Documentation related to Sessions 3 and 4 of the meeting
Click on the links below to see the pre reads and presentations

Malaria Policy Advisory Committee (MPAC) Meeting, 2–4 October 2019

Documentation related to Sessions 3 and 4

Wednesday, 2 October 2019			
	Session 3	**Open**	**For information**
14:00 – 14:45	Update on the RTS,S Malaria Vaccine Implementation Programme Background | Presentation	Dr Mary Hamel Dr David Schellenberg	
14:45 – 15:30	Update from the Malaria Vaccine Advisory Committee Background | Presentation	Dr Chetan Chitnis	**For decision**
15:30 – 16:15	The use of non-pharmaceutical forms of *Artemisia* Background | Presentation	Charlotte Rasmussen	
16:15 – 16:45	*Coffee break*		
	Session 4	**Open**	**For guidance**
16:45 – 17:45	Update on malaria elimination in the Greater Mekong Subregion	Dr Pascal Ringwald	
17:45 – 18:15	Update on the Strategic Advisory Group for malaria eradication	Dr Kim Lindblade	**For information**

Malaria Policy Advisory Committee Meeting
2–4 October 2019, Geneva, Switzerland
Background document for Session 3

Update on the RTS,S/AS01 Malaria Vaccine Implementation Programme

October 2019

Background

The Malaria Vaccine Implementation Programme (MVIP) was developed to act on the 2016 WHO recommendation to pilot implementation of the RTS,S/AS01 malaria vaccine (1). The MVIP supports the introduction of the malaria vaccine in selected areas of Ghana, Kenya and Malawi and the evaluation of the programmatic feasibility of delivering a four-dose schedule, the vaccine's impact on mortality, and its safety in the context of routine use. The primary aim of the Programme is to address outstanding questions related to the public health use of the vaccine in order to enable a WHO policy decision on the broader use of RTS,S/AS01 in sub-Saharan Africa.

The Programme is jointly coordinated by the Global Malaria Programme (GMP), the Immunization, Vaccines & Biologicals (IVB) Department and the WHO Regional Office for Africa, in close collaboration with other WHO departments and country offices, ministries of health in pilot countries, PATH and other partners. Introduction of the malaria vaccine is country-led.

Update since April 2019

WHO welcomed the launch of the world's first malaria vaccine by the Government of Malawi on 23 April 2019, the Government of Ghana on 30 April 2019 and the Government of Kenya on 13 September 2019. This historic milestone generated extensive news interest and coverage in nearly every geographical area.[1] Vaccine uptake and coverage are closely monitored through countries' routine health information systems. Data and feedback received so far suggest good acceptance of the programme by health care workers, caregivers and communities, and generally high demand in areas where communication and sensitization efforts have been strong. Early supervisory visits have identified areas for improvement, and the national immunization programmes (EPI) are taking measures to address these issues, supported by WHO and PATH.

All country-specific pilot evaluation protocols have received ethical approval. The evaluation partners in Ghana and Malawi have completed the first cross-sectional household surveys in pilot areas; the survey in Kenya began in July 2019. Morbidity surveillance has started in sentinel hospitals, and mortality surveillance has started at community level, in Ghana, Malawi and Kenya. Efforts will continue to monitor and improve these surveillance systems. The qualitative longitudinal study led by PATH to assess issues related to vaccine uptake, community perceptions, service delivery and so on has also started in the three countries.

[1] See the MVIP web page for news, stories, videos and other information materials at https://tinyurl.com/MVIP-who-int

WHO/CDS/GMP/MPAC/2019.8

The MVIP's advisory bodies (i.e., the Programme Advisory Group and the Data Safety and Monitoring Board) continue to meet regularly and provide guidance to the Programme.

In April 2019, the Framework for Policy Decision on RTS,S/AS01 was endorsed by the Strategic Advisory Group of Experts (SAGE) and Malaria Policy Advisory Committee (MPAC). The two advisory bodies have agreed to consider a policy decision on the broader use of the vaccine prior to the end of the pilots, as soon as the minimum required data are available (i.e., if and when concerns regarding safety signals observed in Phase 3 trials – related to meningitis, cerebral malaria, and sex-specific mortality – are satisfactorily resolved, and either severe malaria or mortality data trends are assessed as being consistent with a beneficial impact of the vaccine). Refinements to the policy recommendation could be made once the final data from the pilot evaluations are available. This step-wise approach will ensure that a policy decision is made as soon as the risk–benefit of the vaccine is established with the necessary level of confidence and that the vaccine is not withheld unnecessarily from countries in need if it is found to be beneficial.

In a statement released on 26 August 2019, MPAC drew attention to the stalled progress in malaria control in recent years and clarified its view on the first malaria vaccine. The Committee indicated that, if the results of the MVIP are promising, the RTS,S vaccine is likely to be an important additional tool for changing the course of malaria incidence and reducing malaria deaths in African children, in combination with insecticide-treated nets (ITNs) and other control measures (see below).

Current funding commitments by the Global Fund to Fight AIDS, Tuberculosis and Malaria, Gavi the Vaccine Alliance and Unitaid cover MVIP activities to the end of 2020. Efforts are ongoing to secure additional funding for 2021–2023 to complete the MVIP. In May 2019, the Global Fund Board approved a potential allocation of US$ 8 million from Catalytic Investments to complete the pilots (2). This contribution is, however, dependent upon a successful replenishment.[2]

If the data generated by the MVIP lead to a WHO policy recommendation for wider use of the vaccine, malaria-affected countries in sub-Saharan Africa must be able to access sufficient quantities of the vaccine at an appropriate price if they decide to implement the vaccine. There are several funding needs if the full potential of the vaccine is to be realized. WHO and partners have intensified efforts to brief key stakeholders on the current evidence base of the vaccine and the vision for access should there be a policy recommendation. These efforts are expected to intensify in the coming months.

Priorities for the next six months

Key priorities in the coming weeks and months include successful launch of the vaccine in Kenya, continued monitoring of vaccine uptake, documentation of lessons learnt and support for programmatic improvement where needed. Support will also be given to evaluation partners to ensure that the hospital- and community-based surveillance systems are fit for purpose. In addition, the data generated by the MVIP will be coordinated and managed, and resource mobilization efforts for funding beyond 2020 will continue.

Statement by MPAC on the RTS,S/AS01 malaria vaccine Released on 26 August 2019

Globally, 219 million cases of malaria were reported in 2018, and an estimated 435 000 people, including 260 000 African children, died from malaria in 2017. Scale up of WHO-recommended preventive measures resulted in a substantial decline in malaria morbidity and mortality between 2000 and 2015. However, in 2015 and 2016, progress with malaria control stalled and started to reverse, with an upswing in malaria cases, particularly in sub-Saharan Africa. A malaria vaccine such as RTS,S has the potential to help get malaria control back on track, and may prove to be an important

[2] This means that the contribution will only materialize if sources of funds for the 2020–2022 period are greater than or equal to US$ 12.1 billion, representing near full replenishment.

addition to current control tools. The RTS,S vaccine, with its reported level of efficacy, has been shown to provide substantial and significant added protection on top of that provided by optimal case management and high coverage of insecticide-treated mosquito nets (ITNs), reducing clinical malaria by 55% during the 12 months following primary vaccination, and by 39% over 4 years. Recent data from long term follow-up are reassuring regarding its long term efficacy and safety. The well-established Expanded Programme on Immunization can reach even the poorest children, who are generally at highest risk of malaria, and suffer the highest mortality rates.

The opportunity to evaluate the feasibility of delivery, safety and effectiveness of the RTS,S vaccine, through pilot implementation in three countries, comes at a critical time in malaria control: no other malaria vaccine has entered phase 3 clinical trials. Additional preventive tools are in the development pipeline, and MPAC looks forward to reviewing their potential to reduce the malaria burden. However the development, evaluation and deployment of these new tools is expected to take several years. Moreover, it is likely that they will also offer only partial protection.

At a time when the downward trend in malaria cases and deaths has stalled, when our current control efforts are threatened by resistance, and when no new intervention approaching the efficacy of RTS,S is available, MPAC looks forward to reviewing the results of the pilot implementations, in accordance with the Framework for Policy Decision on RTS,S/AS01 approved at the April 2019 MPAC and SAGE meetings. If these results are promising, the RTS,S vaccine, in combination with ITNs and other control measures, is likely to be an important additional tool to change the course of malaria incidence and reduce malaria deaths in African children.

Contact

For more information, please contact:

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David Schellenberg, Scientific Adviser, WHO HQ, Global Malaria Programme, schellenbergd@who.int

References

1. World Health Organization. Malaria vaccine: WHO position paper – January 2016. Wkly Epidemiol Rec. 2016;91(4):33–51 (https://www.who.int/immunization/policy/position_papers/malaria/en/).
2. Catalytic investments for the 2020–2022 allocation period (Board decision GF/B41/DP04). Geneva: The Global Fund to Fight AIDS, Tuberculosis and Malaria; 2019 (https://www.theglobalfund.org/board-decisions/b41-dp04/).

Update on the Malaria Vaccine Implementation Programme

MPAC 2 Oct 2019

WHO/F.Combrink

www.who.int

Outline

1. Background
2. Key data availability and framework for policy decision
3. Vaccine launch in three countries
4. Long term access and stakeholders' meeting
5. Feedback from the Immunization and Vaccines Implemenation Research Advisory Committee (IVRAC)

Partially effective vaccine with potential for high impact

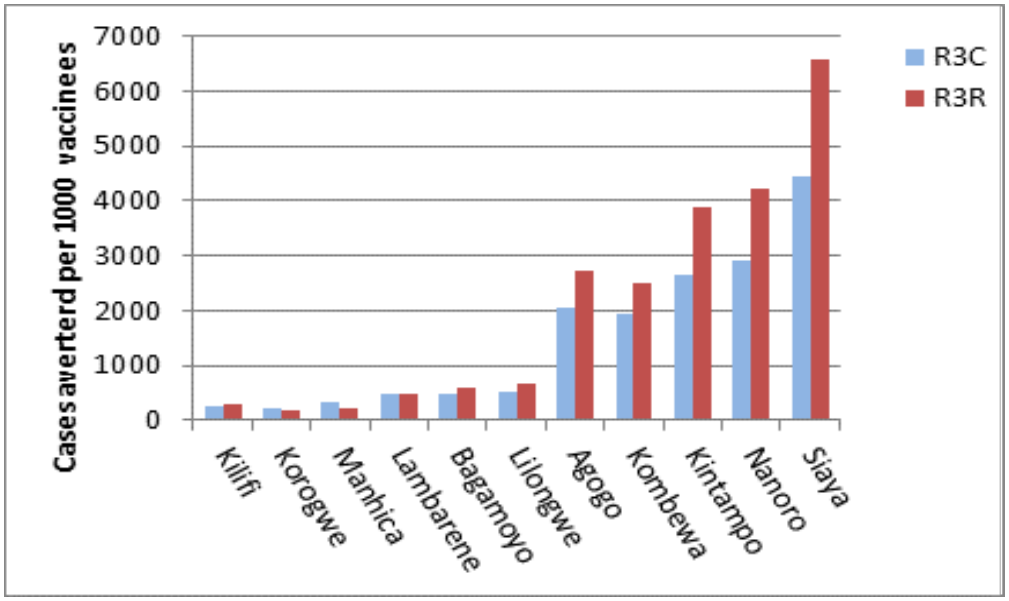
5-17 months at first vaccination, 4 doses, 4 years:

- 39% reduction clinical malaria; 29% reduction severe malaria
- 62% reduction in severe malaria anemia; 29% reduction in blood transfusions
- 37% reduction in malaria hospitalization; 18% reduction all cause hospitalizations

Measured benefit on top of that provided by ITNs, provided to study children

Safety: Well tolerated, febrile convulsions, safety signals without established causality: Meningitis (RR 10:1), Cerebral Malaria; in *post hoc* analysis, greater number of female deaths

Thousands of clinical malaria cases averted over 4 years with 3 *or* 4 doses



Clinical malaria cases averted, 3 or 4 doses, by study site and transmission, Mal 055[3]

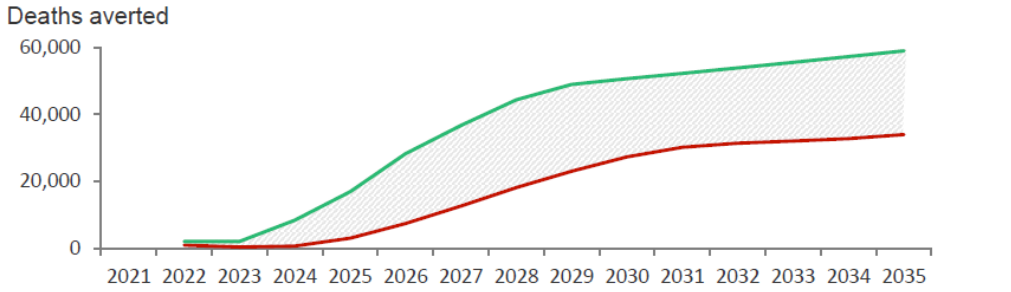
Malaria vaccine could avert between ~254-516K future deaths and ~49-142M future cases through 2035

06a – Appendix 3

Nigeria included

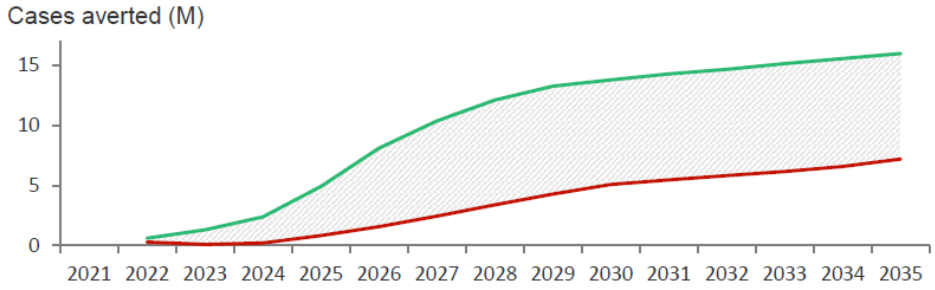
Scenarios: 5-20% parasite prevalence threshold, 100-95-90% or 100-90-80% or 90-80-70% of MCV1 with 15-25% 4th dose dropout

Deaths



	Total deaths averted (2021-2035)	Deaths averted per 100K vaccinated
Max	~516K	~489
Min	~254K	~417

Cases



	Total cases averted (2021-2035)	Cases averted per 100K vaccinated
Max	~142M	~111K
Min	~49M	~98K

20 Range of impact driven by different disease burden estimates and assumptions on duration of immunity used in Swiss TPH and Imperial models
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

Gavi The Vaccine Alliance

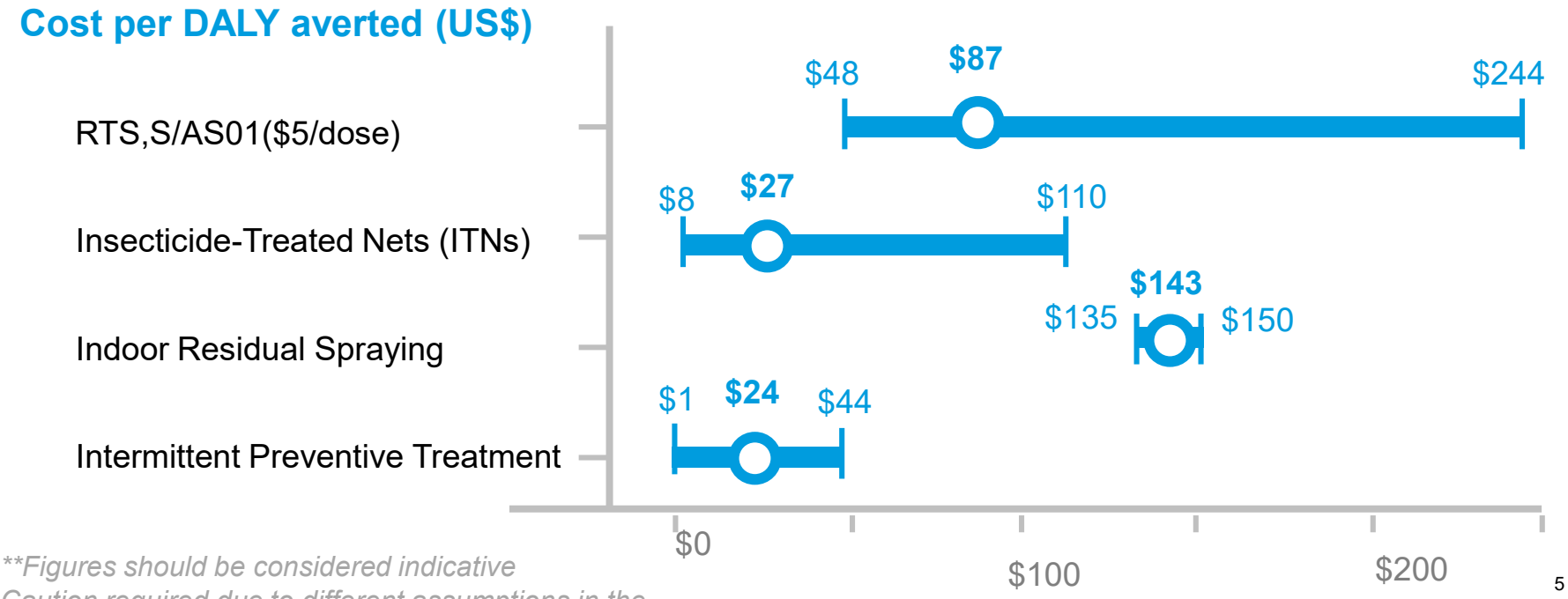
On top of that provided by current malaria control tools, including ITNs

RTS,S/AS01 vaccine is cost effective

At **a hypothetical** vaccine price of $5 a dose

- Median incremental vaccine cost effectiveness ratio is **$87 (range $48-$244) per DALY averted** and $25 ($16-$222) per clinical case averted*
- RTS,S considered to provide value for money in comparison with other vaccines *(Gavi 2018 VIS)*

RTS,S compared with other malaria control tools**



***Figures should be considered indicative Caution required due to different assumptions in the different models & lack of consideration of equity*

*Penny MA et al. Lancet, Vol. 15, pp. 0140-6736

EMA positive opinion
SAGE & MPAC recommended pilots

Recognizing potential for high impact, outstanding questions, recommended pilot phased introduction, in 3-5 countries

- Feasibility of reaching children with 4 doses
- Safety, emphasis on safety signals in Phase III trial
- Impact in routine use

Data will inform policy on wider use of RTS,S/AS01

Call for expressions of interest
- **10 countries**
- **3 selected using standardized criteria**

The four components of the MVIP

World Health Organization

Vaccination

1

RTS,S/AS01 Implementation through EPI Programme

In selected areas

Evaluation

2

Pilot evaluation commissioned by WHO

Incl. sentinel hospitals surveillance; community-based mortality surveillance; 3 household surveys

3

Qualitative assessment (HUS) & economic analyses

commissioned by PATH

4

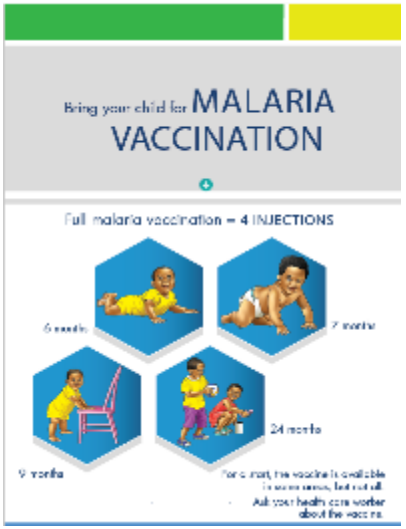
GSK Phase IV study

Safety, effectiveness and impact
Part of GSK's EMA Risk Management Plan

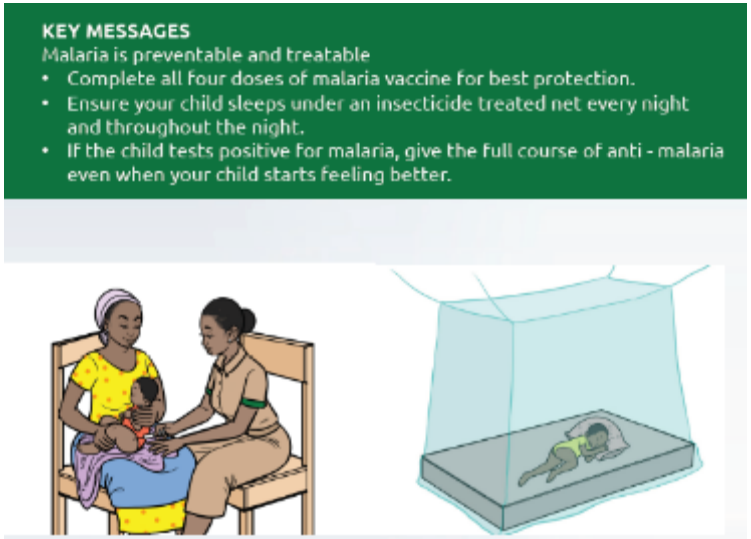
Communication is a key priority

Extracts from countries' information, education and communication materials

Extract from Ghana fact sheet



Extract from Kenya fact sheet



Extract from Ghana Flip chart for health workers

Extract from Kenya Flyer for health workers and caregivers

Extract from Malawi Flyer and Key Facts Booklet

Framework for WHO policy decision – hierarchy of data

Recognizing that any rebound seen with the 3-dose regimen was time limited, and children benefit from 3 or 4 doses:

SAFETY

Reassuring safety data are considered of primary importance and pre-condition for a positive policy recommendation

IMPACT

Data trends assessed as consistent with a beneficial impact of the vaccine for:

- **Impact on severe malaria:** an acceptable surrogate indicator for impact on mortality

or

- **Impact on all-cause mortality**

FEASIBILITY

Recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage including coverage of the 4th dose

Step-wise approach to policy recommendation

World Health Organization

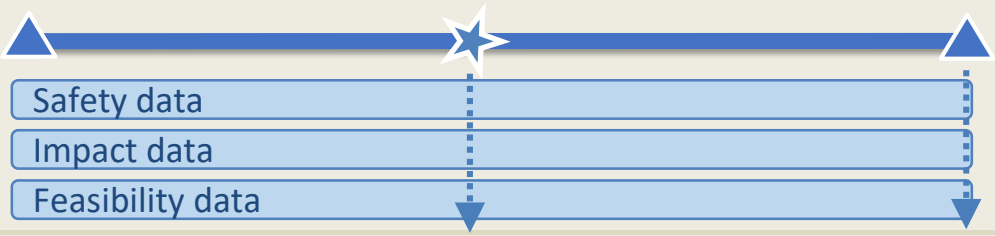
DATA

Malaria Vaccine Implementation Programme

Vaccination start (first country)

