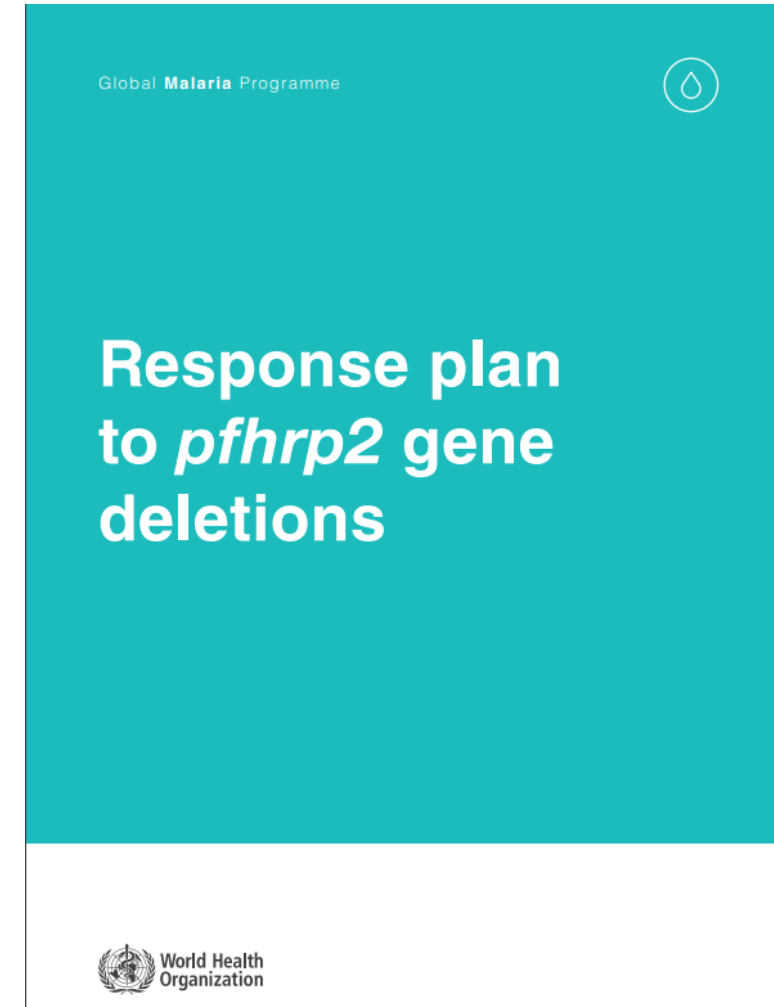


**World Health
Organization**