24 months after start*

Evaluation complete (46 months in last country)



2017	2018	2019	2020	2021	2022	2023

POLICY

1

Policy recommendation for broader use if and when:

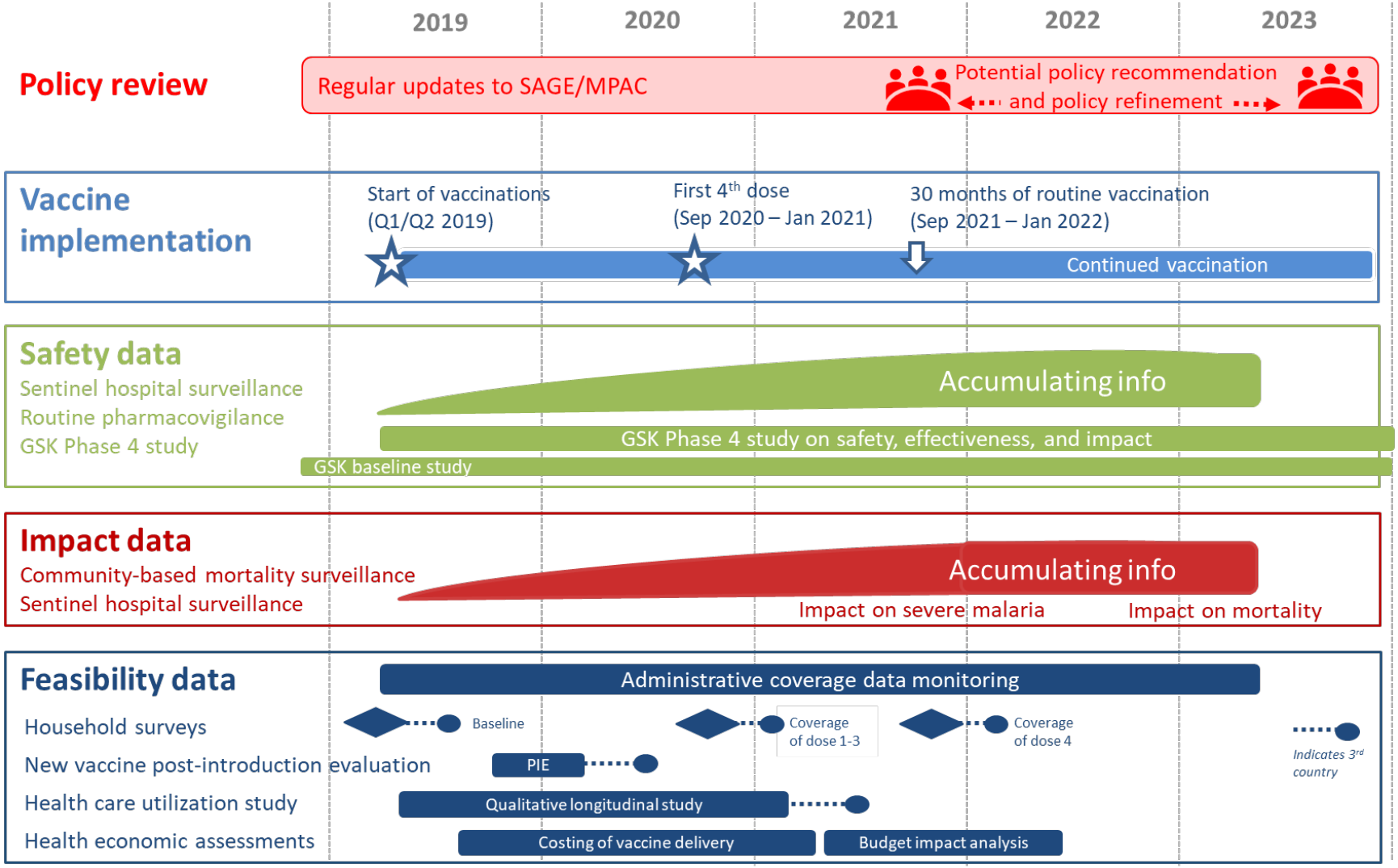
i. Concerns regarding safety signals satisfactorily resolved; and
ii. Severe malaria data trends assessed as *consistent with a beneficial impact* of the vaccine; or
iii. Mortality data trends assessed as *consistent with beneficial impact* of the vaccine

2

Adjustments or refinements to policy recommendation if needed based on the final MVIP data set

**Timing dependent on acquisition of and rate of events (among other factors)*

Timeline of MVIP evidence generation and review



Vaccine Launch:
World's first malaria vaccinations

World Health Organization

World Health Organization (WHO) @WHO · Apr 23

's first #Malaria vaccine pilot is launched in #Malawi, the first country in Africa to roll out this landmark vaccine, known as RTS,S. The vaccine will be available to children from 5 months old to 2 years. bit.ly/2ZpASGN

You, WHOMalawi, WHO African Region and 4 others

41 970 1.5K

23 April 2019 in Malawi

30 April 2019 in Ghana

13 Sept 2019 in Kenya

Building into a functional delivery system

Ghana

As of 04 September 2019

- Launch of vaccination: 30th April 2019
- RTS,S/AS01 introduced into the routine immunization schedule in selected districts of seven regions with combined annual birth cohort of ~168k children[1]
- Monthly reports based on routine administrative data in DHIMS2

Cumulative May – June 2019*	
No. Vaccine doses	51,960
No. of children vaccinated (1st dose)	28,477
No. of reported Adverse Events Following Immunization (AEFI)	40[2]

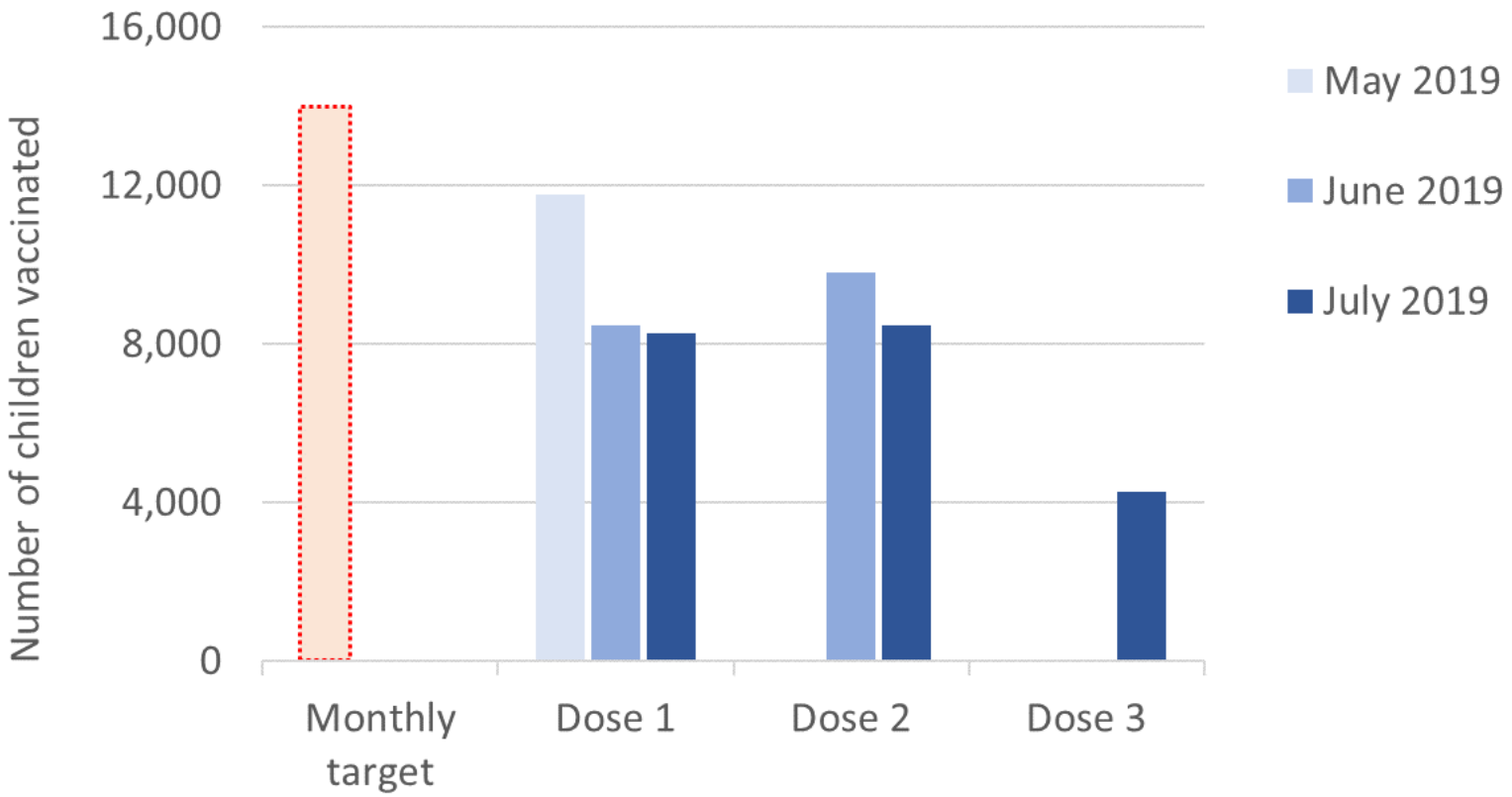
1. Pilot regions: Volta, Oti, Bono, Bono East, Ahafo, Central, Upper East
2. Data for May-June 2019

*Data source: GHS/EPI

Ghana

Children vaccinated with RTS,S from May – July 2019

Cumulatively **28,497** children have received the first dose of the RTS,S vaccine (May-July) representing **68% of the target population**



Source: GHS/EPI DHIMS2 – reported as of Aug 2019

Malawi

As of 4 September 2019

- Launch of vaccination: 23th April 2019
- RTS,S/AS01 introduced into the routine immunization schedule in selected areas of 11 districts with combined annual birth cohort of ~148k children[1]

Cumulative – April - June 2019

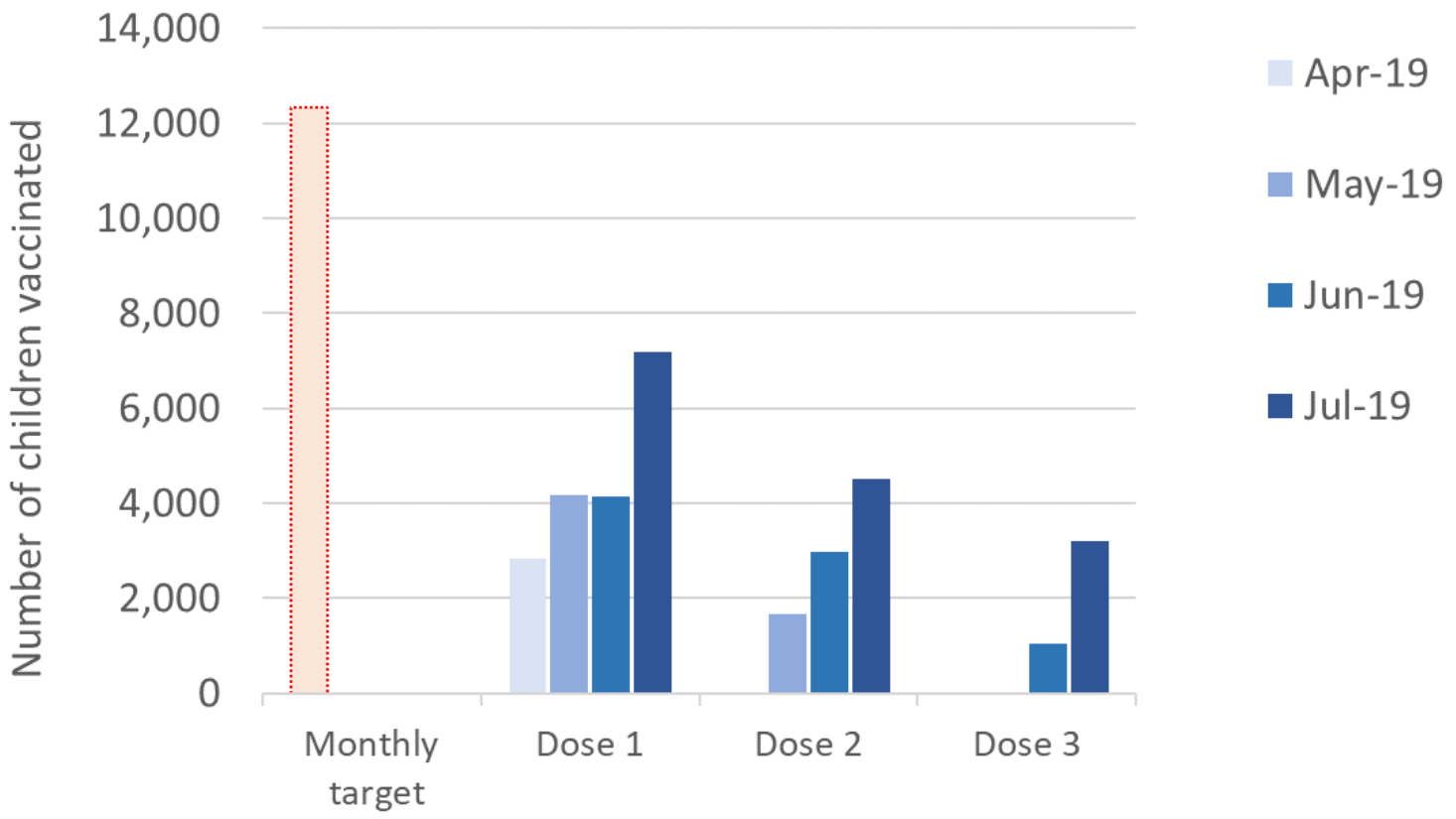
No. Vaccine doses	31,721
No. vaccinated (1st dose)	18,348
No. of reported Adverse Events Following Immunization (AEFI)	31[2]

1. Pilot districts: Karonga, Nkhatabay, Ntchisi, Mchinji, Lilongwe rural, Balaka, Mangochi, Machinga, Phalombe, Chikwawa, Nsanje
2. Data for May-June 2019

Data source: WHO Malawi based on information received from Malawi MOH, including from DHIS2

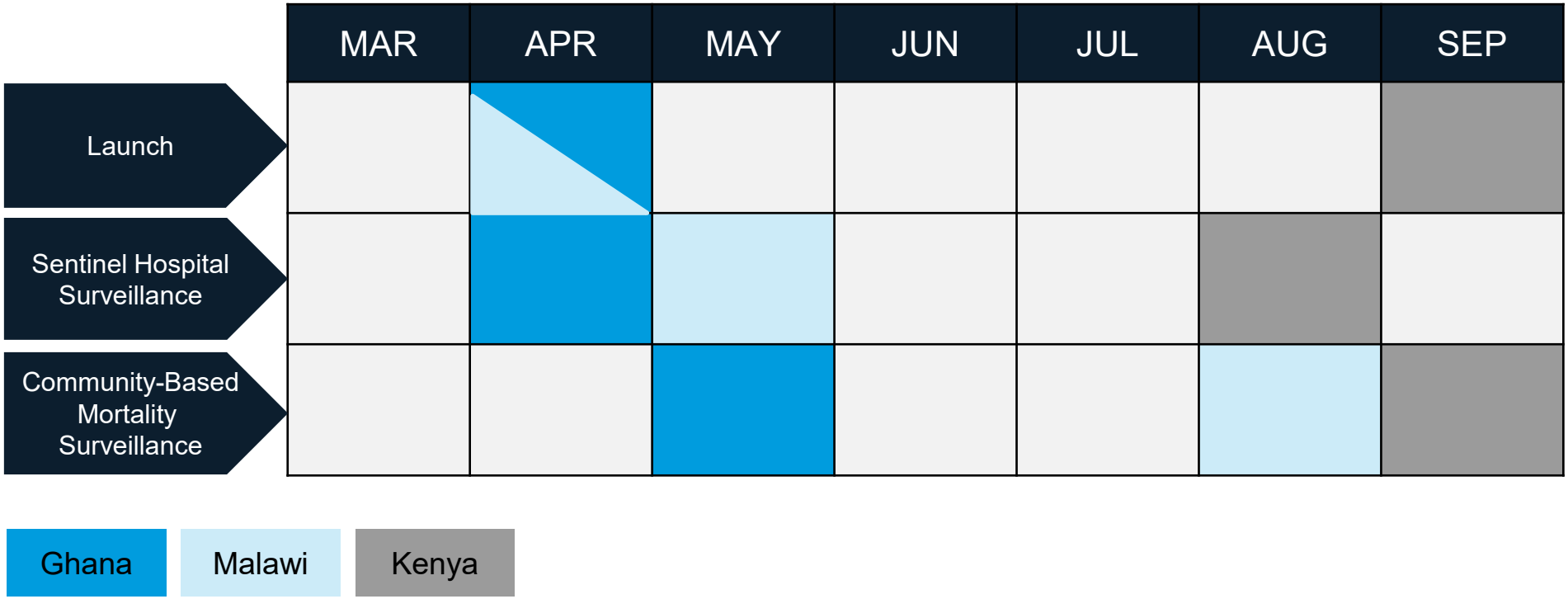
Malawi
Children vaccinated with RTS,S from April – July 2019

Cumulatively 18,348 children have received the first dose of the RTS,S vaccine (23 April-July) representing 46% of the target population



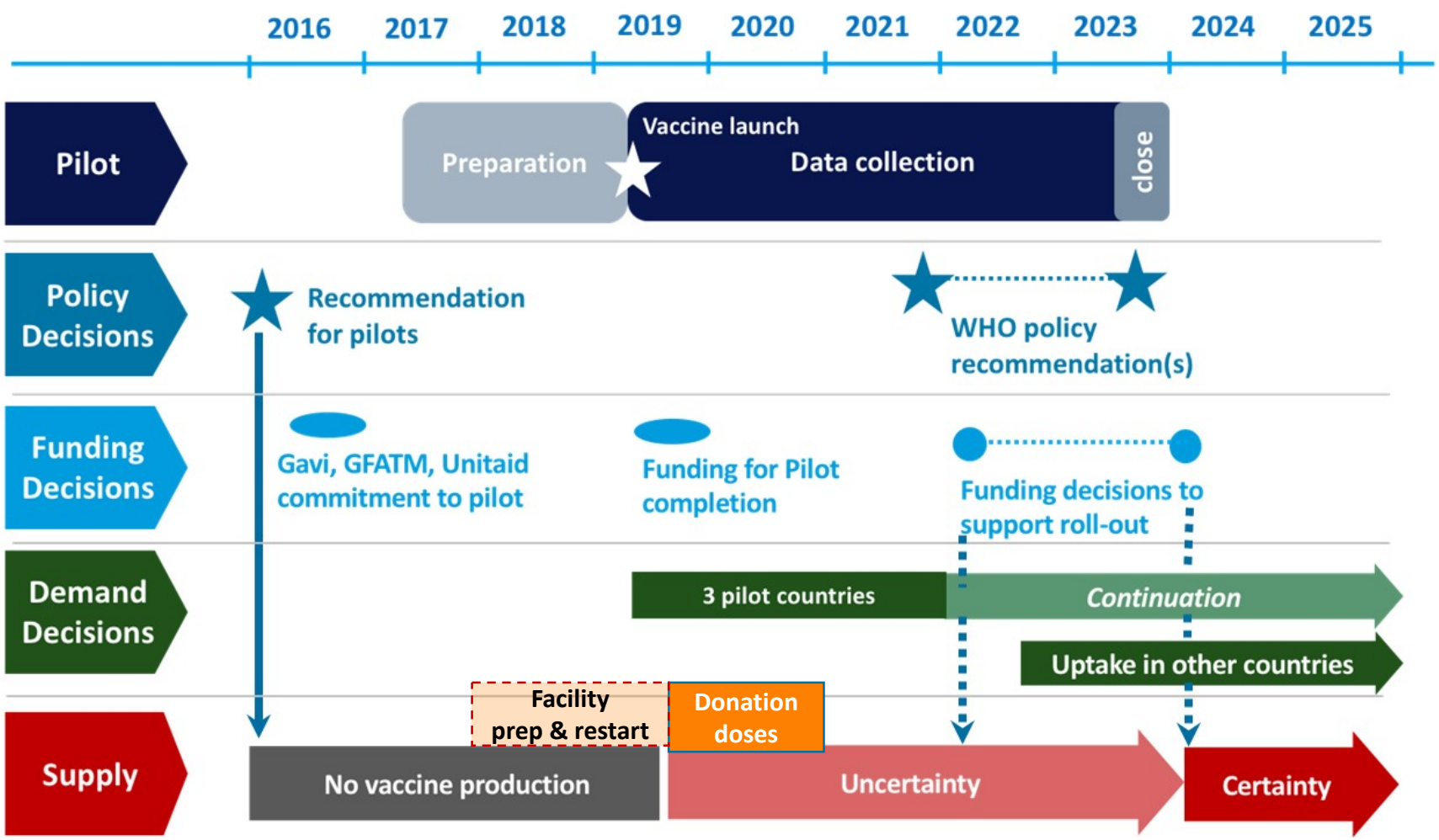
Source: MOH/EPI DHIMS2 – reported as of 03 Sept 2019

Evaluation: Start of safety and mortality data collection



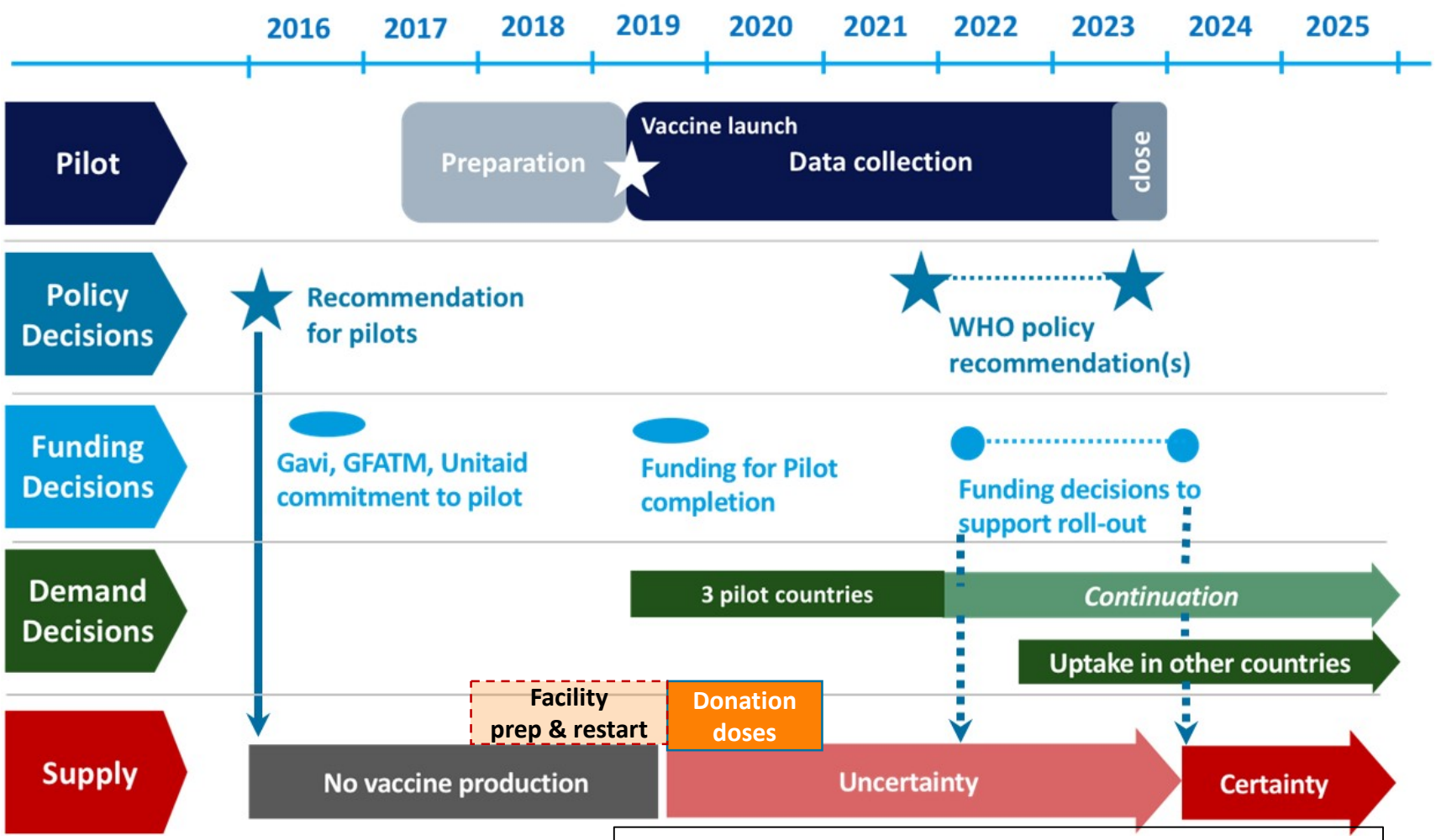
DSMB met 26 Sept, first opportunity to review data from MVIP
Recommended continue programme

Timelines and long-term access considerations *(illustrative)*



Source: World Health Organization (modified)

Timelines and long-term access considerations *(illustrative)*



Source: World Health Organization (modified)

Stakeholders meeting on access
Oct 18, 2019

Immunization and Vaccine Related Implementation Research Advisory Committee (IVIR-AC): Considered CE modeling for malaria vaccines

World Health Organization

- Reviewed selected papers on CE related to RTS,S (Penny, 2016; Wilkins 2017; Sauboin 2019)
- Considered how CE models should be used to inform policy (final report pending):
  1. Models should look at packages of interventions, in a realistic scenario, rather than assessing sequential introduction, which is not practical.
  2. Equity, including poverty/financial risk protection should be incorporated. Consider heterogeneity across SES in malaria burden, vaccine/intervention coverage, delivery costs, and malaria transmission.
  3. Indirect effects of reducing malaria infection should be considered
  4. CE is one of many inputs that inform policy decisions; broader societal and economic benefits should be considered, including equity, poverty protection, protection from catastrophic health care costs, improved performance in school, etc

MPAC statement on MVIP & RTS,S

Globally, 219 million cases of malaria were reported in 2018, and an estimated 435,000 people, including 260,000 African children, died from malaria in 2017. Scale up of WHO-recommended preventive measures resulted in a substantial decline in malaria morbidity and mortality between 2000 and 2015. However, in 2015 and 2016, progress with malaria control stalled and started to reverse, with an upswing in malaria cases, particularly in sub-Saharan Africa. A malaria vaccine such as RTS,S has the potential to help get malaria control back on track, and may prove to be an important addition to current control tools. The RTS,S vaccine, with its reported level of efficacy, has been shown to provide substantial and significant added protection on top of that provided by optimal case management and high coverage of insecticide-treated mosquito nets (ITNs), reducing clinical malaria by 55% during the 12 months following primary vaccination, and by 39% over 4 years. Recent data from long term follow-up are reassuring regarding its long term efficacy and safety. The well-established Expanded Programme on Immunization can reach even the poorest children, who are generally at highest risk of malaria, and suffer the highest mortality rates.

The opportunity to evaluate the feasibility of delivery, safety and effectiveness of the RTS,S vaccine, through pilot implementation in three countries, comes at a critical time in malaria control: no other malaria vaccine has entered phase 3 clinical trials. Additional preventive tools are in the development pipeline, and MPAC looks forward to reviewing their potential to reduce the malaria burden. However the development, evaluation and deployment of these new tools is expected to take several years. Moreover, it is likely that they will also offer only partial protection.

At a time when the downward trend in malaria cases and deaths has stalled, when our current control efforts are threatened by resistance, and when no new intervention approaching the efficacy of RTS,S is available, MPAC looks forward to reviewing the results of the pilot implementations, in accordance with the Framework for Policy Decision on RTS,S/AS01 approved at the April 2019 MPAC and SAGE meetings. If these results are promising, the RTS,S vaccine, in combination with ITNs and other control measures, is likely to be an important additional tool to change the course of malaria incidence and reduce malaria deaths in African children.

August 26, 2019

The Ministry of Health
1 hr ·

World Health Organization

The Cabinet Secretary for Health Sicily Kariuki spoke at the ongoing 74th regular Session of the General Assembly, GAVI Alliance and Global Fund side event on putting the U in UHC where she highlighted how Kenya is reaching the previously unreached populations in a bid to leave no one behind .

The CS highlighted initiatives like the recently launched malaria vaccine in Kenya among three African countries and took the opportunity to invite participants to the ICPD 25+ conference which will be held in Nairobi in November, 25 years after it was held last in Cairo.

Questions?

World Health Organization

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Thank you

World Health Organization

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Malaria Policy Advisory Committee Meeting
2–4 October 2019, Geneva, Switzerland
Background document for Session 3

WHO consultation on malaria vaccines and biologicals R&D and MALVAC meeting

October 2019

In 2017, malaria caused an estimated 219 million cases of illness and 435 000 deaths. Although there were fewer cases in 2017 than in 2010, progress stagnated in the 2015–2017 period. The Malaria Vaccine Advisory Committee (MALVAC) was established while pilot implementation of RTS,S/AS01 is ongoing, so that experts can help WHO rearticulate its vision, product preferences and recommendations on malaria vaccine research and development (R&D) priorities. The goal is to accelerate progress towards next-generation malaria vaccines able to provide higher protection and reduce transmission. This MALVAC meeting was organized after a two-day consultation on the status of malaria vaccine R&D to which a variety of stakeholders were invited to present their activities and perspectives.

During this landscaping consultation, participants presented recent changes in global malaria epidemiology, highlighting the impetus for vaccines as an additional tool. Changes in the world of immunization were presented, with a focus on equity and coverage, a future including immunization all along the life course and a value-based decision framework. Considerations related to programmatic feasibility are essential. Researchers and practitioners from the front lines discussed the medical need for *Plasmodium falciparum and P. vivax* malaria vaccines and associated use cases in various epidemiological settings. Recent changes in key capacities and standards in research were discussed. An expansion in the role of sporozoite and blood stage controlled human malaria infection models, as well as man-to-mosquito transmission models could be considered. Lessons from recent trials in conditions of natural exposure should inform future strategies and trial design. Target Product Profiles, clinical development strategies, programmatic suitability and cost-effectiveness considerations were discussed for specific product development programmes undergoing clinical testing. Perspectives from organizations that coordinate and fund malaria vaccine development, as well as a GSK 'look back' exercise, were presented, highlighting the challenges in developing an end-to-end integrated vision through to product availability and impact.

During the MALVAC consultation, work packages of priority interest were discussed. Participants agreed that how next-generation malaria vaccines would best be used in various epidemiological settings and preferences for associated product profiles should be defined. The role of highly effective short-acting products, such as monoclonal antibodies and seasonal vaccination strategies, was discussed. Guidance on product development pathways, trial design and endpoints should be updated to reflect new knowledge and goals. Intermediate thresholds and consensus stage gates could assist in rational resource allocation and disinvestments from failed projects. The best approach to product combination for the development of highly effective multi-stage, multi-component vaccines should be considered. Drawing from available evidence and understanding the consequences of delayed acquisition of immunity derived from vaccine-induced reduction in natural exposure would help manage potential associated risks. *P. falciparum* and *P. vivax* will be the scope of the MALVAC discussions. The public availability of malaria vaccine clinical activity landscaping should be further supported. Altogether, R&D guidance will support the production of data packages that will enable robust policy decisions and subsequent action.

Following the meeting, MALVAC has worked on the expression of a position statement aimed at highlighting its commitment to supporting R&D efforts towards the availability and use of a high-impact next-generation malaria vaccine. To further reduce burden and maintain momentum towards malaria elimination, a malaria vaccine is considered an important addition to the malaria intervention toolkit. Two complementary approaches are

WHO/CDS/GMP/MPAC/2019.9

recommended: i) promote the short- to medium-term deployment of first-generation vaccine candidates, and ii) support innovation and discovery to identify and develop highly effective, long-lasting and affordable next-generation malaria vaccines. For this to succeed, the key will be to identify efficient and cost-effective clinical development, financing and regulatory pathways.

Malaria Vaccine Advisory Committee

MALVAC – An Update

Chetan Chitnis

Chair, MALVAC

Malaria Policy Advisory Committee Meeting

Geneva

2nd October 2019

World Health Organization

WHO and Malaria Vaccine Research

- IMMAL Committee – research and capacity building in immunology of tropical infectious diseases 80s-90s
- VDR Committee – research and capacity building in vaccine development for tropical infectious diseases

WHO and Malaria Vaccine Research

- IMMAL Committee – research and capacity building in immunology of tropical infectious diseases 80s-90s
- VDR Committee – research and capacity building in vaccine development for tropical infectious diseases
- MALVAC: Malaria Vaccine Advisory Committee 2008-2013
  - Advise WHO on strategic priorities, technical issues related to malaria vaccine development
  - Meetings/working groups to develop consensus views on priorities and best practices for vaccine R & D strategies
    - Adjuvants
    - Controlled human malaria infection (CHMI) – challenge trials
    - Assays and trial designs for transmission blocking vaccines
    - Whole organism vaccines (eg. attenuated sporozoites)
    - R & D for *P. vivax* vaccines

The evolving landscape of malaria

- Major changes in malaria epidemiology
  - Intensive malaria control efforts have greatly reduced malaria incidence and mortality 2000 – 2015
  - IRS, ITN, RDT, ACT
  - 219 million malaria cases, 435,000 deaths in 2017
  - No further reduction in malaria incidence or mortality since 2015
- Are further reductions possible with currently available tools especially in high transmission settings?

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- Are further reductions possible with currently available tools especially in high transmission settings?
- 1st malaria vaccine in pilot implementation studies - RTS,S/AS01
  - 39% protection over 4 years in 5-17 month children with 4 dose regimen
  - Pilot implementation initiated in 3 African countries mid-2018
- Other vaccines under development – R21, PfSPZ, PfRH5, PvDBPII
- Role for vaccines/other tools in malaria control and elimination?

Reconvening MALVAC

- Assist WHO in the prioritisation of specific malaria vaccine R&D avenues
- Review the state-of-the-art in malaria vaccine development
- Define priority targets and preferred clinical development pathways, mindful of emerging data and changing public health priorities
- Update the vision for the role of vaccines in future malaria control and elimination efforts
- Jointly convened by WHO's Initiative for Vaccine Research (IVR) & Global Malaria Program (GMP)

The Committee

- Members:
  - Edwin Asturias, University of Colorado, Denver
  - Philip Bejon, KEMRI-Wellcome Trust Research Programme
  - Chetan Chitnis, Institut Pasteur, Paris (Chair)
  - Katharine Collins, Radboud University
  - Brendan Crabb, Burnet Institute
  - Socrates Herrera, Consorcio para la Investigacion Cientifica, Cali
  - Miriam Laufer, University of Maryland
  - Regina Rabinovich, IS Global
  - Meta Roestenberg, Leiden University Medical Centre
  - Adelaide Shearley, John Snow Inc
  - Halidou Tinto, Institut de Recherche en Sciences de la Santé
  - Marian Wentworth, Management Sciences for Health (WHO Product Development for Vaccines Advisory Committee)
- Committee may be supplemented by other experts, including those from other WHO advisory groups

Highlights of Consultation on Malaria Vaccines and Biologicals R &D: July 15/16, 2019

MALVAC Meeting July 17, 2019

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  - Fractional dose of RTS,S regimen
- R21 – an RTS,S-like particle – showing promise
  - PfCSP-HBsAg fusion produced in *P. pastoris*
  - Formulated with Matrix M
  - Protection in Phase IIa challenge model
  - Currently being tested in Phase IIb field trials
  - R21 manufactured by Serum Institute of India, commitment for commercial supplies

Highlights of Consultation on Malaria Vaccines and Biologicals R &D: July 15/16, 2019

- Attenuated sporozoite vaccine: PfSPZ
  - 1046 volunteers, 12 countries including 3 countries in Africa
  - 11 trials (9 in Africa), 5 m – 65 y, PfSPZ/saline similar AE profiles
  - No breakthrough infections - safe
  - Efficacy in CHMI (heterologous): 83% at 10 wks, 55% at 8 m
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- PfSPZCVAC: sporozoites under chemoprophylaxis cover
  - 100% VE at 13 wks (heterologous)
  - 1/5th dose needed for PfSPZ
- Next generation - genetically attenuated SPZ
  - PfSPZ-GA1
  - PfSPZ-GAP3KO

Highlights of Consultation on Malaria Vaccines and Biologicals R &D: July 15/16, 2019

- PfRH5 – *P. falciparum* blood stage vaccine
  - PfRH5-Basigin interaction is essential for RBC invasion
  - PfRH5.1/AS01 Phase I/IIa blood stage challenge trial
  - 33% reduction in parasite multiplication rate (PMR) *in vivo*
  - 50% reduction in GIA *in vitro* at IgG conc. of 2.5 mg/ml
  - Next gen PfRH5 construct: PfRH5-VLP conjugation

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- Transmission blocking vaccines
  - Lead candidate: Pfs230-EPA/AS01
  - Blocking of transmission in membrane feeding assays
  - Direct skin feeding assays following CHMI with Pf
  - Pvs230-EPA/AS01: CHMI with Pv
  - Field trials – cluster randomized trials to measure efficacy in the field
  - Clinical development path – dialog with regulatory authorities

Highlights of Consultation on Malaria Vaccines and Biologicals R &D: July 15/16, 2019

- *P. vivax* vaccines
  - Standard malaria control measures are less effective against *P. vivax*
  - Hypnozoite stage: contributes >50% of *P. vivax* cases in PNG
  - Partially effective PEV can have significant impact on Pv transmission
  - Combination of PEV + BSV + TBV can significantly drive down transmission – modeling
  - Vaccine candidates under development
    - PvCSP/AS01; PvR21/Matrix M
    - PvDBPII/GLA-SE safe and immunogenic in Phase I
    - PvDBPII to be tested against blood stage challenge in CHMI
    - Pvs230D1-EPA/AS01 – transmission blocking vaccine

Highlights of Consultation on Malaria Vaccines and Biologicals R &D: July 15/16, 2019

- Monoclonal antibodies for malaria?
  - Human mAbs to PE and BS antigens
  - Target 80% efficacy for 3-6 months (cover a transmission season)
  - Prevent infection and reduce transmission
  - Combine with an anti-malarial to clear parasites and provide prophylaxis over a transmission season
  - Evaluate efficacy in CHMI to validate mAbs
  - Likely to be safe, cost-effective, ease of administration and delivery

Developments in CHMI

- Controlled Human Malaria Infection (CHMI) increasingly used to evaluate vaccines
  - Sporozoite and blood stage challenge – evaluate both PEV and BSV
  - Dose & formulation optimization, duration of protection
  - Define and evaluate immune correlates
  - Development of CHMI platforms in malaria endemic countries
- Use of CHMI to evaluate transmission-blocking vaccines
- CHMI for *P. vivax*
  - Blood stage and sporozoite challenge
  - Measure transmission blocking activity

Highlights of Consultation on Malaria Vaccines and Biologicals R &D: July 15/16, 2019

MALVAC Meeting July 17, 2019

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Malaria Policy Advisory Committee Meeting
2–4 October 2019, Geneva, Switzerland
Background document for Session 3

WHO technical document of the use of non-pharmaceutical forms of *Artemisia*

October 2019

Introduction

Research on the herbal remedies used in the past has led to the discovery of malaria treatments that have saved millions of lives. The powdered bark of the cinchona tree was used to treat malaria, initially in South America and later across the globe. Quinine was first isolated from cinchona tree bark in 1820, and the pure compound quickly demonstrated greater potency than the hot infusions of the bark. With the availability of the pure compound, appropriate dosage could be established and the first modern chemotherapeutic agent against malaria was born *(1,2).*

Today, the most widely used antimalarial treatments, artemisinin-based combination therapies (ACTs), are produced using the pure artemisinin compound extracted from plant *Artemisia annua.* A full malaria treatment course with an ACT costs less than US$ 2 to procure. There are still ACTs available, capable of treating all malaria strains globally, despite artemisinin partial resistance in South East Asia and resistance to some of the partner drugs used in ACTs. However, for those in need in malaria-endemic countries, ACTs are not always available, are only available at high prices, or are of substandard quality. These difficulties are used as part of the argument in promoting *Artemisia* plant materials as affordable and self-reliant medicines against malaria.

Traditional herbal remedies have several limitations, especially when they are utilized for treating potentially fatal diseases such as malaria. The main limitations are related to standardization of plant cultivation and preparation of formulations, dosages, quality assurance, and evidence of clinical safety and efficacy. The aim of this technical document is to review the evidence on the effectiveness of non-pharmaceutical forms of *Artemisia* and to discuss the limitations specific to these herbal remedies.

The discovery of artemisinin

The search for new antimalarial drugs was fuelled by the spread of resistance to the most widely used antimalarial drugs. Chloroquine was introduced in 1934 but was not in wide-scale use until the 1950s. Chloroquine resistance emerged around 1957 in two locations: South America and along the Cambodia–Thailand border. The resistance spread from the Cambodia–Thailand border areas throughout South-East Asia *(3).* During the Viet Nam–American war, the North Vietnamese government requested assistance from China to manage the chloroquine drug-resistant malaria that was affecting their military forces *(4).*

In 1967, China launched Project 523 – a project aimed at finding new drugs for the treatment of malaria. The project involved 60 research organizations and more than 500 scientists *(5)*. As part of the project, Chinese scientists examined ancient medical texts, reviewing more than 2000 recipes and testing extracts from more than 100 plants on rodent malaria parasites *Plasmodium berghei.* The plant

WHO/CDS/GMP/MPAC/2019.10

A. annua was mentioned in several of the recipes, and the first extracts from *A. annua* did show antimalarial activity. However, this activity was highly variable, and the results were not satisfactory. A recipe from 341 A.D. for the treatment of fever, prescribed the juice of *A. annua* produced using cold water rather than tea produced through the traditional method of boiling herbs. There is no evidence that the Chinese used *A. annua* as a tea. Professor Tu Youyou, awarded the Nobel Prize in Medicine in 2015 for the discovery of artemisinin, realized that high temperatures could be causing the instability in the antimalarial activity and suggested that the leaves were likely the part of the plant with the most activity. Inspired by this, the Chinese researchers produced an extract using a low-temperature method with ether. This extract was shown to be highly efficacious against rodent and monkey malaria. The results led to a countrywide effort involving a large number of scientists from many institutions. The goal was to extract large quantities of the pure ingredient and determine its chemical structure and synthesis. The active antimalarial was identified in 1972 and named qinghaosu (or artemisinin in English) *(6).*

Clinical trials initiated in 1972 confirmed the high antimalarial activity of artemisinin for both uncomplicated and severe malaria, with results published in English in 1979 *(5,7).* Despite recent progress in producing semi-synthetic artemisinin using yeast extraction, *A. annua* plants remain the main source of the drug *(8).*

Artemisinin and its derivatives

Artemisinin was identified as a sesquiterpene lactone peroxide and is essentially insoluble in water and oil. This, together with the high recrudescence rates observed, prompted the Chinese scientists to conduct further research on developing artemisinin derivatives. It was found that the peroxy group in artemisinin was essential for the antimalarial activity and had to be maintained in any derivatives to exhibit antimalarial effect. Treating artemisinin with sodium borohydride generated dihydroartemisinin, which was found to be an even more potent antimalarial than artemisinin. Dihydroartemisinin served as the basis for the development of oil- and water-soluble derivatives. Of the derivatives developed from dihydroartemisinin, Chinese researchers selected two compounds for larger scale trials based on their stability and high antimalarial efficacy: the oil-soluble artemether and the water-soluble artesunate *(9–11).*

Pharmacokinetics and metabolism

Several formulations and routes of administration for artemisinin have been tested. Although artemisinin does not dissolve in oil or water, the first trials included administration of artemisinin suspended in oil or water in addition to rectal and oral administration. Chinese researchers and others used a dose of 10 mg/kg of artemisinin per day, with the possibility of a loading dose of 20 mg/kg on the first day *(12)*. Unlike artesunate or artemether, artemisinin is not metabolized to dihydroartemisinin, but acts as the primary antimalarial. Artemisinin is converted primarily into inactive metabolites, such as deoxyartemisinin and dihydrodeoxyartemisinin *(13,14).*

The elimination half-life of artemisinin is approximately one to three hours *(15,16)*. Following the administration of a drug, the total drug exposure across time depends both on the drug's absorption and the elimination rate. For artemisinin, rapid but incomplete absorption has been observed. An early study found a relative bioavailability of 32% when comparing oral administration of artemisinin with intramuscular administration of artemisinin suspended in oil *(17).* Several artemisinin drugs are inducers of drug-metabolizing enzymes, which augment the drug's clearance and lead to decreased drug plasma levels following repeated dosing *(18).* Studies have shown that artemisinin exhibits an auto-inductive effect on drug metabolism of an unusual magnitude *(19).* Artemether also undergoes auto-induction, but to a lesser extent than artemisinin *(20,21).* Artemisinin's auto-induction results in a five- to seven-fold decrease in the artemisinin plasma concentration over five to seven days of administration *(19).* The overall induction capacity of a drug depends on the combined effect of the

parent drug and the drug metabolites. Unlike artemether, artemisinin metabolizes into at least one inducing metabolite, deoxyartemisinin. This helps explain why auto-induction persists for days after a single dose of artemisinin, despite artemisinin's short elimination half-life *(14,18,19,21–23).* Consequently, when given repeatedly, the dose of artemisinin must be increased to achieve the same plasma concentrations. If not, the repeated dose could yield sub-therapeutic drug levels.