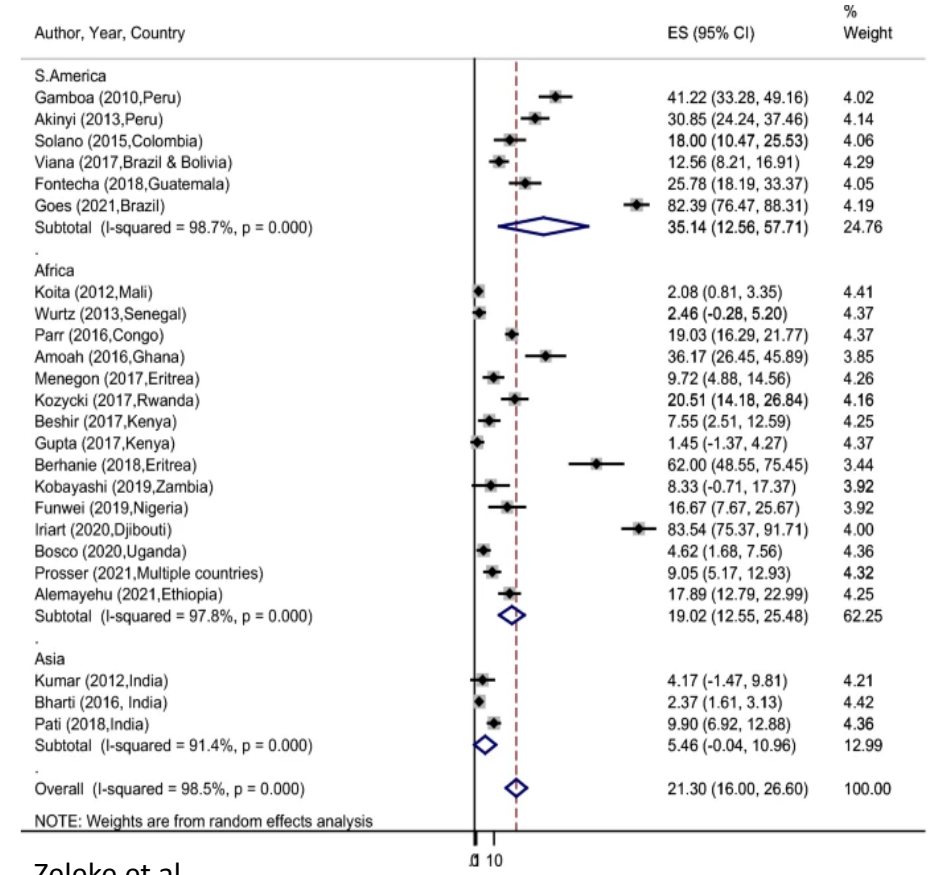
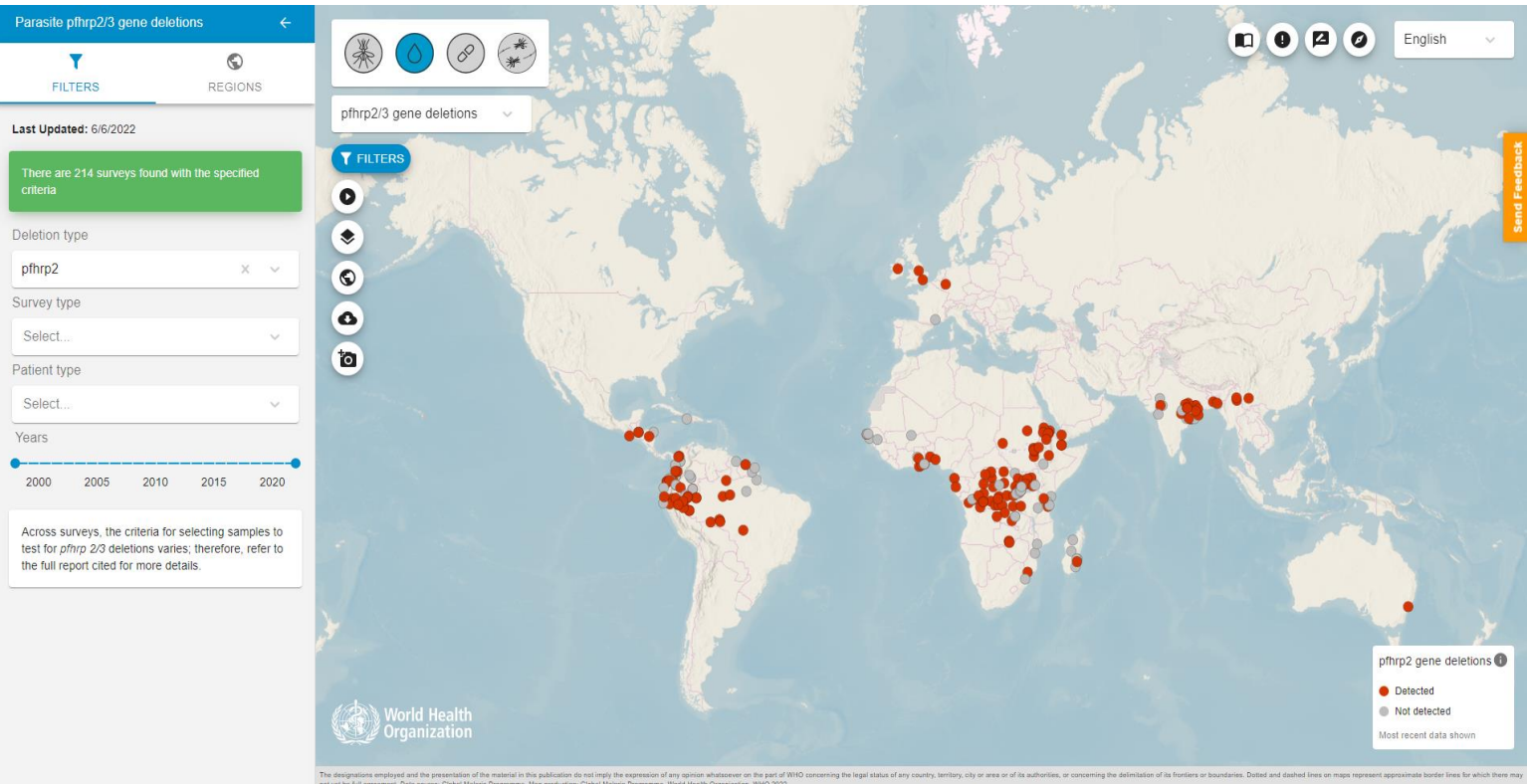
Core objectives