Efficacy

The potency of artemisinin and its derivatives has been evaluated in various in vitro experiments with different strains of *P. falciparum.* When investigating the drug concentration needed to inhibit 50% of the parasites' activity, the IC_{50}, artemisinin has consistently been found to be two to five times less potent than its derivatives dihydroartemisinin, artesunate and artemether *(24,25)*. Consequently, higher doses of artemisinin are required to achieve the same antimalarial activity.

In vivo drug efficacy is evaluated with respect to the proportion of patients in whom infection recurs within a defined period and, to a lesser extent, the speed at which symptoms resolve and parasitaemia declines. Artemisinin and its derivatives affect a broader range of the asexual stages of parasites than other antimalarials. As a result, artemisinin and its derivatives can quickly reduce the parasitaemia, leading to a rapid clinical response. However, already the earliest Chinese studies showed that if artemisinin is given orally for only three days, a high proportion of patients will have a recurrence of parasitaemia within 28 days. To prevent recurrent parasitaemia, seven days of treatment is needed when using artemisinin or an artemisinin derivative as a monotherapy *(7,26).* In practice, however, the rapid clinical response means that patients feel well after a few days of treatment, making adherence to the full seven-day treatment low.

Development of ACTs

The advantages and disadvantages of artemisinin and artemisinin derivatives have been clear from the earliest clinical trials. The drugs are well tolerated and fast-acting, and quickly reduce the number of parasites in the blood. However, effective drug concentration levels are only maintained in the plasma for a relatively brief period after drug administration, and short oral treatment courses result in high rates of recrudescence. Based on these findings, the idea to combine an artemisinin derivative with a partner drug with a longer half-life emerged quickly. ACTs take advantage of the rapid action of the artemisinin derivatives, while the partner drug helps to prevent recrudescence, even after a short three-day treatment *(27).*

The following artemisinin derivatives are used in the ACTs currently recommended by WHO for the treatment of uncomplicated *P. falciparum* malaria (see **box 1** for recommendations):

- artemether (in artemether-lumefantrine),
- artesunate (in artesunate-amodiaquine, artesunate-mefloquine, artesunate-sulfadoxine-pyrimethamine, and artesunate-pyronaridine[1]), and
- dihydroartemisinin (in dihydroartemisinin-piperaquine) *(20)*.

Artemisinin-based medicines are difficult to manufacture and co-formulate with other compounds, and they are susceptible to degradation in high temperatures and humidity. The pharmaceutical industry has contributed to the improvement of antimalarial drug quality by ensuring that formulations, manufacturing, and storage adhere to Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP). The WHO Prequalification Programme (WHO/PQP) evaluates the quality

[1] Currently recommended for use only in areas with multidrug resistance and with few alternative treatments.

of specific pharmaceutical products based on the review of product dossiers submitted by the manufacturing company and inspection of the manufacturing facilities.

Box 1: WHO recommendations for the treatment of malaria

WHO recommendations

WHO recommends ACTs as the first-and second-line treatment for uncomplicated *P. falciparum* malaria, as well as for chloroquine-resistant *P. vivax* malaria. Currently, five different ACTs are recommended by WHO *(20)*. In areas where other ACTs are failing, the use of artesunate-pyronaridine, a new ACT that has received a positive scientific opinion from the European Medicines Agency, is to be considered. For severe malaria, injectable artesunate is recommended or injectable artemether where artesunate is not available. Treatment with injectable artesunate or artemether must be followed by a full three-day treatment with an ACT when they have received at least 24 hours of parenteral therapy and can tolerate oral therapy.

Resistance

Treatment failure occurs when a treatment fails to clear parasites from a patient's blood or fail to prevent their recrudescence. Drug resistance is one potential cause of treatment failure, but other factors can contribute to treatment failure, including incorrect dosage, poor patient compliance, poor drug quality, and drug interactions (for definitions see **box 2**).

Drug resistance arises as a result of genetic changes that occur at random. If a genetic trait gives a parasite a survival advantage when exposed to a drug, this genetic trait can be selected for under drug pressure. For some drugs, a single genetic event may be all that is required; in other cases, multiple independent events may be necessary *(28).* Selection of a genetic trait that provides a survival advantage is more likely when the parasite population is exposed to sub-therapeutic levels[2] of an antimalarial drug *(29).*

The loss of other drugs and the dependency on artemisinin derivatives to treat millions for *P. falciparum* malaria every year raised considerable concerns that resistance would also emerge to artemisinin and its derivatives. The development of ACTs combining an artemisinin derivative with a partner drug helps to ensure that parasites are not exposed to therapeutic or sub-therapeutic doses of artemisinin alone. However, widespread use of different forms of oral artemisinin-based monotherapy (oAMT) continued to pose a threat to artemisinin and its derivatives. The risks of oAMT are augmented by many patients prematurely stopping treatment. Consequently, in 2007, WHO Member States adopted World Health Assembly resolution WHA60.18, which calls for a progressive removal of oAMTs from markets and the deployment of ACTs instead *(30).*

Full resistance to artemisinin and its derivatives has not yet been identified anywhere in the world. In the Greater Mekong Subregion, there has been a shift where parasite clearance is delayed after treatment, so more patients still have parasites in the blood on day 3 after a treatment with oAMT or with an ACT. This delayed clearance is called artemisinin partial resistance. However, provided that the monotheraphy is given at correct doses for seven days or that ACT partner drug is efficacious, the parasites will be cleared, and the patient cured. The changes in clearance time have been found to be associated with several genetic mutations in the *PfKelch13* (K13)-propeller domain *(31)*.

[2] A concentration below the concentration that provides the maximum possible effect

Box 2: Definition of resistance

- *Treatment failure*: the inability to clear parasites from a patient's blood or to prevent their recrudescence after the administration of an antimalarial. Many factors can contribute to treatment failure, including incorrect dosage, poor patient compliance, poor drug quality, and drug interactions and resistance
- *Antimalarial resistance:* the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject
- *Multidrug resistance (MDR)*: resistance to more than two antimalarial compounds of different chemical classes. This term usually refers to *P. falciparum* resistance to chloroquine, sulfadoxine-pyrimethamine, and a third antimalarial compound.
- *Artemisinin partial resistance*: delayed parasite clearance following treatment with an artesunate monotherapy or with an ACT

Surveillance of recommended treatment for uncomplicated malaria

Recommendations on the first- and second-line treatment for malaria patients need to be based on updated information on drug efficacy. Therapeutic efficacy studies (TESs) done at regular intervals at the same sites allow for early detection of changes in parasite susceptibility and timely revision of malaria treatment policies. TESs are done in accordance with a standard protocol wherein drug administration is supervised, the results of microscopic examinations of blood films are validated, and the origin and quality of the drugs are verified. Therapeutic outcomes are assessed on the final day of the study (day 28 or 42) *(32).* TESs can be supplemented by the monitoring of genetic changes associated with resistance.

Some countries recommend only one specific ACT as first-line treatment, while others recommend several ACTs as potential first-line treatment. Artemether-lumefantrine or artesunate-amodiaquine are the first-line treatment policies used in most African countries for the treatment of uncomplicated *P. falciparum* malaria. Some countries also allow for the use of dihydroartemisinin-piperaquine as first-line treatment. TESs have shown generally very high efficacy rates for the ACTs tested. Between 2010 and 2017, TESs using artemether-lumefantrine, artesunate-amodiaquine and dihydroartemisinin-piperaquine showed average efficacy rates of 98.1%, 98.5% and 99.3%, respectively. There have been a few outliers where studies showed higher failure rates. However, when these studies were repeated, similar failure rates were not reported *(33).*

Non-pharmaceutical use of *Artemisia* for malaria

Artemisia is a large, diverse genus of plants with nearly 400 species. Artemisinin is found in highest quantities in *A. annua,* but it has also been found in minor quantities in *A. apiacea* and *A. lancea.* Some scholars believe that it was not *A. annua* but *A. apiacea* that was used in China 2000 years ago *(34). A. afra* is an *Artemisia* species that does not contain artemisinin but has been proposed for the treatment of malaria.

The overview below focuses primarily on *A. annua* and secondarily on *A. afra*, as these are the *Artemisia* species for which most information is available, and that are most often promoted as potential treatments for malaria.

A. annua

A. annua is so named because it is the only member of the genus with an annual cycle. It is an herb native to Asia, but it now grows in many countries, including in Africa, Europe and South America. Although *A. annua* originated in temperate climates, it has been grown in subtropical and tropical areas *(35).*

Cultivation and processing of *A. annua*

The amount of artemisinin found has varied, and concentrations from 0.02% to 1.07% have been reported in the dried leaves of wild samples. Hybrids have been cultivated with a reported artemisinin content of 1.38% in the dried leaves. In experiments, concentrations of up to 2% has been achieved. In addition to genetics, many factors can affect the artemisinin content, including when in the season the harvesting takes place, temperature, nutrient availability, and from where on the plant the leaves are harvested *(36).*

Processing, drying procedures and storage conditions further influence the artemisinin content. Too high moisture content in the leaves can cause mould, yeast and bacteria. During storage, the relative air humidity and temperature can have a big impact on artemisinin's stability. Even at 20 °C, a relative air humidity of 85% will cause degradation of artemisinin after six months of storage. No matter the humidity, storage over 40 °C will cause loss of artemisinin content *(37).*

In addition to artemisinin, *A. annua* contains many compounds from different chemical classes, including terpenes, flavonoids and phenolic acids *(38,39).* There is only limited information available of the effects of the farming, harvesting, drying, storage and preparation methods on the amounts of the other chemical compounds found in *A. annua (38).* However, the content of other compounds is known to be affected by where the plant is grown, and the strain used.

WHO has developed guidelines on good agricultural and collection practices (GACP) for medicinal plants *(40),* including specific guidelines for *A. annua L. (41).* While the idea of home-grown or small-scale cultivation of *Artemisia* as a source of malaria treatment is compelling, the practices and procedures needed to ensure that the materials used have the expected content are difficult to establish and maintain. These practices are generally not possible to implement in the context of small-scale cultivation. Comparing large- and small-scale cultivators have shown an average drop of 0.3 percentage point in the artemisinin content. Consequently, the content and quality of the *Artemisia* plant materials promoted for use in herbal remedies for malaria treatment and prevention vary substantially.

Preparation methods for herbal remedies using *A. annua*

Different preparation methods have been proposed for the use of *A. annua* plant materials. These include preparation of juice from the whole fresh plant or preparation of tea from the dried leaves. Recently, some researchers have suggested the ingestion of the powdered dried leaves for therapeutic use instead of tea. The powdered leaves are either encapsulated in cellulose or gelatine capsules, or compressed into tablets *(38,42–45)*.

In the ancient text of Chinese *Materia Medica*, the method prescribed consisted of soaking the fresh plant (leaves and stem) in water, and then wringing out the whole plant and ingesting its juice. In later Chinese references, another method involved soaking the plant in urine rather than water or pounding the fresh herb to produce a juice *(34,46).*

Those promoting artemisinin tea, typically suggests adding 1 L of boiling water to 5 g of dried leaves, leaving the mixture to cool for 15 minutes and then filtering it. The recommendation given most often is to drink 1 L of this tea over a 24-hour period for seven consecutive days (https://maison-artemisia.org) *(47)*. Some go so far as to suggest administering the tea rectally as an enema in

unconscious patients (https://anamed.org/en/). Alternative preparation methods tested for the tea include adding 9 g instead of 5 g of dried leaves per litre of water; allowing the leaves to stand in the water for shorter or longer than 15 minutes before filtering; stirring the tea repeatedly while cooling; or squeezing residual water out of the leaves after filtration. Another alternative method tested is, instead of adding boiling water to the dried leaves, adding the leaves to the water, heating the mixture to boiling point, and keeping it boiling for a period before filtering *(47–51).*

Content of *A. annua* herbal remedies

The method of preparation affects the amount of artemisinin and other chemical compounds that will be administered and absorbed. Little research has been done on the traditional methods of soaking the fresh whole plant in water followed by wringing or pounding. One study using a hybrid *A. annua* plant found that the pounded juice contained up to 20 times as much artemisinin per litre than the tea made from the dried leaves of the same *A. annua* hybrid *(46).* No information is available on how quickly the artemisinin content degrades in the juice.

Different studies have examined the extraction efficiencies of artemisinin in the making of artemisinin tea. Van der Kooy and Verpoorte *(49)* found extraction efficiencies of 26.1% by adding boiling water to 9 g of dried leaves and allowing the leaves to remain in the water for 10 minutes. This approach resulted in artemisinin concentrations of 23.9 ± 5.1 mg/L. When Räth et al. *(52)* used a similar method, steeping 9 g of dried leaves for 10 minutes but briefly stirring the mixture and squeezing the leaves after filtration, they achieved extraction efficiencies of 76%. Their method resulted in artemisinin concentrations of 94.5 mg/L. Van der Kooy and Verpoorte *(49)* were able to increase the extraction efficiencies by boiling the mixture for two to five minutes; boiling for 10 minutes reduced the extraction efficiencies. Overall, studies done in controlled conditions using 5 or 9 g hybrid *A. annua* found that tea content varied from 8.36 mg to 117.2 mg artemisinin per litre of tea, depending on the method and plant material used. Only in one of the reviewed studies did the artemisinin content exceed 100 mg artemisinin per litre, equivalent to the daily dose of artemisinin that would be given to a child weighing 10 kg *(51,53,54).*

The low content of artemisinin in juice extractions, teas and infusion preparations of plant materials led Elfawal et al. *(44)* to emphasize that: "*WHO has cautioned against use of nonpharmaceutical sources of artemisinin because of the risk of delivering subtherapeutic doses that could exacerbate the resistance problem. This warning is valid given the low artemisinin content of juice extractions, teas and infusion preparations of plant materials used for most nonpharmaceutical plant-based therapies."* The authors then argued for the consumption of dried leaves.

Some authors have proposed that artemisinin's low water solubility is overcome by the presence of plant constituents with amphiphilic properties *(48).* Other authors have concluded that other constituents of the plant may decrease artemisinin's solubility *(52).* Stability studies indicate that artemisinin, when present in tea, does not degrade at room temperature for 24 hours *(49).* No information is available on the effect of the type of water (i.e., rain water, river water or tap water) on the extraction and stability of artemisinin *(53).*

Only a portion of the total number of compounds found in the *A. annua* plant material have been identified in the cold-water extracts and teas. Van der Kooy and Sullivan *(53)* reported that more than 600 different secondary metabolites have been identified in *A. annua,* but only 37 compounds have been identified in cold-water extracts and teas. These mainly consist of terpenes, phenols, acetylenes, coumarins and flavonoids *(53).* Even the preparation of capsules or tablets from powdered leaves has been shown to alter the content. Therefore, it cannot be assumed that the compounds in tablets or capsules are the same as in the dried leaves used to produce them *(42).*

Other *Artemisia* species used in herbal remedies

The species *A. afra* grows throughout the southern and eastern parts of Africa and has been used in traditional medicine to treat a variety of ailments from asthma and rheumatism to malaria. It is a perennial woody shrub growing up to 2 m tall. It is used in different forms, including as an infusion wherein fresh leaves are added to a cup of boiling water and left for 10 minutes before straining.

Large variation in the chemical compounds of *A. afra* has been identified both between and within geographical areas. Large variation has also been found between the cultivated and wild populations. *A. afra* does not contain artemisinin, but contains terpenes that include sesquiterpene lactones and a number of other compounds including flavonoids. Concerns over the potential cardio- and neurotoxicity of some of the compounds have been reported *(55).*

Efficacy of non-pharmaceutical forms of *Artemisia* for malaria

To cure malaria, an efficacious dose of antimalarials needs to be administered to the patient. The variable effect of the preparation method on the content of the final herbal remedy means that even if it were possible to provide consistent and good-quality *Artemisia* plant material, the provided dose of artemisinin and other compounds would vary substantially. The WHO-recommended ACTs for treating uncomplicated *P. falciparum* malaria do not contain artemisinin but the more potent derivatives artesunate, artemether or dihydroartemisinin. Since artemisinin has an auto-inductive effect, when given repeatedly, the dose of artemisinin must be increased to achieve the same plasma concentrations in patients. Thus, the administration of non-pharmaceutical forms of *A. annua* could potentially lead to sub-therapeutic dosages of artemisinin due to both the inconsistencies in the artemisinin content of the herbal remedies and the pharmacokinetics of artemisinin.

Those promoting the use of *A. annua* have proposed that other chemical compounds in the plant enhance its efficacy compared to administration of the pure artemisinin compound. It is suggested that the antimalarial activities of other plant compounds make the plant material function as a combination therapy, or that some compounds may increase the efficacy or bioavailability of artemisinin.

Comparing the in vitro efficacy of artemisinin and *A. annua* extract, some researchers have concluded that the in vitro activity cannot come from the artemisinin content alone *(56,57).* However, a number of other studies have found that the in vitro efficacy of the tea correlates well with the artemisinin content in the different extracts tested *(54,58).* Wright et al. *(46)* tested the antimalarial activity of *A. annua* juice in vitro and in mice and found that the efficacy of the juice was consistent with the artemisinin content of the juices tested.

Several of the other compounds found in *A. annua* have been shown to have some weak antimalarial activity against *P. falciparum*, but the concentrations needed are orders of magnitude higher than for artemisinin *(51).* To be considered a compound with strong antimalarial activity, a compound needs to have an IC_{50} measured in nanograms per ml. Mouton et al. *(54)* found pure artemisinin to have an IC_{50} of 5.48 ± 1.54 ng/ml. Other compounds in artemisinin tea, such as terpenes, phenolic acids and flavonoids, have an IC_{50} measured in micrograms per ml, meaning that the needed concentration is about 1000- to 10 000-fold higher than for artemisinin – a level that is incompatible with therapeutic efficacy *(51,59).*

Synergism between artemisinin and other constituents rather the antimalarial effect of the other constituents has been proposed as playing a role in the efficacy of non-pharmaceutical forms of artemisinin. Testing the synergetic effect of individual compounds, Liu et al. *(60)* found that adding five different flavonoids at concentrations too low for the flavonoids alone to appear to have any effect (5µM/l) reduced the IC_{50} of artemisinin in the range of 9% to 55%. Testing individual compounds at higher levels of concentration, Suberu et al. *(51)* found some compounds to be antagonistic

(including casticin), some to be additive, and some to be synergistic. Weathers and Towler *(61)* confirmed the presence of flavonoids such as casticin and artemetin in *A. annua* tea, but stated that the extraction efficiency of these flavonoids was too low; therefore, they ruled out synergism. The poor extraction efficiency of flavonoids and their rapid degradation in tea has led some to propose administration of the whole plant material instead of the extract *(61).*

A recent in vitro study by Czechowski et al. *(62)* focused on the potential effect of flavonoids. The study compared extracts from three strains of *A. annua*: one wild-type; one with a mutation inhibiting flavonoid biosynthesis but containing artemisinin; and one with mutations severely impairing artemisinin production but not affecting flavonoid biosynthesis. Comparing the efficacy of *A. annua* extracts with and without flavonoids showed no significant difference, indicating that the flavonoids did not contribute to antimalarial activity. To investigate any potential antiplasmodial activity of artemisinin-unrelated compounds in *A. annua*, the researchers tested extracts from *A. annua* without artemisinin. The extracts that were among the highest in total flavonoid content of the material used showed very low to no antiplasmodial activity. The authors concluded that the in vitro bioactivity of flavonoids against *P. falciparum* is negligible compared to that of artemisinin.

Looking at bioavailability, a study in mice by Weathers et al. *(43)* found increased bioavailability of artemisinin when using whole plant dried leaves. However, when studying the bioavailability of artemisinin in tea in healthy human males, Räth et al. *(52)* arrived at different results. Here, the authors found that artemisinin's bioavailability in tea was similar to that found in the administration of pure artemisinin in tablets.

Overall, the evidence does not support the claim that other compounds in *A. annua* with antimalarial activity are present in the herbal remedies at concentrations at which such herbal remedies could be considered anything other than monotherapies. If research had shown there to be compounds in the plants that could stabilize, could increase the bioavailability, or could increase the efficacy of artemisinin, it would warrant further research, but it would not change the reality that the extracts at best function as weak artemisinin monotherapies.

Testing the in vitro efficacy of tea made using two different samples of *A. afra*, one from Uganda and one from South Africa, Mouton et al. *(54)* were unable to detect antimalarial activity. Studies indicate that any antiplasmodial compounds of *A. afra* may be more soluble in lipophilic solvents than in hydrophilic solvents. The IC_{50} reported not using water but lipophilic, dichloromethane or methanolic extract range from 4.0±1 µg/ml to 15.3 ±1 µg/ml *(55).* A recent review by du Toit and van der Kooy *(63)* likewise concluded that tea infusions do not appear to show any in vitro activity.

Clinical trials using non-pharmaceutical forms of *Artemisia*

The in vivo effectiveness of *Artemisia* extracts has mainly been assessed through animal models of rodent malaria. While these models are useful for research purposes, including for drug screening, results cannot be extrapolated to human *P. falciparum* malaria. In general, the few clinical studies completed have often been of relatively low quality, been conducted with few patients, included too short a follow-up period, or been poorly controlled for bias. In some studies, it was unclear how the patients were diagnosed or whether the WHO criteria were used to classify the patients as having asymptomatic, uncomplicated or severe malaria. When malaria rapid diagnostic tests (RDTs) are used, the patient may be classified as having malaria weeks after the parasites are cleared from the blood.