- I. Define the frequency and distribution of diagnostically relevant mutations in circulating *P. falciparum* strains.
- II. Provide concrete guidance to countries on malaria diagnosis and treatment in settings where such mutations are found to be frequent.
- III. Identify gaps in knowledge on the genesis and spread of strains with *pfhrp2* and/or *pfhrp3* deletions and the actions required to develop new, accurate tests for malaria based on alternative target antigens.
- IV. Coordinate advocacy and communication with donors, policy-makers, test developers, research agencies, technical partners and disease control programmes to assist in planning





Define the frequency and distribution of diagnostically relevant mutations in circulating *P. falciparum* strains.



Zelege et al.

<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-022-04051-7>

Define the frequency and distribution of diagnostically relevant mutations in circulating *P. falciparum* strains.

- Harmonized protocols and dashboard for planned and ongoing studies

Surveillance template protocol for
pfhrp2/pfhrp3 gene deletions



P. falciparum *hrp2/3* gene deletions

The global database on *P. falciparum* *hrp2/3* gene deletions was established in 2017 based on a review of published and unpublished reports. It aims at accelerating the understanding of the geographical distribution of *pfhrp2/3* gene deletions and how this evolves over time.

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 to 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](#)

<https://www.who.int/publications/i/item/9789240002036>

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

Update protocol: correct sampling sample error (design effect not included); support to countries that have completed surveys; expand impact of MOI and seasonality ; lab methods; consider model for sentinel surveillance

Define the frequency and distribution of diagnostically relevant mutations in circulating *P. falciparum* strains.

- Laboratory network (8 labs) – increased interest, experience and desire
 - ? expansion - criteria
 - Complement expansion efforts for drug resistance monitoring

Provide concrete guidance to countries on malaria diagnosis and treatment in settings where such mutations are found to be frequent.

- Guidance laid out in response plan and update planned based on lessons learned
- Confusion – prevalence of pfhrp2 deletions vs prevalence of clinically significant pfhrp2 deletions = result in NEGATIVE RDTs

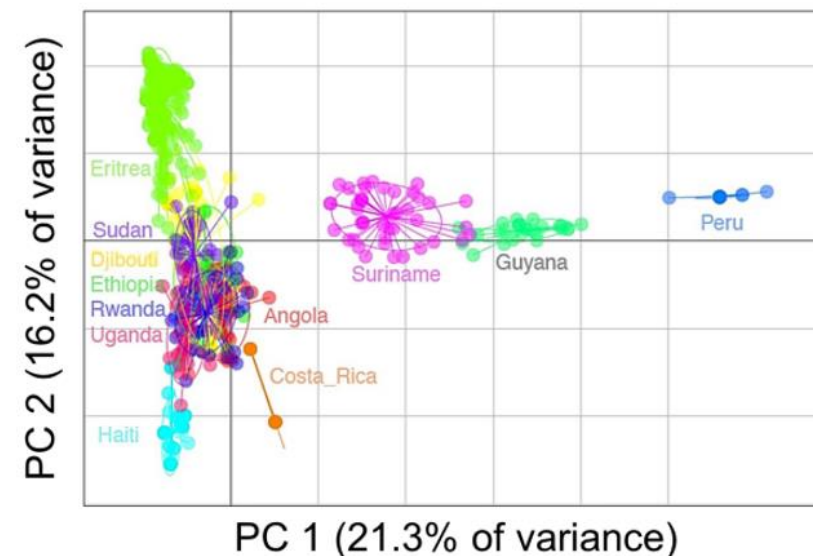
$$\begin{array}{lcl} \text{Proportion of } P. \text{ falciparum cases} & & \# \text{ of confirmed falciparum patients with } pfhrp2/3 \text{ gene} \\ \text{with false-negative HRP2 RDT} & = & \text{deletions and HRP2 RDT negative results} \\ \text{results due to } pfhrp2/3 \text{ deletions} & & \hline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

- Should 5% threshold for change be reconsidered
 - Based on data pf-LDH vs HRP2 test line performance ?
 - Based on availability of pf-LDH RDTs that meet WHO PQ requirements ?
- Track research on the evolution and spread of *pfhrp2/3* deletions in parasite populations.

Identify gaps in knowledge on the genesis and spread of strains with *pfhrp2* and/or *pfhrp3* deletions and the actions required to develop new, accurate tests for malaria based on alternative target antigens.

Emerging genetic analysis

- excludes distant importation eg from South America to Africa
- supports separate deletion events and selection pressure of *pfhrp2* deleted parasites due to HRP2 RDTs and more distant *pfhrp3* deletions
- clonal expansion of *pfhrp2/3* deletions in Peru
- Association between *pfhrp2/3* deleted parasites and R6221 K13 mutation – Eritrea



Rogier et al https://wwwnc.cdc.gov/eid/article/28/10/22-0695_article

Suggest: Control >> containment

Identify gaps in knowledge on the genesis and spread of strains with *pfhrp2* and/or *pfhrp3* deletions and the actions required to develop new, accurate tests for malaria based on alternative target antigens.

- Pf-LDH RDTs in PQ pipeline – PQ ++ demands related to COVID-19 EUL ; ERPD approval
- New pf-LDH RDTs in field trials
- Future may be 2 suppliers - what risks does this pose ? ; new incentives and/or agreements needed to ensure supply security
- Plans – risk-based transition plan and forecast for pf-LDH RDTs over next 5 years - identify highest risk countries – prioritize surveillance and plan switch - what is the tipping point ?

Coordinate advocacy and communication with donors, policy-makers, test developers, research agencies, technical partners and disease control programmes to assist in planning.

- Policy change – Eritrea, Djibouti, Ethiopia – data driven
- Increased awareness, forums, published reports
- Incorporation into other malaria molecular surveillance efforts, GF applications, strategy drug resistance in Africa
- New pf-LDH based tests – RapiGen and Abbott - WHO PQ will need resources to accelerate
- MTM + Dashboard of planned and ongoing studies will give donors, policy makers, program managers and manufacturers better visibility

Guidance from MPAG

- Feedback on current and planned activities
- Still many outstanding questions: prevalence and clinically significant deletions; timing of switch; impact of switch; mechanisms of deletions; driving forces ; fitness, association with molecular markers of drug resistance, transmission capacity.....
- Where should WHO focus efforts and how best to coordinate other actors so that we can minimize negative impacts, optimize continued use of HRP2-RDTs and maintain healthy RDT markets ?