The studies have reported no adverse effects. However, if non-pharmaceutical forms of *A. annua* can lead to the administration and absorption of significant levels of artemisinin, there may be concerns, for instance, when giving these forms to pregnant women in the first trimester.

A small randomized study by Mueller et al. *(64)* in eastern Democratic Republic of the Congo in 2001 enrolled 132 *P. falciparum* patients. When using the regimen most frequently proposed (5 g of dried *A. annua* leaves in 1 L of water per day for seven days), 21 out of 32 patients (65.6%) had recurrent

parasitaemia on day 35. In the group receiving tea made from 9 g of dried leaves per litre, 21 out of 30 patients (70%) had recurrent parasitaemia on day 35. In the control group receiving quinine, seven out of 34 patients (21%) had recurrent parasitaemia on day 35. Genotyping was not used to distinguish between reinfections and recrudescence. The authors concluded that the much lower recurrence rate in the parallel quinine group indicated that the observed recurrences in the *A. annua* group were due to recrudescence and not reinfection. Because of this high rate of recrudescence and the risk of possible resistance development, the authors concluded that monotherapy with tea preparations from *A. annua* could not be recommended as a treatment option for malaria.

In 2002–2003, Blanke et al. *(65)* did a small study in semi-immune adults in the United Republic of Tanzania. Seven patients were assigned to a group treated with *A. annua* tea made from 5 g of dried leaves per litre, six patients were treated with *A. annua* tea made from 9 g of dried leaves per litre, and 10 patients were treated with sulfadoxine-pyrimethamine. On day seven, three of the 13 patients who were treated with *A. annua* tea had been excluded: two because they took sulfadoxine-pyrimethamine and one because the patient developed signs of severe malaria on day one and was given a rescue treatment (quinine). Of the 10 remaining patients treated with *A. annua* tea, seven did not show parasitaemia on day seven. In the group treated with sulfadoxine-pyrimethamine, one was excluded due to hyperparasitaemia on day zero. Of the nine remaining patients, seven did not show parasitaemia on day seven. On day 28, nine of the 10 patients treated with *A. annua* tea were parasitaemic. In the group treated with sulfadoxine-pyrimethamine, one was lost to follow-up before day 28. Of the eight remaining patients, five were parasitaemic. Sulfadoxine-pyrimethamine resistance was already widespread at the time of the study and therefore the high failure rate was not surprising. Due to the high rate of recrudescence in all three groups, the study was stopped, and the authors concluded that *A. annua* tea could not be recommended for treating uncomplicated *P. falciparum* malaria.

A study to evaluate the efficacy and safety of locally grown *A. annua* in patients with uncomplicated falciparum malaria was conducted in Benin *(66).* Artemisinin content in the plant was 0.30% of dry weight mass. Tea was made using 12 g/L of dried leaves, infused for 15 minutes, and then administered in four doses of 250 ml over a 24-hour period (or 125 ml in children of 10–13 years of age) for seven consecutive days – the equivalent of receiving 36 mg (or 18 mg for children) of artemisinin in four divided doses. The study consisted of a single open-label cohort of 108 (out of 130 patients enrolled) who completed both the treatment and the follow-up visit up to day 28. Authors reported an adequate clinical and parasitological response of 100% at day 28.

A study of the safety and efficacy of *A. annua* and *A. afra* was conducted in the Democratic Republic of the Congo *(67)*. The study consisted of three groups of adult patients with uncomplicated *P. falciparum* malaria who were treated with capsules containing powdered leaves of *A. annua* from Luxembourg (AAL) (20 patients), *A. annua* from Burundi (AAB) (37 patients), or *A. afra* (AAF) (25 patients). Each patient received 15 capsules: three administered on the first day and two capsules on each of the following six days, corresponding to a total of 15 g of AAL, 7.5 g of AAB, or 7.5 g of AAF. Fever clearance occurred within 48 hours, and 85% were free of parasites after seven days for AAL, 76% for AAB, and 40% for AAF. There is no information on whether patients were followed up beyond day seven and whether rescue treatment was given to patients who were still parasitaemic after their treatment course.

Daddy et al. *(68)* reported on the treatment of 18 patients in 2016 in the Democratic Republic of the Congo with tablets made of powdered dried *A. annua* leaves. Although the patients had previously been treated with three days of artemether-lumefantrine, all reportedly still had parasites in the blood and fever with symptoms, which led the authors to classify them as having severe malaria. The patients received intravenous artesunate, but the treatment failed for all 18 patients. The patients were then treated with 0.5 g of dried leaves twice a day for five days, with a reduced dose for patients weighing less than 30 kg. Adults received a total dose of 55 mg artemisinin. The patients were released from hospital when parasites were microscopically undetectable and clinical symptoms were cleared.

No further follow-up was done. The authors concluded that since the dried *A. annua* leaves were administered 24 hours after the last intravenous artesunate treatment, the dried leaves alone had treated what they labelled as artemisinin-resistant malaria.

Onimus et al. *(45)* reported on the use of capsules with powdered *A. annua* leaves in 25 patients with asymptomatic parasitaemia being operated on for orthopaedic disorders. Eleven patients received five capsules over 36 hours, and 14 patients received seven capsules over 60 hours. Each capsule contained 200–250 mg dried leaves, and the artemisinin content was 0.1%. Thus, the patients received a total artemisinin dose of 1–1.75 mg. The aim of the *A. annua* treatment was not to eradicate parasites from the blood but to prevent malaria attacks in the first post-operative days. Only one patient was found to be cleared of parasites post-treatment. The reported parasitaemia pre-treatment was on average 432 parasites/ml and 165 parasites/ml post-treatment. The reported parasitaemia was so low that it would not have been possible to detect, so there may have been a mistake in the reporting. The article does not list other treatments given to the patients in connection to the operations, nor does the article state whether any curative treatments were offered to the patients, as should be done.

A large study was conducted in 2015 in the Kalima district, Democratic Republic of the Congo by Munyangi et al. *(69)*. The aim of the study was to show that *A. annua* and/or *A. afra* infusions were superior or at least equivalent to artesunate-amodiaquine against malaria. The study followed a multi-centre, randomized, double-blind design with a follow-up of 28 days. It was conducted in children (> 5 yrs) and adults with confirmed, uncomplicated *P. falciparum* malaria. The study was approved by local authorities. Out of 2000 patients screened, 957 patients were enrolled from five different locations: 472 were enrolled in the artesunate-amodiaquine group, and 471 in the *Artemisia* groups (248 in *A. annua*, 223 in *A. afra*). The patients in the artesunate-amodiaquine arm received artesunate-amodiaquine for three days followed by placebo tablets for four days; they were also given tea infusions containing 0.2 g of plant material per litre for the seven days. In the *Artemisia* arms, the patients were given 0.33 L of tea every eight hours for seven days. The tea was made by adding 1 L of boiling water to 5 g of dried leaves and twigs of *A. annua* or *A. afra* and infused for 10 minutes. The patients in the *Artemisia* arms received placebo tablets for seven days. Artesunate-amodiaquine tablets were obtained from the manufacturer. The artesunate-amodiaquine placebo was a pill-shaped saccharose/glucose tablet purchased at a pharmacy. On day 28, the authors reported recurrent parasitaemia in nine out of 248 patients (3.6%) treated using *A. annua*, in 25 out of 223 patients (11.2%) treated using *A. afra,* and in 310 out of 472 patients (65.7%) treated using artesunate-amodiaquine. They reported that some of those treated with artesunate-amodiaquine were found to have parasites 14 days after the start of treatment. The reported treatment failures with artesunate-amodiaquine occurred mainly within the first 14 days.

Munyangi et al.'s *(69)* results for artesunate-amodiaquine conflict with other available data. Even in areas of high drug resistance in South-East Asia, parasites never remain in patients 14 days after the administration of an ACT. When treatment failures occur with ACTs, they almost always occur at the end of the follow-up period. Between 2011 and 2013, 13 TESs were done in the Democratic Republic of the Congo. The studies looked at the efficacy of artesunate-amodiaquine, artesunate-lumefantrine and dihydroartemisinin-piperaquine; the ACTs tested all showed high efficacy (94.8–100%) *(70).* Seven of the studies tested artesunate-amodiaquine by enrolling a total of 695 patients. The studies were done by Médecins Sans Frontières *(71),* Mahidol Oxford Research Unit *(72)* and the national malaria control programme. These studies showed an efficacy of 95.3–100%. In 2017, the University of Kinshasa conducted TESs for three different ACTs (artesunate-amodiaquine, artesunate-lumefantrine and dihydroartemisinin-piperaquine) in five sites in the Democratic Republic of the Congo. These studies also found high efficacy for all three ACTs (95–100%). In the treatment arms testing artesunate-amodiaquine, a total of 451 malaria patients were enrolled and the efficacy was ≥ 95.0% (K. Mesia 2019, personal communication).

Furthermore, Munyangi et al.*'s (69)* study reported that artesunate-amodiaquine had higher efficacy in children (50%) than in adults (30%). In endemic areas, efficacy is normally higher in adults who are likely to be semi-immune. In the patients treated with *A. annua*, a surprising result was to find only 3.6% of patients with parasites on day 28 after treatment, considering the drug has a short half-life. Even with efficacious treatment, some reinfections would be expected. The cure rate of *A. afra* was reported to be 88.8%, which is unexpectedly high but still below the WHO-recommended threshold of 95% for a new malaria treatment *(20).* As *A. afra* does not contain any known compounds with substantial antimalarial activity, some authors (*63*) suggest that the only way to explain its surprising efficacy is that *A. afra* may contain an as yet unknown pro-drug that becomes active after metabolization.

It is difficult to explain Munyangi et al.'s *(69)* results, but the design and conduct of their study suffered from a number of deficiencies and potential biases. For example, there is insufficient information on the randomization procedures and treatment assignment; the artesunate-amodiaquine placebo tablet obtained from a pharmacy and given to those receiving tea may not have been identical to the active tablets, thus compromising the double-blinding; amodiaquine blood concentrations were not assessed; data collection and analysis were not blinded; genotyping studies were not performed, apparently due to degradation of blood samples; and no clear definitions of outcomes and classifications were provided.

Artemisia herbal remedies have also been promoted for the prevention of malaria. However, the short half-life of artemisinin means that this drug is not suitable for prevention. *A. annua* capsules and liquid formulations are being sold over the Internet, claiming their safety and efficacy for the prophylaxis and treatment of malaria. Lagarce et al. *(73)* reported two cases of severe *P. falciparum* malaria that required intensive care following prophylaxis with non-pharmaceutical *A. annua* in French travellers.

Ogwang et al. *(74)* conducted a randomized trial with 132 flower farm workers. Participants were randomized to a group receiving *A. annua* tea (67 participants) once a week or a group receiving a tea made of *Thea sinensis* (65 participants) once a week. A total of 84 workers (41 in the *A. annua* group and 43 in the control group) were followed up for nine months. The authors found that at the end of the study, 12 in the *A. annua* group and 26 in the control group had reported more than one episode of malaria. The authors speculated this this may have been due to compounds other than artemisinin such as flavonoids. The two groups appear to have been well randomized in terms of age and sex, but there was a significant difference in bed net use, as 35.8% of the group receiving *A. annua* but only 18.5% of the control group reported using a bed net at the start of the study.

WHO's position on the use of non-pharmaceutical forms of *Artemisia*

WHO does not support the promotion or use of *Artemisia* plant material in any form for the prevention or treatment of malaria.

WHO's position is based on the following considerations:

- **The content of the *Artemisia* herbal remedies given for malaria treatment and prevention varies substantially.**

  The content and quality of the *Artemisia* herbal remedies are affected by variations in the content of the plant material and the preparation method**.**

  A range of factors can affect the content of *Artemisia*, including genetics, when in the season the harvesting takes place, temperature, nutrient availability, and from where on the plant the leaves are harvested. Processing, drying procedures, and storage conditions further influence the content of plant materials. It is not feasible to implement the required level of quality control for cultivation, harvest and post-harvest aspects of *Artemisia* in the context of home-grown or small-scale cultivation.

The preparation method will cause further variation. The content of *Artemisia* tea is highly influenced by factors such as the temperature of the water. Even given in tablet or capsule form, the content of these will differ from the original source material.

- **Content in *Artemisia* herbal remedies is often insufficient to kill all the parasites and to prevent recrudescence.**

  To achieve high efficacy rates, sufficient levels of artemisinin needs to be administrated and absorbed over seven days. The pharmacological properties of artemisinin mean that higher levels of artemisinin need to be administered on the last days of treatment than on the first days in order to achieve the same artemisinin blood levels. Too short treatments or too low blood levels of artemisinin will result in either failure to clear parasites from the blood or high levels of recrudescence. *A. annua* contains varying levels of artemisinin. Herbal remedies prepared using *A. annua* with significant artemisinin content may improve symptoms, but are likely to result in high recrudescence rates. The available evidence does not support claims that the antimalarial activity of other plant constituents or synergism between artemisinin and other constituents will significantly increase the efficacy of non-pharmaceutical forms of *A. annua.*

  A. afra does not contain artemisinin or any other compound identified as having significant antimalarial activity in vitro.

- **Widespread use of *A. annua* herbal remedies could hasten the development and spread of artemisinin resistance.**

  Artemisinin and artemisinin derivatives are the key compound in the ACTs used to treat millions suffering from malaria. The artemisinin derivative, artesunate, is used to save the lives of those suffering from severe malaria. Resistance causing the loss of these drugs would be a disaster. In 2007, WHO Member States adopted World Health Assembly resolution WHA60.18 calling for a progressive removal of oral artemisinin-based monotherapies from markets and deployment of ACTs instead. This decision was made to help protect artemisinin drugs from resistance. If consumption of *A. annua* becomes widespread, any potential weak antimalarial activity of other compounds in *A. annua* would not be sufficient to protect artemisinin from resistance. Resistance is more likely to develop and spread when a parasite population is exposed to sub-therapeutic levels of an antimalarial drug. The varying artemisinin content of *A. annua* herbal remedies means that widespread use of these remedies could lead to many people having such sub-therapeutic levels of artemisinin in their blood.

- **Artemisinin in any form does not work well as prevention against malaria.**

  Artemisinin has a short elimination half-life, meaning that it only remains in the blood at therapeutic levels for a short time. Therefore, artemisinin is not promoted for use in malaria chemoprophylaxis in any form.

- **Affordable and efficacious treatments for malaria are available.**

  WHO recommends ACTs for the treatment of uncomplicated *P. falciparum* malaria. Artemisinin partial resistance and resistance to some partner drugs do pose a challenge in parts of South-East Asia. However, there are still highly efficacious treatments available that can cure all strains of malaria. A complete treatment with an ACT can be procured for less than US$ 2. We need to remain committed to ensure that all those affected by malaria have access to ACTs. Countries need to strengthen their regulatory systems to protect patients from counterfeit and substandard treatments; this includes any products promoted for treatment of malaria without the necessary information in terms of their content, quality, safety and efficacy.

Herbal medicines have been a key source for the discovery of antimalarial medicines. It is possible that future antimalarial compounds will also be discovered through research on the herbal treatments used in the past. However, any research needs to respect the ethical principles for medical research involving human subjects and be approved by local ethical committees. The well-being of the individual research subject must take precedence over all other interests. Medical research involving human subjects must conform to generally accepted scientific principles and be based on thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory experimentation *(75).*

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Use of non-pharmaceutical forms of *Artemisia*

Charlotte Rasmussen
Drug efficacy and response unit

Global **Malaria** Programme

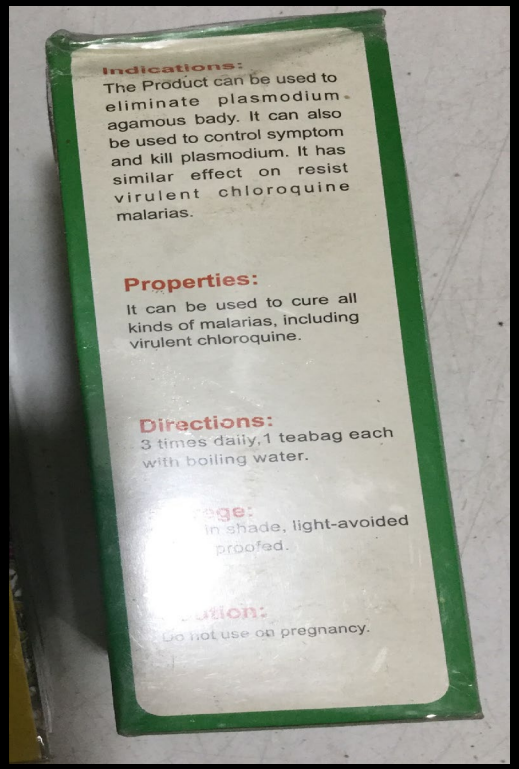
World Health Organization

Background

- WHO issued a position statement in 2012 on the effectiveness of non-pharmaceutical forms of *Artemisia annua* against malaria
- In this, it is stated that "*WHO does not recommend the use of* A. annua *plant material in any form, including tea, for the treatment or the prevention of malaria*"
- Since then, the use of non-pharmaceutical forms of *Artemisia* has received increased attention

Background

- Number of different products available, including in the form of tea or capsules
- These products are promoted for the prevention and treatment of malaria
- Mostly made from *A. annua* and, more recently, *from A. afra*



Artemisia Afra African Wormwood malaria treatment 60 x 400mg tab

R125.00

Add to cart

Artemisia afra is a medicinal plant which has been used for treating a variety of ailments such as coughs, fevers, colds, chills, dyspepsia, loss of appetite, colic, croup, whooping-cough, malaria, diabetes, bladder and kidney disorders. It is also used as a moth repellent, and in organic insecticidal sprays.
Artemisia is effective for prevention and treatment of malaria
Also known as: Wormwood or Sagewood (English); wildeals (Afrikaans); umhlonyane (Xhosa); umhlonyane (Zulu); lengana (Sotho).

Dosage:
Adults: 2 tablets daily, Children between 6 â€“ 12 years 1 tablet daily
Best taken one day before visiting a malaria area, then daily until 4 days after leaving malaria area.

Video – narrative

Arguments used to promote non-pharmaceutical forms of *Artemisia*

- Key arguments used focus on:
  - the products as a cheap and self-reliant alternative to ACTs;
  - the products as unlikely to be falsified; and
  - that due to the different compounds in a natural herb, *A. annua* cannot be considered a monotherapy
- European NGOs and faith-based organization are playing a role in the promotion. The material can include specific instructions on use:

Table V. Dosages of Artemisia tea, taken orally or as an enema. (Update from 11/2014)

Weight of patient (kg)	Age	Artemisia tea taken orally. ..g leaves in ..ml of water per day for 7 days	or Artemisia tea as an enema ..g leaves in ...ml of water per day until the patient regains consciousness
5-6	2-3 months	0.5g/100ml	1,5g/50 ml
7-10	4-11 months	1g/200ml	3g/100ml
11-14	1-2 years	1.5g/300ml	4,5g/150ml
15-18	3-4	2g/400ml	5g/200ml
19-29	5-9	3g/600ml	9g/300ml
30-39	10-11	3.5g/700ml	10,5g/350ml
40-49	12-13	4g/800ml	12g/400ml
50+	adults	5g/1000ml	15g/500ml

10. Children 12-13 years old (or bodyweight up to 49 kg)

You may use artemisia: Pour 800 ml of boiling water over 4g of dried artemisia leaves (or over 20 g of fresh artemisia leaves). Wait at least 15 minutes, then filter, divide into 4 cups and give one cup 4 times a day. Repeat this procedure for at least 7 days. If this treatment alone is not effective, add two and a half sulfa-pyri* tablets once, or a total dose of 1200 mg of chloroquine base divided over 3 days, or a total dose of 1200 mg of amodiaquine base divided over 3 days. Give plenty to drink (lemon grass tea, water...).

From *Anamed Artemisia Reader - Cultivation and uses* (https://www.anamed-edition.com/en/downloads.html)

Review

- WHO GMP has done a review of available literature for non-pharmaceutical forms of *Artemisia*
- The conclusions are in-line with previous WHO statement in that WHO still *does not support the promotion or use of Artemisia plant material in any form for the prevention or treatment of malaria.*
- This conclusion is based on findings regarding:
  - Content
  - Efficacy
  - Risk of artemisinin resistance
  - Other treatments available

A. annua

- Native to Asia, originating in temperate climates
- Now grows naturally in many countries also in subtropical and tropical areas.
- In wild samples, artemisinin concentration found is 0.02% to 1.07% of dried plant material. Hybrids have been cultivated with higher artemisinin content.
- Other compounds includes flavonoids and phenolic acids.
- A Chinese recipe from 341 A.D. prescribed *A. annua* juice produced using cold water for the treatment of fever.
- *A. annua* tea never used for malaria treatment in China (according to Prof. Tu Youyou, Nobel laurate)

Artemisia

A. afra

- Native to Africa, with a wide distribution in Southern and Eastern parts of Africa.
- Large variation in the chemical compounds in *A. afra* between geographical areas.
- *A. afra* does not have any significant content of artemisinin.
- Has been used in traditional medicine for a variety of ailments including asthma, diabetes and fevers.

Content

- **The content of the *Artemisia* herbal remedies given for malaria treatment and prevention varies substantially**

  - Plant content affected by genetics, harvesting time, temperature, nutrient availability, and from where on the plant the leaves are harvested.
  - Content of final product further affected by processing, drying, storage conditions, and preparation method.
    - studies done in controlled conditions using 5 or 9 g hybrid *A. annua* found that tea content varied from 8.4 mg to 117.2 mg artemisinin per liter of tea.

Efficacy

- **Content in Artemisia herbal remedies often insufficient to kill the parasites and to prevent recrudescence**

- Too short treatments or too low blood levels of artemisinin result in failure to clear parasites or recrudescence.
- Artemisinin auto-inducts so higher levels need to be administrated after first day to achieve same blood-levels
- No evidence that antimalarial activity of other plant constituents or synergism with artemisinin, significantly increase the efficacy of non-pharmaceutical forms of *A. annua.*
- *A. afra* does not contain artemisinin or any other compound identified as having significant antimalarial activity in vitro.