WHO initiative to stop the spread of *Anopheles stephensi* in Africa



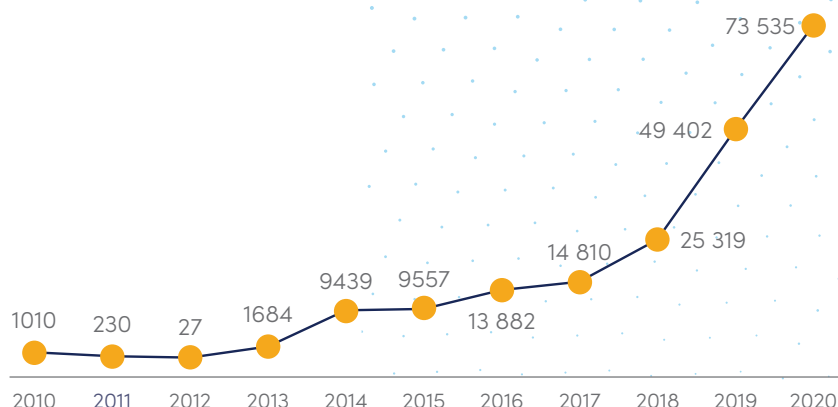
Anopheles stephensi at a glance

Anopheles stephensi is a mosquito species that is capable of transmitting both *Plasmodium falciparum* and *P. vivax* malaria parasites. It was originally native to South Asia and parts of the Arabian Peninsula but has been expanding its range over the last decade, with detections reported in Djibouti (2012), Ethiopia and Sudan (2016), Somalia (2019) and Nigeria (2020). Although *An. stephensi* has likely spread to other African countries, it has yet to be detected as systematic, large-scale surveillance of the vector is still in its infancy.

Anopheles stephensi has the capacity to thrive in urban environments, setting it apart from the other main mosquito vectors of malaria that primarily breed in rural areas. Where *An. stephensi* has been reported in Africa, it has been found to be resistant to many of the insecticides used in public health, posing an added challenge to its control.

The invasion of *An. stephensi* in sub-Saharan Africa – where the burden of malaria is highest and over 40% of the population lives in urban environments – is particularly worrying. Since 2012, *An. stephensi* is thought to have contributed to a resurgence of malaria in Djibouti City and at least one outbreak of the disease in Ethiopia. While the overall contribution of *An. stephensi* to malaria transmission in the region is unclear, the rapid growth of many African cities, coupled with the invasion and spread of this highly efficient and adaptable malaria vector, could undermine the gains made in reducing the burden of the disease.

Number of reported malaria cases in Djibouti, 2010–2020

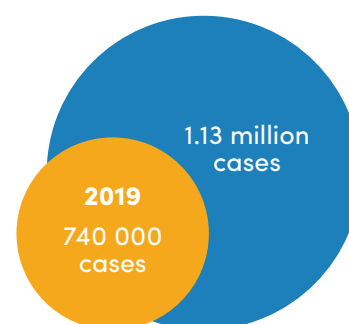


In a [2019 vector alert](#), the World Health Organization (WHO) identified the spread of *An. stephensi* as a significant threat to malaria control and elimination – particularly in Africa. This new WHO initiative, launched in September 2022, aims to stop the further spread of *An. stephensi* in the region and to determine whether it can be eliminated from areas that have already been invaded.

Modelling the potential impact of *Anopheles stephensi*

Recent mathematical modelling studies have attempted to show how and where *An. stephensi* might be spreading, and the potential implications for malaria transmission and control in Africa. One [study](#) projected that *An. stephensi* could put an additional 126 million people in Africa at risk of malaria if the mosquito vector were to spread unchecked. Another [study](#) estimated that the number of malaria cases in Ethiopia could increase by 50% if *An. stephensi* were to spread to all receptive areas. However, these models are based on assumptions that have not been fully validated in the African context, and any results should be interpreted with caution.

Projected increase in malaria cases in Ethiopia if *An. stephensi* were to spread to all receptive areas



Malaria hits hardest in the African Region

In 2020, the vast majority of all malaria cases (95%) and deaths (96%) were found in the WHO African Region. Young African children bear the brunt of the disease: an estimated 80% of all malaria deaths in the region are among children under the age of 5.

Many African countries with moderate to high malaria transmission saw a significant reduction in their malaria burden between 2000 and 2015. However, the rate of progress has levelled off in recent years, and disruptions to malaria services during the COVID-19 pandemic have further jeopardized malaria control efforts in the region.

In 2020 the WHO African Region reported

228 million
NEW MALARIA CASES

602 000
MALARIA-RELATED DEATHS

NEW WHO INITIATIVE

To support an effective response to *An. stephensi* on the African continent, WHO is launching this initiative aimed at:



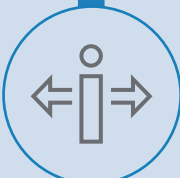
Increasing COLLABORATION

National malaria control programmes, researchers, funders, and other actors conducting surveillance, research and control of *An. stephensi* must collaborate effectively to ensure that knowledge is shared, resources are used optimally, and key activities are prioritized. As *An. stephensi* has the potential to spread quickly, cross-border collaboration is essential, and countries should work together to ensure an effective regional approach.