Study on in vitro activity of *A. annua* compounds

- A recent in vitro study by Czechowski et al. (2019) focused on the potential effect of flavonoids.
- Comparing in vitro efficacy of *A. annua* extracts with and without flavonoids showed no significant difference.
- Testing extracts from *A. annua* without artemisinin showed very low to no antiplasmodial activity.
- The authors concluded that the in vitro bioactivity of flavonoids against *P. falciparum* is negligible compared to that of artemisinin.

Czechowski et al. Flavonoid Versus Artemisinin Anti-malarial Activity in *Artemisia annua* Whole-Leaf Extracts. *Front Plant Sci*. 2019 10:984.)

Studies on efficacy

- The few clinical studies completed, mostly of relatively low quality, been conducted with few patients, included too short a follow-up period, or been poorly controlled for bias
- Many studies find a recrudescence rate up to 90% by day 28 using *A. annua*.
- One study stands out:

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Phytomedicine

journal homepage: www.elsevier.com/locate/phymed

Artemisia annua and *Artemisia afra* tea infusions *vs.* artesunate-amodiaquine (ASAQ) in treating *Plasmodium falciparum* malaria in a large scale, double blind, randomized clinical trial

Jérôme Munyangi[a], Lucile Cornet-Vernet[b,*], Michel Idumbo[c], Chen Lu[d], Pierre Lutgen[e], Christian Perronne[f], Nadège Ngombe[g], Jacques Bianga[h], Bavon Mupenda[i], Paul Lalukala[j], Guy Mergeai[k], Dieudonné Mumba[l], Melissa Towler[m], Pamela Weathers[m]

Munyangi et al. Effect of Artemisia annua and Artemisia afra tea infusions on schistosomiasis in a large clinical trial. *Phytomedicine*. 2018, 51:233-240

Study by Munyangi et al (2018)

- Conducted in 2015 in the Democratic Republic of the Congo
- Multi-centre, randomized, double-blind design with a follow-up of 28 days
- 957 patients enrolled in five different locations:
  - 472 enrolled in a artesunate-amodiaquine arm, and
  - 471 enrolled in the *Artemisia* arm (248 *A. annua*, 223 *A. afra*).
- On day 28, Munyangi et al. reported recurrent parasitaemia in:
  - 9 out of 248 patients (3.6%) treated using *A. annua*,
  - 25 out of 223 patients (11.2%) treated using *A. afra*,
  - 310 out of 472 patients (65.7%) treated using artesunate-amodiaquine.

Study by Munyangi et al (2018)

- Munyangi et al. furthermore reported that:
  - In some treated with artesunate-amodiaquine, parasites found 14 days after the start of treatment.
  - Treatment failures with artesunate-amodiaquine occurred mainly within the first 14 days.
  - Artesunate-amodiaquine had higher efficacy in children (50%) than in adults (30%).

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Threat of resistance

- **Widespread use of *A. annua* herbal remedies could hasten the development and spread of artemisinin resistance.**

- Resistance is more likely when parasites are exposed to sub-therapeutic levels of an antimalarial drug.
- If consumption of *A. annua* becomes widespread, any potential weak antimalarial activity of other compounds in *A. annua* would not be sufficient to protect artemisinin from resistance.

- **Artemisinin in any form does not work well as prevention against malaria**

- Artemisinin has short elimination half-life, and is not promoted for use in malaria chemoprophylaxis in any form.

Efficacious treatments

❑ Affordable and efficacious treatments for malaria are available

- ACTs are still highly efficacious
- Complete treatment with an ACT can be procured for less than US$ 2.
- Countries need to strengthen their regulatory systems to protect patients from counterfeit and substandard treatments;
  - this includes any products promoted for treatment of malaria without the necessary information in terms of their content, quality, safety and efficacy.

Thank you for your attention

Malaria Elimination in the Greater Mekong Subregion (GMS)

Malaria Policy Advisory Committee (MPAC)

2-4 October 2019

Global **Malaria** Programme

World Health Organization

Malaria elimination in the GMS: Targets

By 2020 or earlier

- Transmission of *P. falciparum* malaria interrupted in all areas of multidrug resistance (and in Cambodia)
- All species of human malaria eliminated in Yunnan Province, China

By 2025

- *P. falciparum* malaria eliminated in all countries of the GMS
- All species of human malaria eliminated in Cambodia and Thailand

By 2030

- All species of human malaria eliminated in all countries of the GMS

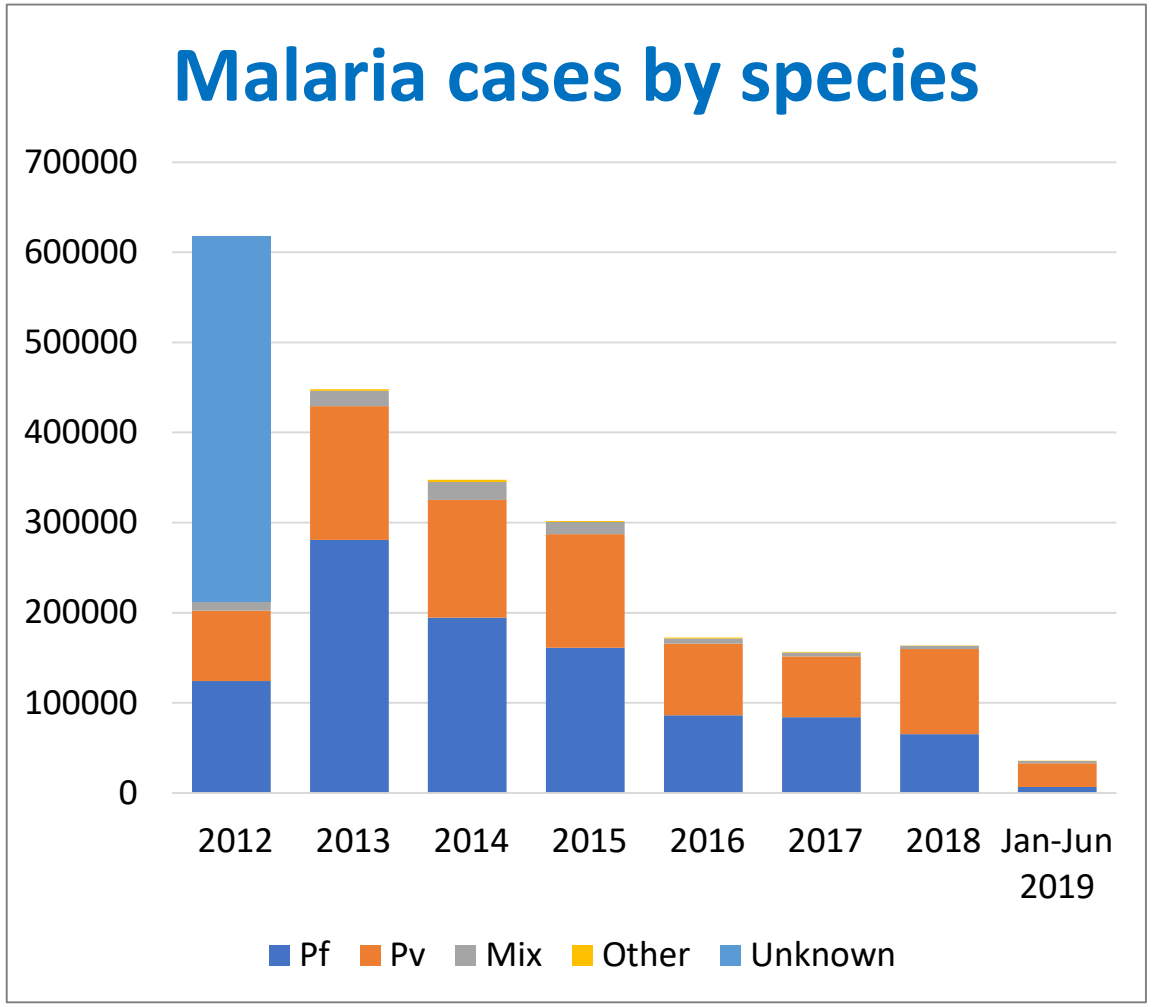
World Health Organization

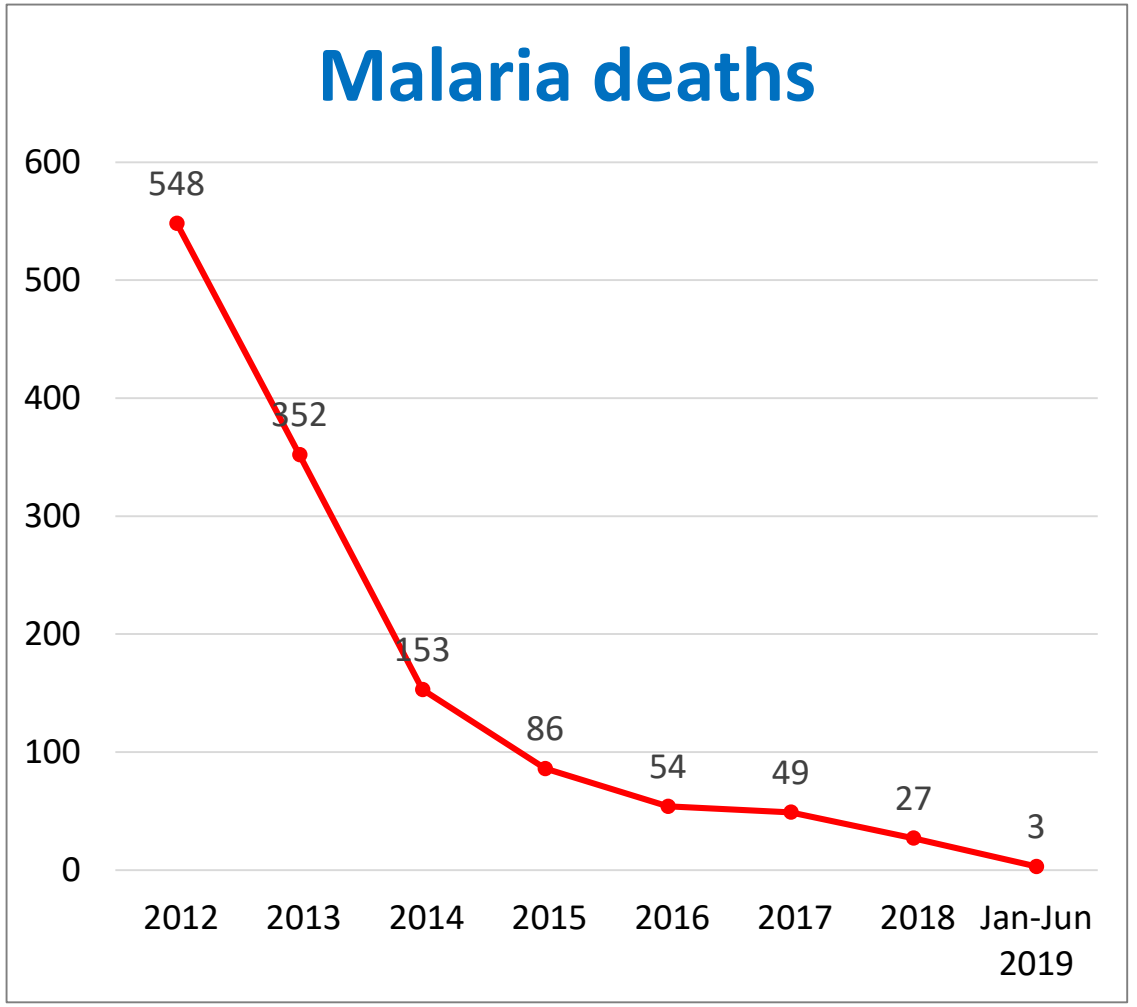
Outline

- Updates on progress
- Priorities in the GMS
- WHO support to GMS
- Summary

World Health Organization

Progress: Significant decrease in cases (2012-2019)



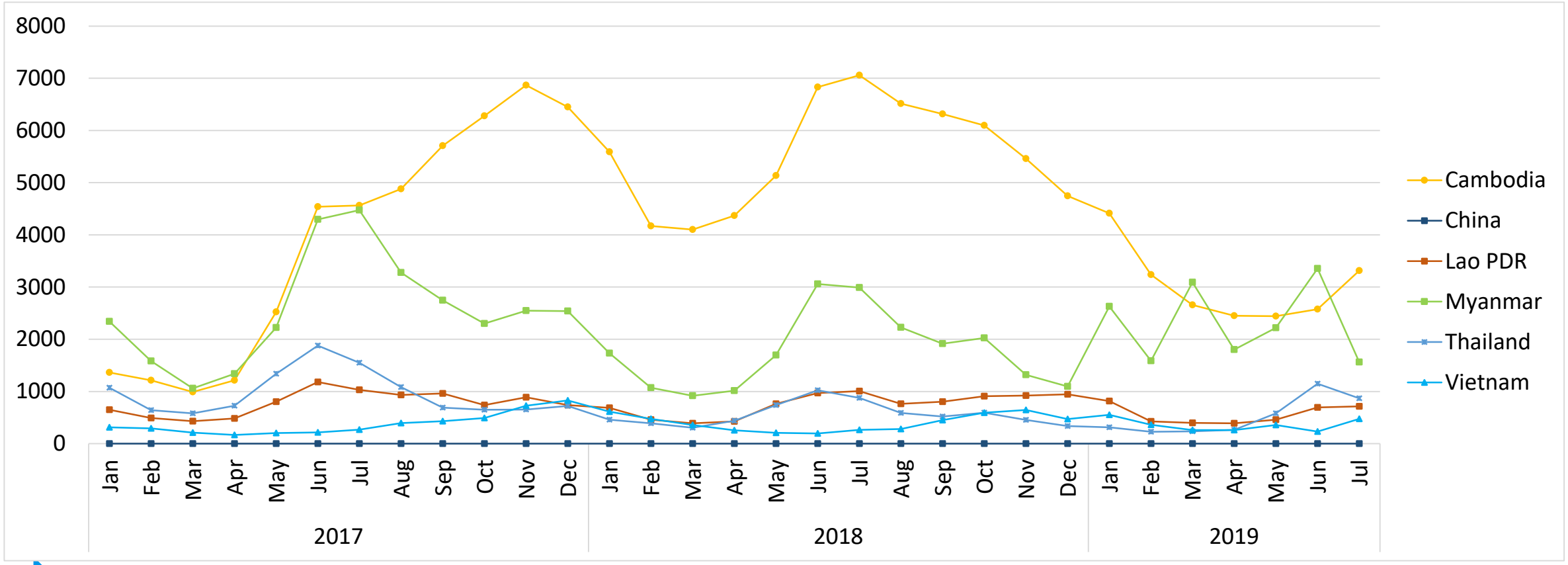


Source: WHO subregional database

World Health Organization

Monthly case trend in the GMS

Number of monthly cases in the GMS (2017-2019)



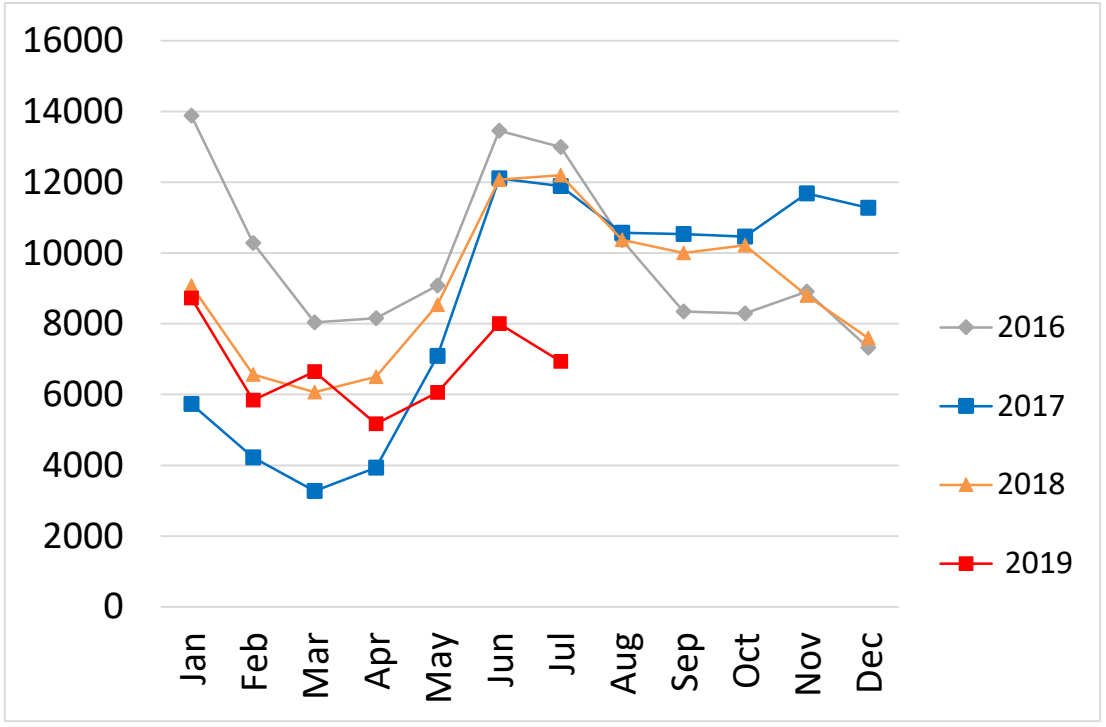
Case burden in Cambodia started to decrease in 2H 2018.

Source: WHO subregional database. Myanmar cases include only public sector data.

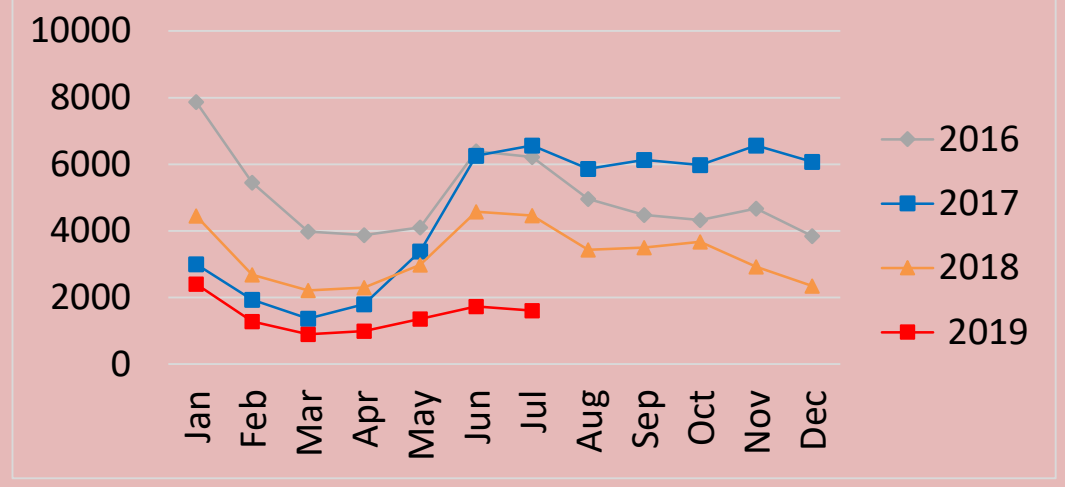
World Health Organization

Progress toward *Pf* elimination

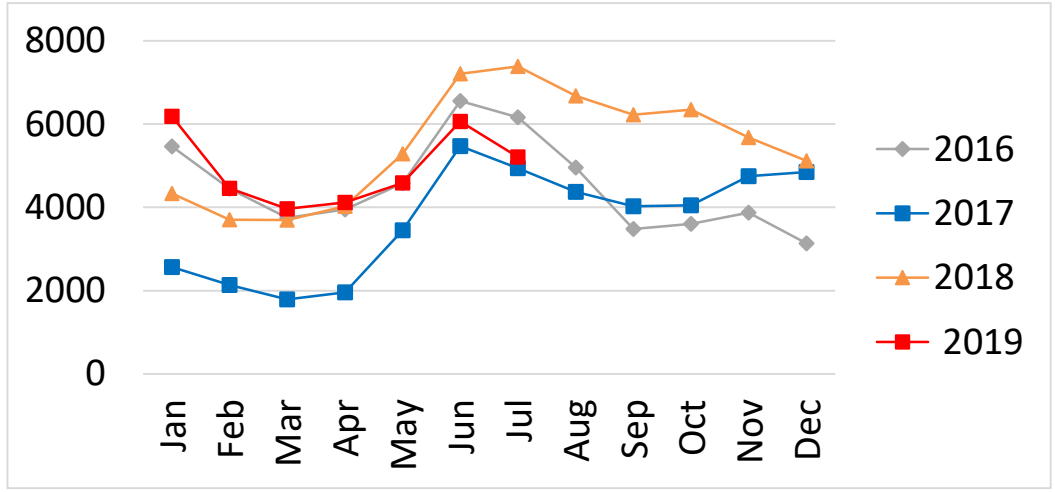
Total confirmed cases (2016-2019)



P. falciparum cases



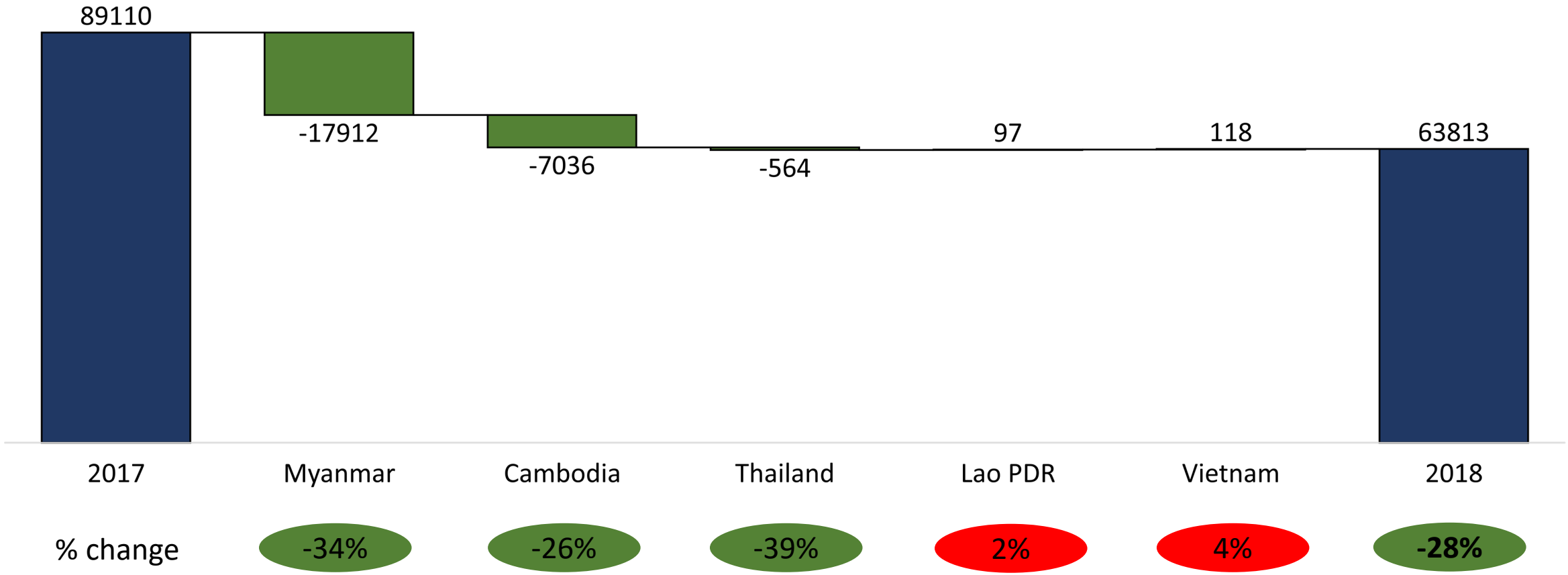
P. vivax cases



Source: WHO subregional database, excluding mixed cases.

Progress toward *Pf* elimination (2017 vs. 2018)

Changes in *Pf* + Mix Cases from 2017 to 2018

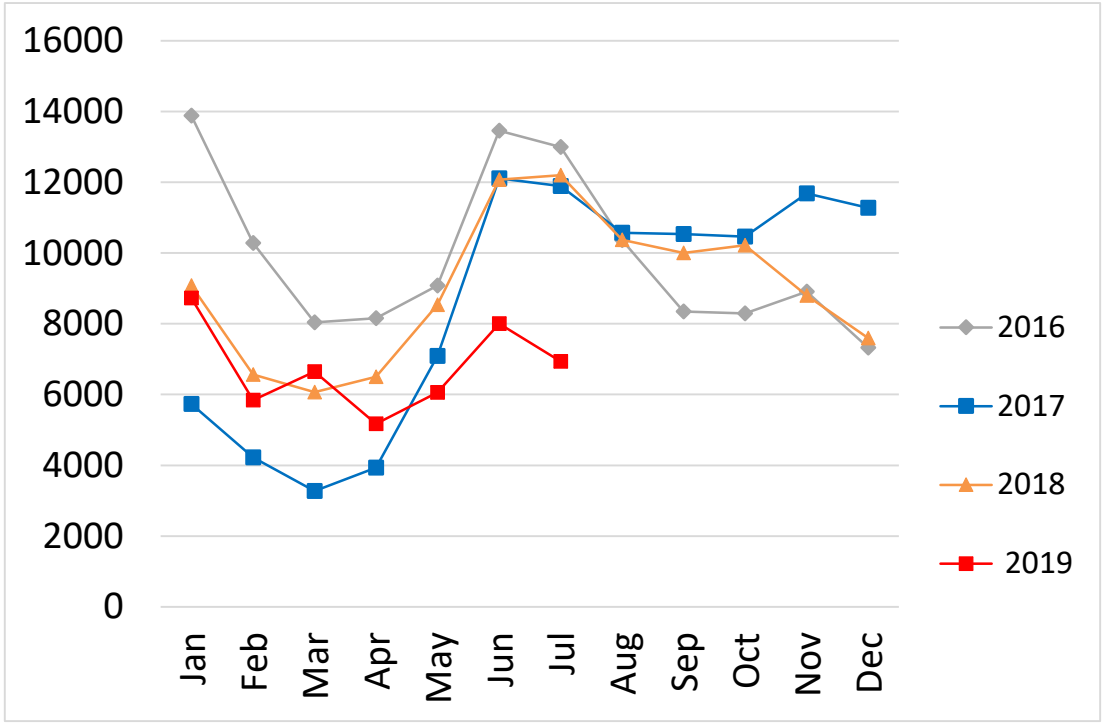


Source: WHO subregional database

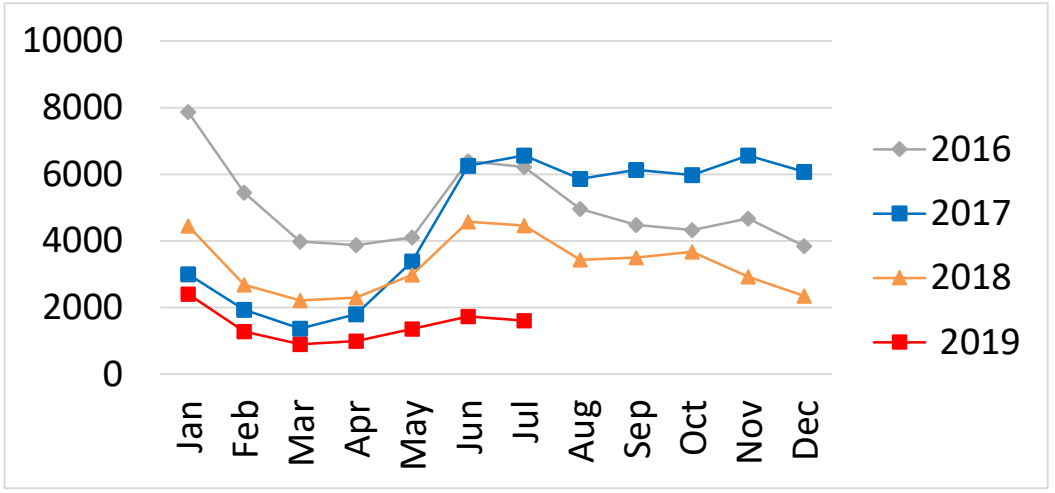
World Health Organization

Progress toward *Pv* elimination

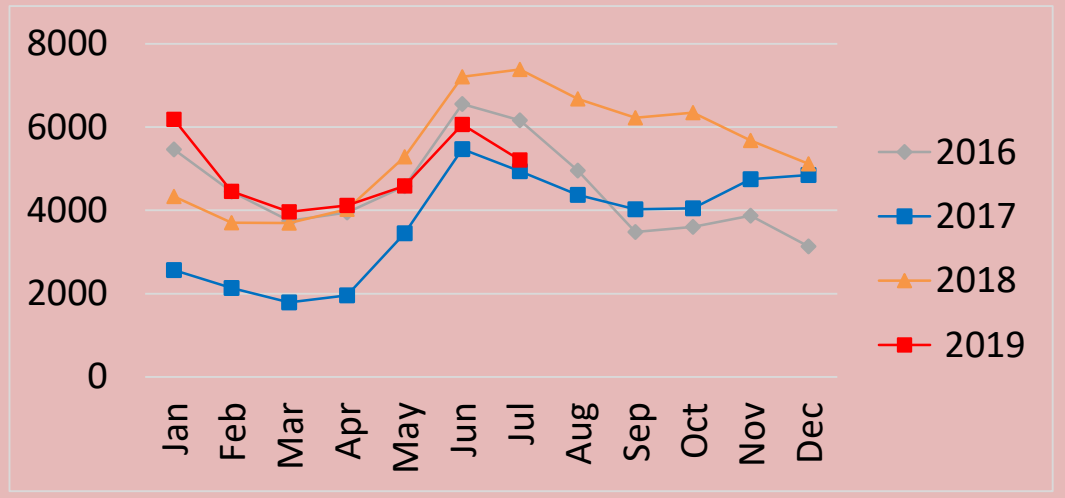
Total confirmed cases (2016-2019)



P. falciparum cases



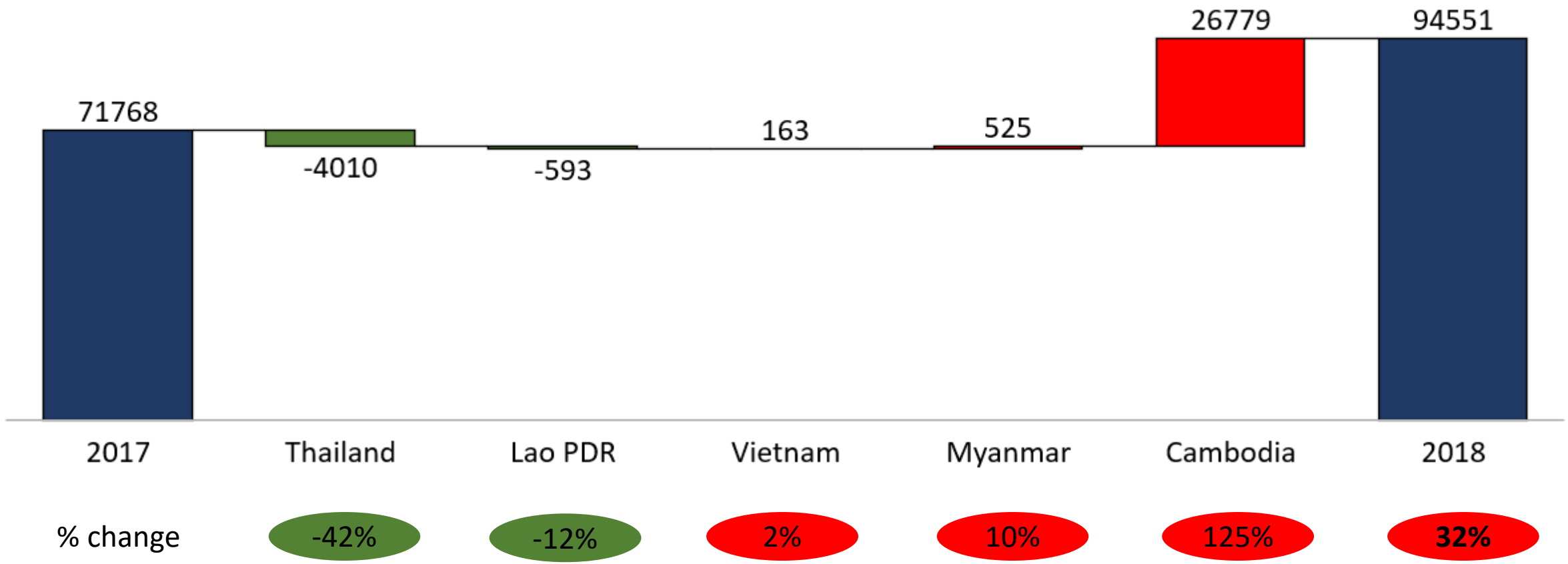
P. vivax cases



Source: WHO subregional database, excluding mixed cases.

Progress toward *Pv* elimination (2017 vs. 2018)

Changes in *Pv* + Mix Cases from 2017 to 2018

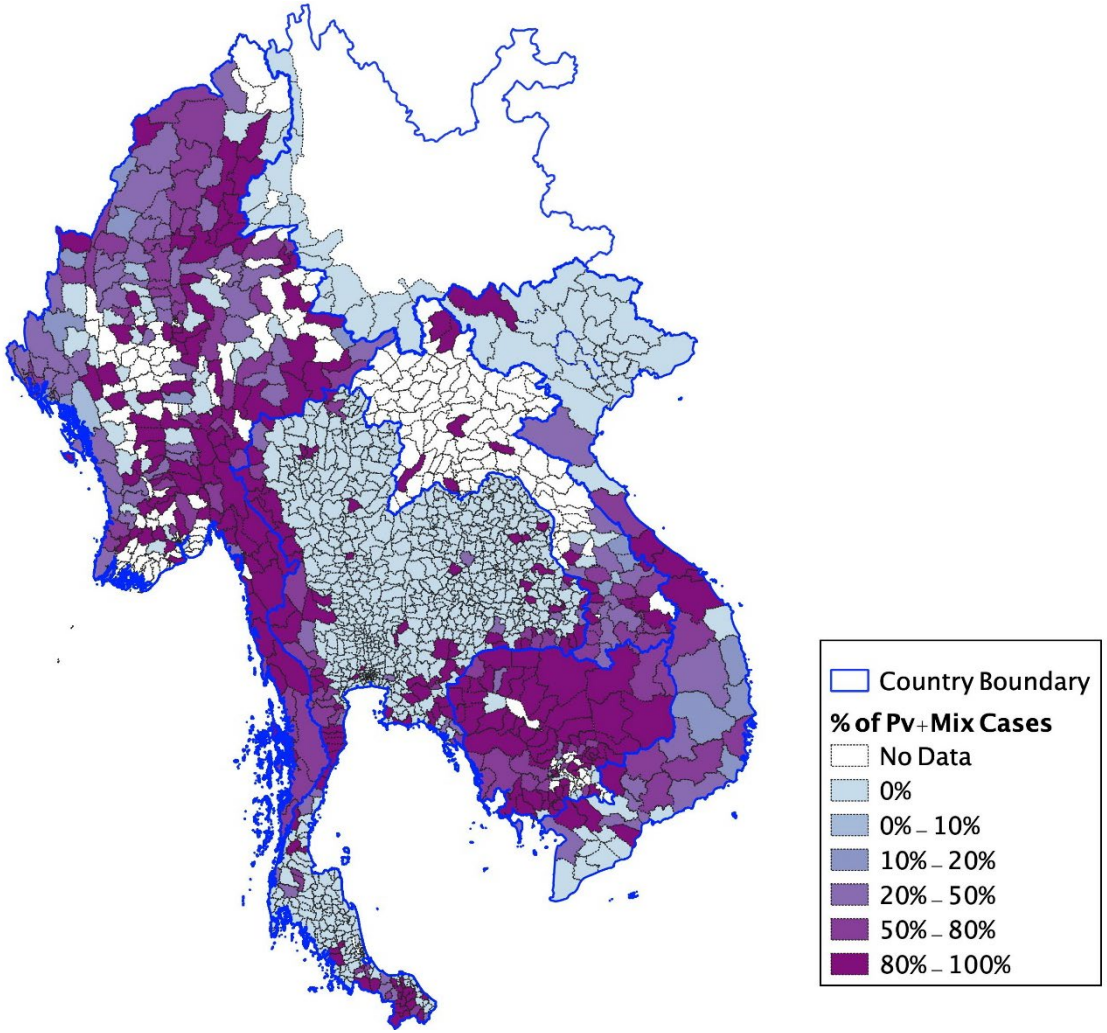


Source: WHO subregional database

World Health Organization

Pv distribution in GMS

% of Pv+Mix cases by district* (Jan-Jun 2019)



- In 1H 2019, approx. 79% of cases were *Pv* or *Pv+Pf*
- Relative importance of *Pv* cases is likely to increase as countries approach elimination
- Insufficient or lack of implementation of radical cure with primaquine in Cambodia and Lao PDR

Source: WHO subregional database. *Viet Nam data are provincial level.

World Health Organization

Percentage of *Pv* + Mix cases in GMS (2016-2019)

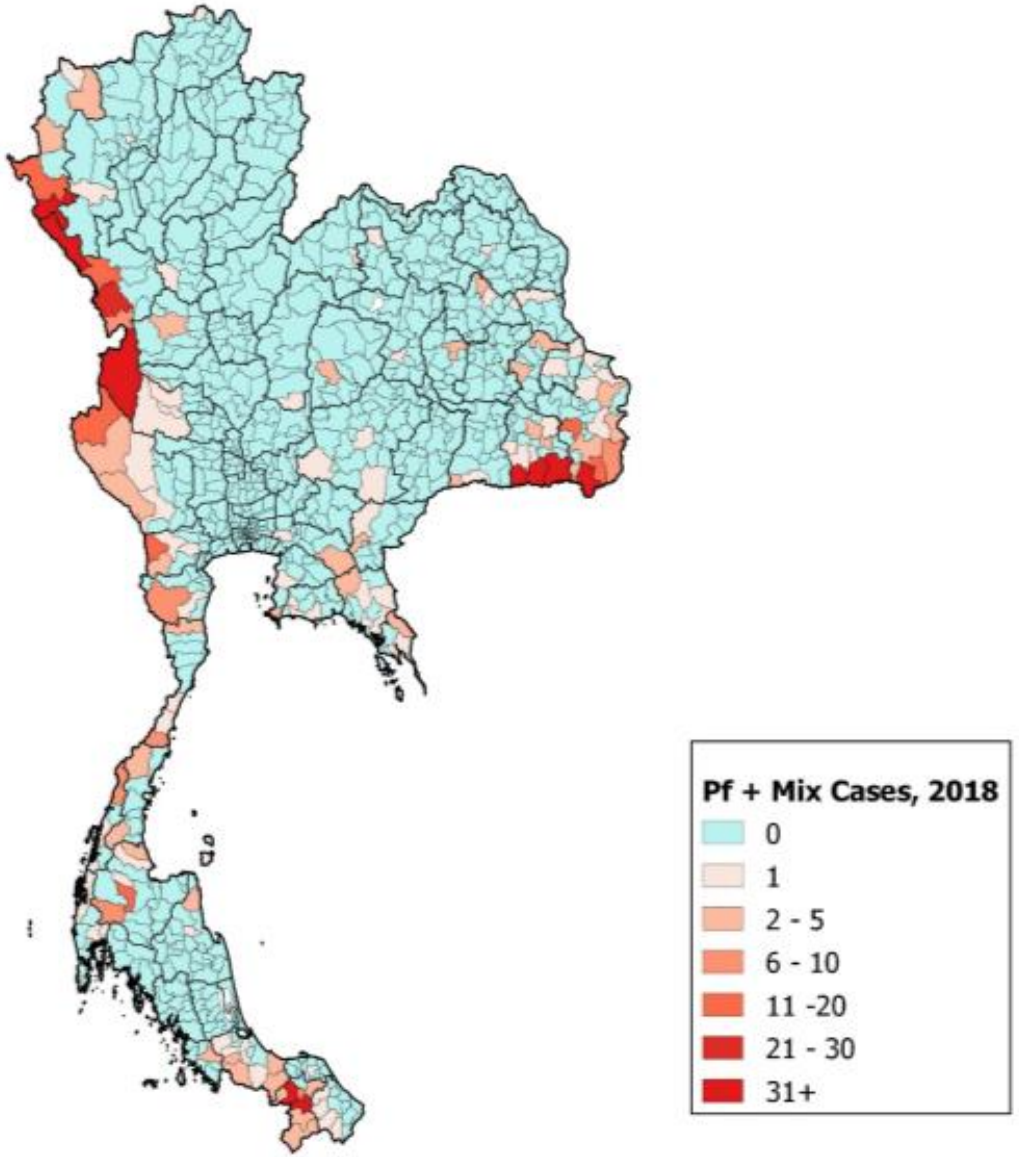
Country	2016	2017	2018	Jan-Jun 2019
Cambodia	48%	46%	73%	87%
Lao PDR	63%	51%	47%	68%
Myanmar	43%	32%	51%	78%
Thailand	76%	84%	83%	80%
Viet Nam	44%	37%	38%	34%

Source: WHO subregional database

World Health Organization

Thailand is nearing *Pf* elimination

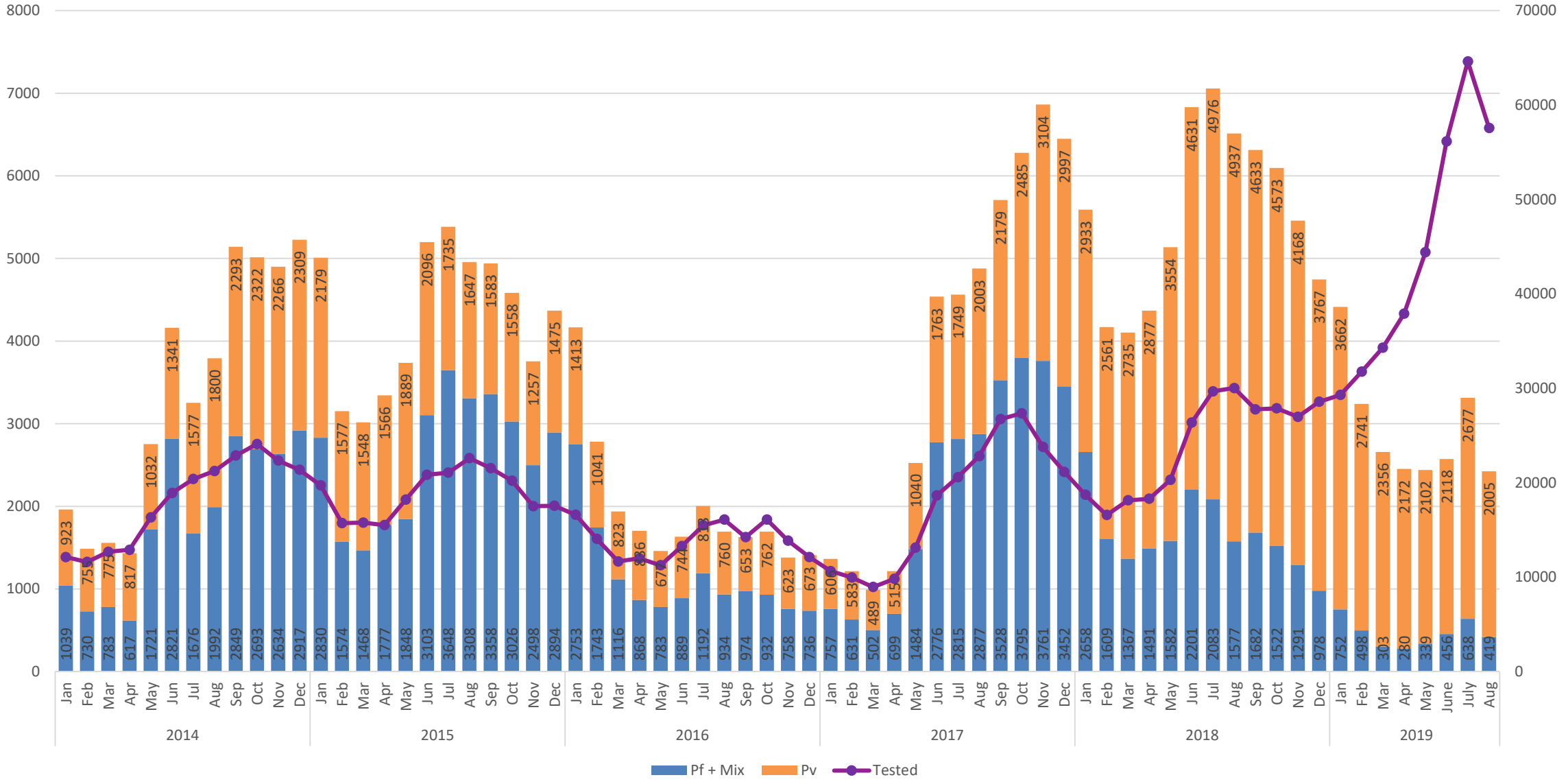
***Pf* + Mix cases in 2018**
(*n* = 876 cases)