Strengthening SURVEILLANCE

Entomological surveillance can determine the extent of the spread of *An. stephensi* and its role in transmission; it is essential to target specific control measures and assess their impact. Human malaria case surveillance should be used to investigate the potential impact of the vector's presence on malaria, particularly in urban areas. Such surveillance might provide an indication of the presence of *An. stephensi* in areas where it has not yet been detected.



Improving INFORMATION EXCHANGE

Information on the presence of *An. stephensi*, as well as on successes and failures in attempts to control the vector, needs to be documented and shared widely and rapidly – at both national and international levels – to determine best practices and inform the response across invaded areas.



Developing GUIDANCE

National malaria control programmes need evidence-based guidance on the appropriate ways to conduct surveillance, implement control measures, develop by-laws, and devote resources to their response to *An. stephensi*. WHO provided an initial set of recommendations in its [2019 vector alert](#). This guidance will be reviewed and, where appropriate, updated based on best practices and other evidence identified as part of the regional initiative.



Prioritizing RESEARCH

It will be important to evaluate the impact of vector control interventions, and particularly new tools, against *An. stephensi*. Conducting research focused on *An. stephensi* will enable programmes to find better ways of responding to this invasive vector and of integrating control efforts with those targeted at other mosquito vectors.

Strategies against invasive vectors

Generally, in responding to invasive species, three main strategies can be considered:



Control

Accepting that the species has invaded certain areas, and controlling it to mitigate a potential increase in the malaria burden where it is present.



Containment

Allowing the species to remain in a certain area but conducting surveillance and intensive control, particularly at the fringes, to prevent further spread.



Elimination

Eliminating the species from the invaded area by building on efforts made under strategies 1 and 2.

While the feasibility of these strategies is not yet known when it comes to *An. stephensi* in Africa, it is essential that action be taken to build an evidence base to assess their validity while responding to the task at hand of halting the spread of this invasive vector across Africa.

Building and maintaining an integrated response

National responses to *An. stephensi* should be part of a comprehensive response to malaria vectors, guided by the WHO [Global technical strategy for malaria 2016–2030](#). Where feasible, integration with efforts to control other vector-borne diseases should be explored, as for example in the area of breeding site surveillance in urban and in peri-urban areas. The WHO [Global Vector Control Response 2017–2030](#) provides a framework for investigating and implementing such integration across vector-borne diseases.

Its four pillars of action are:

1

Strengthening inter- and intra-sectoral action and collaboration

2

Engaging and mobilizing communities

3

Enhancing vector surveillance and monitoring the evaluation of interventions

4

Scaling up and integrating tools and approaches

Tracking the spread of *Anopheles stephensi*

The WHO [Malaria Threats Map](#) features a dedicated section on invasive vectors, including *An. stephensi*. All confirmed reports of the presence of *An. stephensi* should be [reported to WHO](#) to enable an open sharing of data and an up-to-date understanding of the vector's distribution and spread. This knowledge will ultimately provide a basis to assess the effectiveness of any efforts to control or eliminate *An. stephensi*.



WHO initiative to stop the spread of *Anopheles stephensi* in Africa



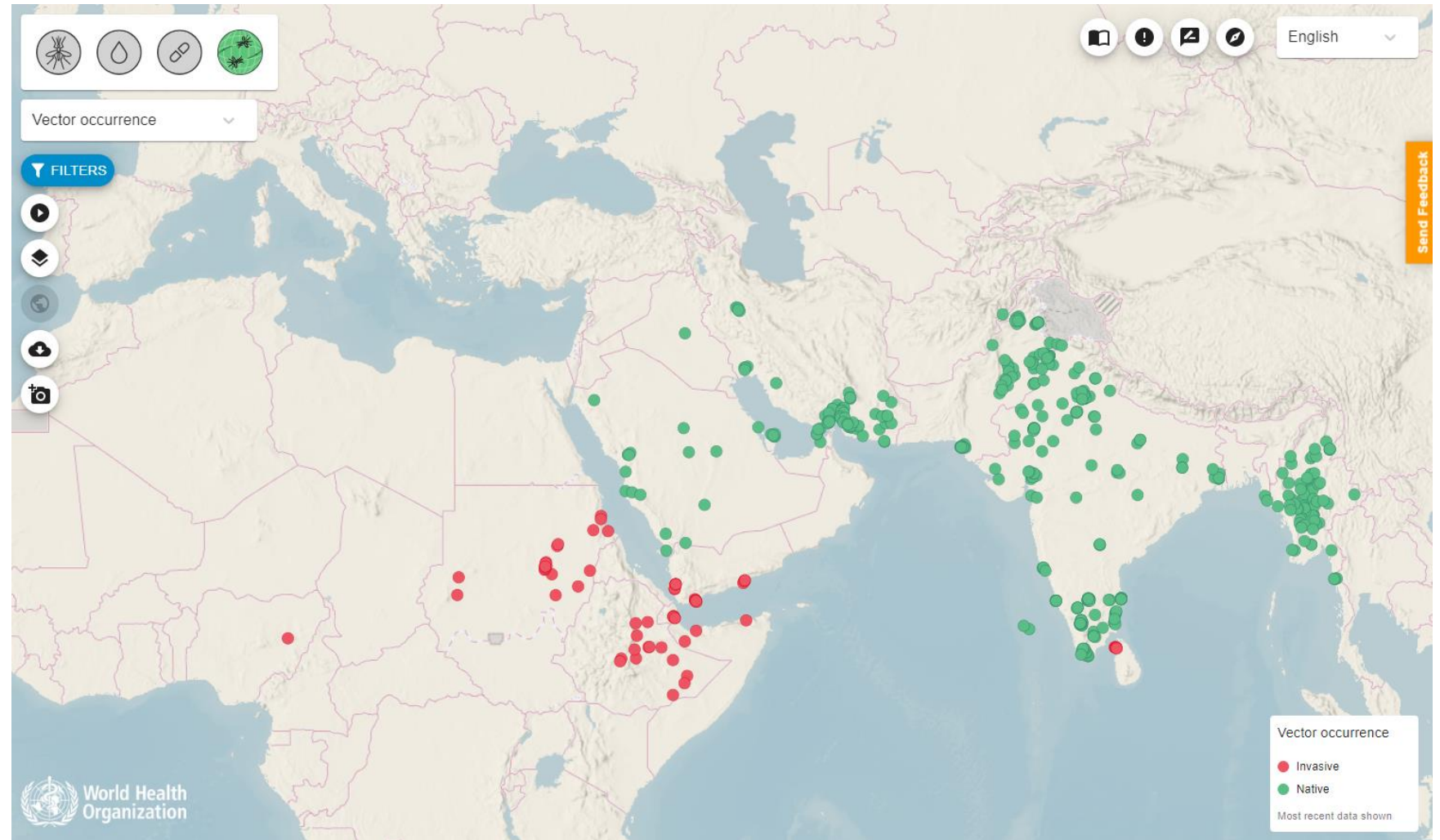
Anopheles stephensi

- Major malaria vector from south Asia
- First reported finding in Africa in 2012
- Flexibility in larval site choice, especially able to use urban larval sites
- Host preference for cattle/goats
- Good biological vector for *P. falciparum* and *P. vivax*
- Resistant to many insecticides used for public health



Tracking the spread

- Malaria Threats Map
 - Native occurrences
 - Invasive occurrences
 - Negative findings (soon)

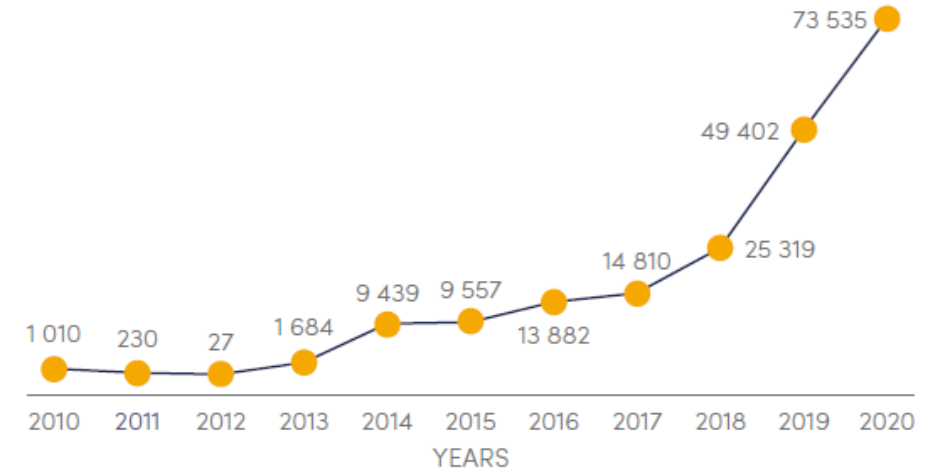


Impact – monitored and modelled

Epidemiological impact

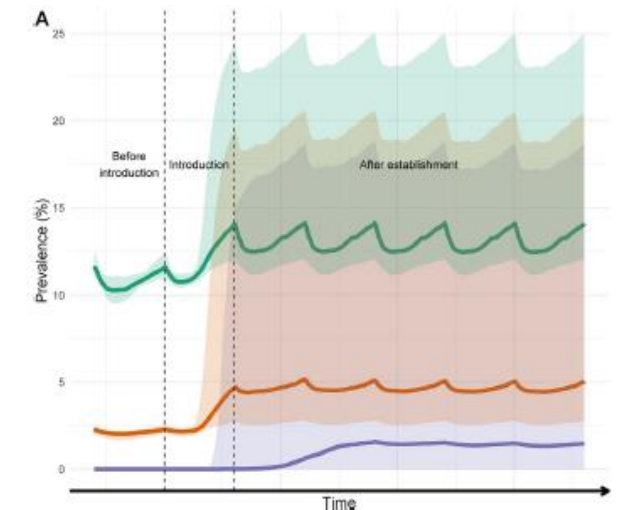
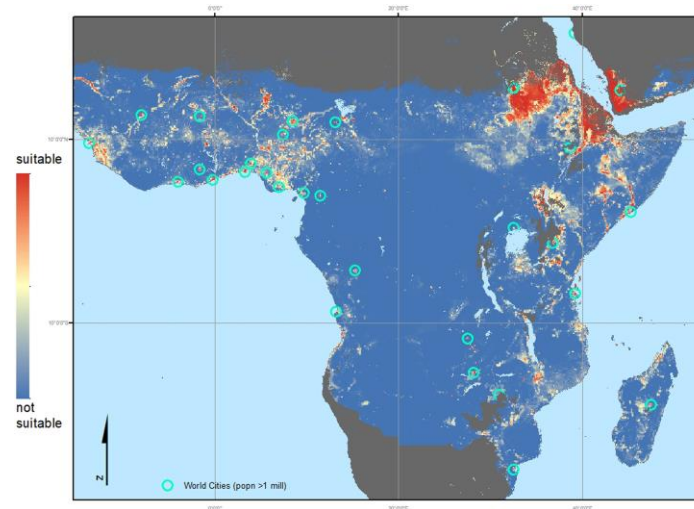
- Djibouti – increase in cases since 2012
- Dire Dawa – outbreak in 2022

Number of Reported Malaria Cases in Djibouti, 2010 – 2020

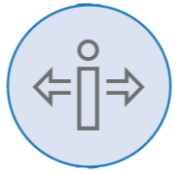


Modelled impact

- Modeled spread of *An. stephensi* in Africa – 126 million at increased risk
- If *An. stephensi* spread to all suitable areas in Ethiopia, there could be a 50% increase in cases (95% CI: 14-90%)



WHO initiative



Information exchange



Increasing collaboration



Strengthening surveillance



Prioritizing research



Developing guidance



Appropriate response

Risks

- Too much investment
 - Reduced funds/attention for malaria in rural areas
- Too little investment
 - Delay in determination of appropriate control tools, leading to increased spread across Africa
 - Increased malaria in urban settings

Next steps

- Update of Vector Alert (2022)
- Partners convening in Ethiopia (March 2023)
- Quarterly *An. stephensi* calls
- Deep dive into past successes and failures of *An. stephensi* control (2023)