Source: WHO subregional database

World Health Organization

Pf+Mix vs Pv in Cambodia (2014 - Aug 2019)



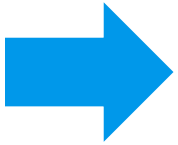
Source: WHO subregional database

Priorities in GMS (MPAC, April 2019)

- Targeting high-risk populations, including:
  → Forest goers in remote areas
  → Mobile and migrant populations

- Monitoring drug efficacy and updating/implementing national treatment guidelines, including:
  → Replacing ineffective first-line drugs and identifying second-line drugs
  → Implementing Pv radical cure

- Cross-border collaboration, including:
  → Regional data-sharing platform (RDSP)
  → Partner coordination



For each category, it is encouraged to explore innovative approaches

World Health Organization

Priorities in GMS

- Targeting high-risk populations, including:
  - → Forest goers in remote areas
  - → Mobile and migrant populations

- Monitoring drug efficacy and updating/implementing national treatment guidelines, including:
  - → Replacing ineffective first-line drugs and identifying second-line drugs
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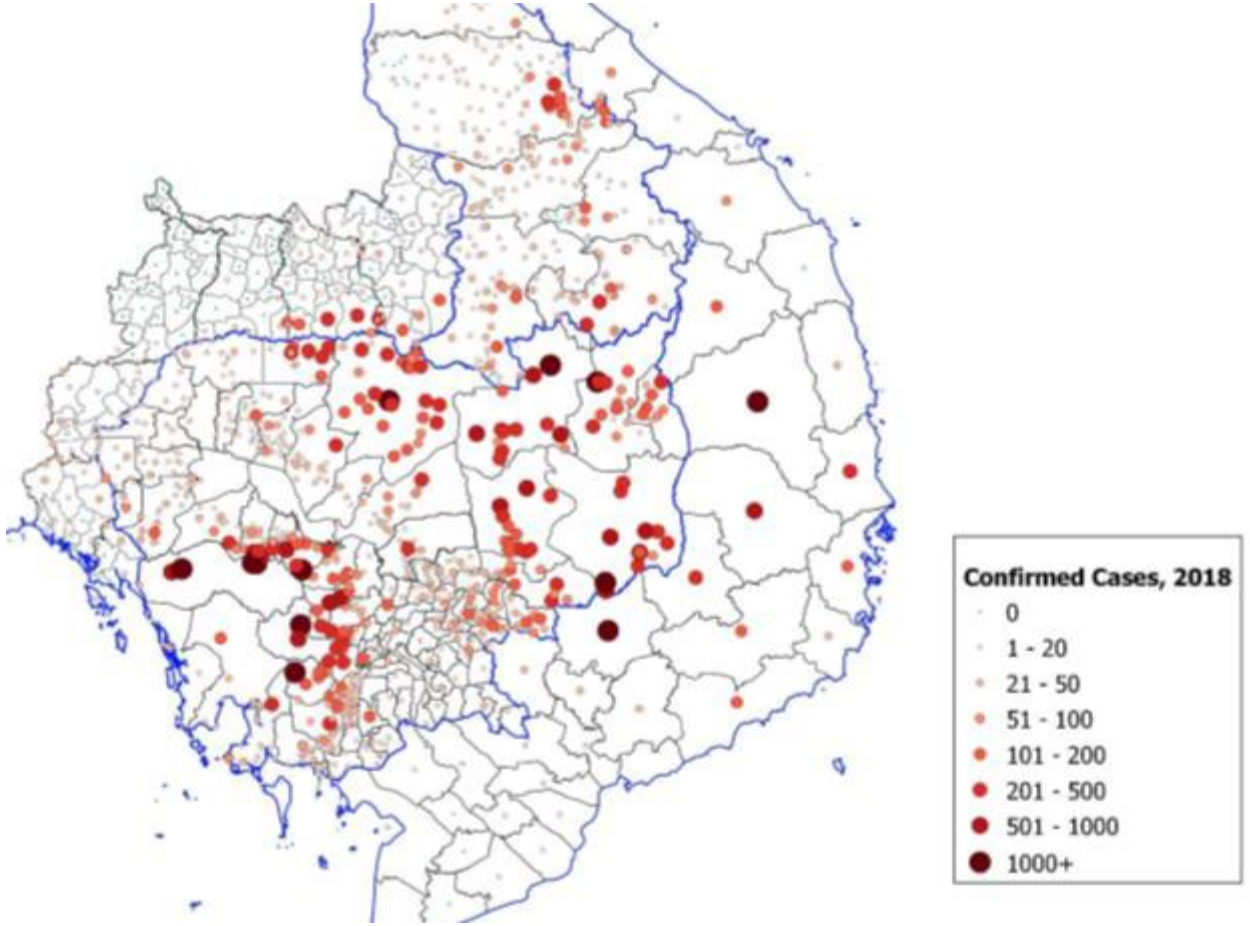
  - → Regional data-sharing platform (RDSP)
  - → Partner coordination

World Health Organization

Cases are highly concentrated

Case distribution in northern Cambodia and adjacent provinces (Jan-Dec 2018)



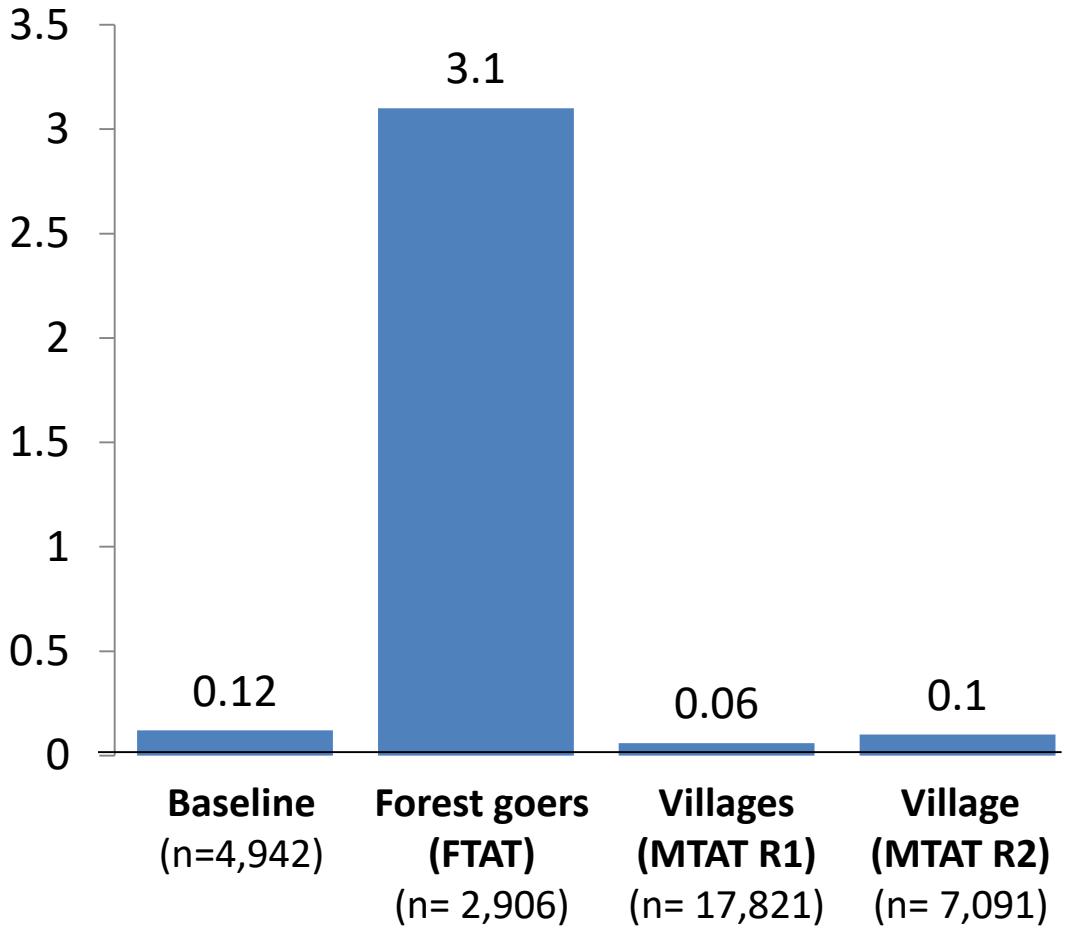
- Cases are highly concentrated in a few health centres in Cambodia and Lao PDR
- In both Cambodia and Lao PDR, top 20 facilities account for approx. 40% of cases, while top 50 account for approx. 60% of cases (Jan-June, 2018)

Source: WHO subregional database. Cambodia/Lao PDR data are commune/HC level; Thailand data are district level; and Viet Nam data are provincial level.

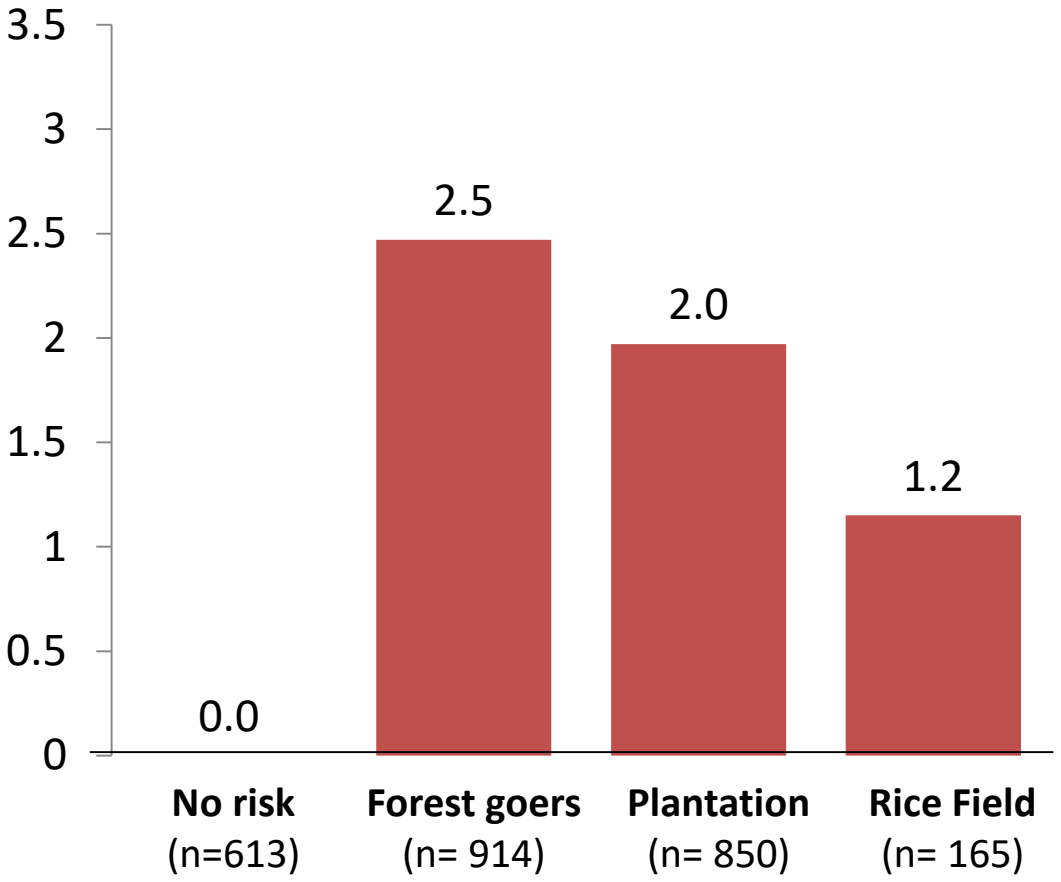
World Health Organization

Most cases are among forest goers (Results from UCSF and MSF)

Prevalence of all malaria parasites (RDT)
(% of all positive case, Champasak, Lao PDR)



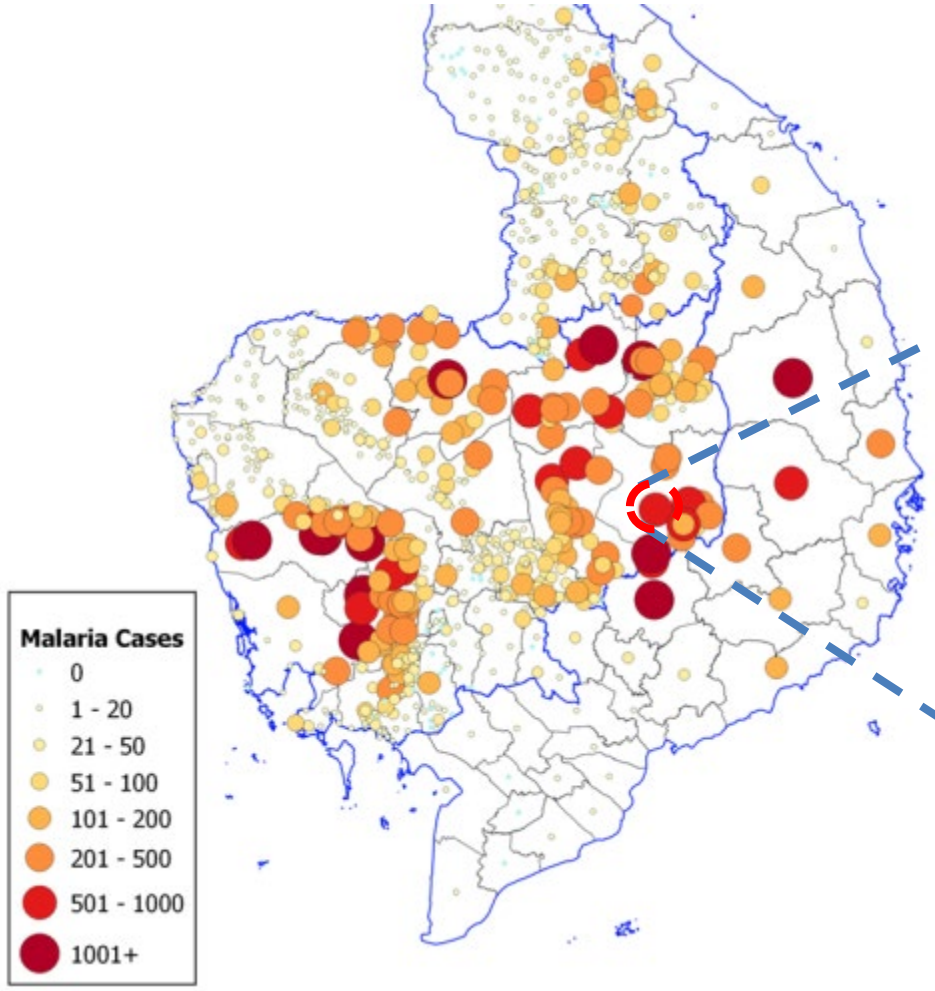
Prevalence in malaria in ACD (PCR)
% of positive Pf case, N= 2772 (Preah Vihear, Cambodia)



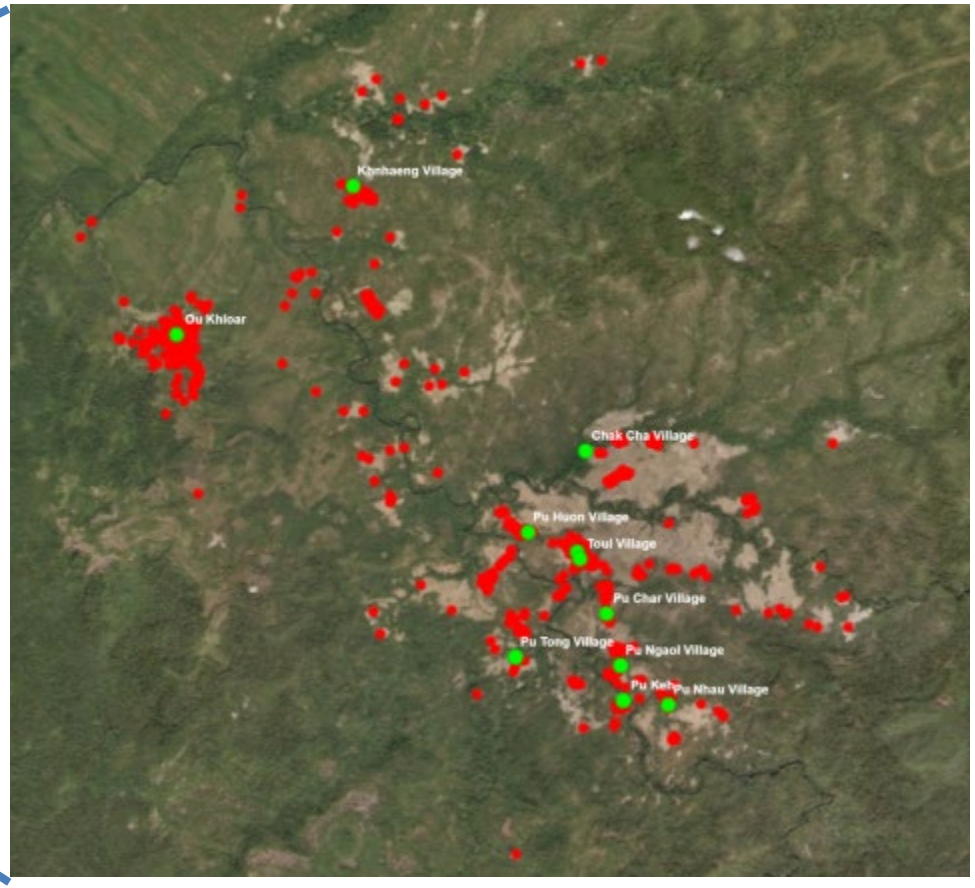
Source: UCSF (Lao PDR) and MSF (Cambodia).

World Health Organization

Challenge: Forest sites are widely dispersed



Possible Forest Sites in Me Mang, Mondulkiri, Cambodia



Source: WHO subregional database

World Health Organization

Need for community-based approach

- Mobility patterns, group size and access to communications differs significantly across forest goers. As a result, there is no one-size-fits-all solution to reaching forest goers.
- To develop effective and tailored intervention strategies, it is helpful to work hand-in-hand with the community, government and partners.
- This will also improve the ownership of the communities in resource-scarce settings.

World Health Organization

Priorities in GMS

- Targeting high-risk populations, including:
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  - → Mobile and migrant populations

- Monitoring drug efficacy and updating/implementing national treatment guidelines, including:
  - → Replacing ineffective first-line drugs and identifying second-line drugs
  - → Implementing Pv radical cure

- Cross-border collaboration, including:
  - → Regional data-sharing platform (RDSP)
  - → Partner coordination

World Health Organization

Evolution and expansion of multidrug-resistant malaria in southeast Asia: a genomic epidemiology study

William L Hamilton*, Roberto Amato*, Rob W van der Pluijm, Christopher G Jacob, Huynh Hong Quang, Nguyen Thanh Thuy-Nhien, Tran Tinh Hien, Bouasy Hongvanthong, Keobouphaphone Chindavongsa, Mayfong Mayxay, Rekol Huy, Rithea Leang, Cheah Huch, Lek Dysoley, Chanaki Amaratunga, Seila Suon, Rick M Fairhurst, Rupam Tripura, Thomas J Peto, Yok Sovann, Podjanee Jittamala, Borimas Hanboonkunupakarn, Sasithon Pukrittayakamee, Nguyen Hoang Chau, Mallika Imwong, Mehul Dhorda, Ranitha Vongpromek, Xin Hui S Chan, Richard J Maude, Richard D Pearson, T Nguyen, Kirk Rockett, Eleanor Drury, Sónia Gonçalves, Nicholas J White, Nicholas P Day, Dominic P Kwiatkowski, Arjen M Dondorp, Olivo Miotto

Summary

Background A multidrug-resistant co-lineage of *Plasmodium falciparum* malaria, named KEL1/PLA1, spread across Cambodia in 2008–13, causing high rates of treatment failure with the frontline combination therapy dihydroartemisinin-piperaquine. Here, we report on the evolution and spread of KEL1/PLA1 in subsequent years.

Lancet Infect Dis 2019; 19: 943–51

Published Online July 22, 2019

- 1. Emergence of KEL1 in different parts of SE Asia with notable localized geographic distribution.
- 2. Rapid expansion of a related group of parasites that shared a specific lineage of KEL1 and a specific lineage of plasmepsin amplification (PLA1) that caused DHA-PPQ treatment failure in western Cambodia.
- 3. KEL1/PLA1 co-lineage that has spread across the region and differentiated into sub-lineages that vary in geographical distribution and phenotype.

World Health Organization

Determinants of dihydroartemisinin-piperaquine treatment failure in *Plasmodium falciparum* malaria in Cambodia, Thailand, and Vietnam: a prospective clinical, pharmacological, and genetic study

Rob W van der Pluijm, Mallika Imwong, Nguyen Hoang Chau, Nhu Thi Hoa, Nguyen Thanh Thuy-Nhien, Ngo Viet Thanh, Podjanee Jittamala, Borimas Hanboonkunupakarn, Kitipumi Chutasmit, Chalermpon Saelow, Ratchadaporn Runjarern, Weerayuth Kaewmok, Rupam Tripura, Thomas J Peto, Sovann Yok, Seila Suon, Sokunthea Sreng, Sivanna Mao, Savuth Oun, Sovannary Yen, Chanaki Amaratunga, Dysoley Lek, Rekol Huy, Mehul Dhorda, Kesinee Chotivanich, Elizabeth A Ashley, Mavuto Mukaka, Naomi Waithira, Phaik Yeong Cheah, Richard J Maude, Roberto Amato, Richard D Pearson, Sónia Gonçalves, Christopher G Jacob, William L Hamilton, Rick M Fairhurst, Joel Tarning, Markus Winterberg, Dominic P Kwiatkowski, Sasithon Pukrittayakamee, Tran Tinh Hien, Nicholas PJ Day, Olivo Miotto, Nicholas J White, Arjen M Dondorp

Lancet Infect Dis 2019; 19: 952–61

Published Online July 22, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30391-3

See Comment page 916

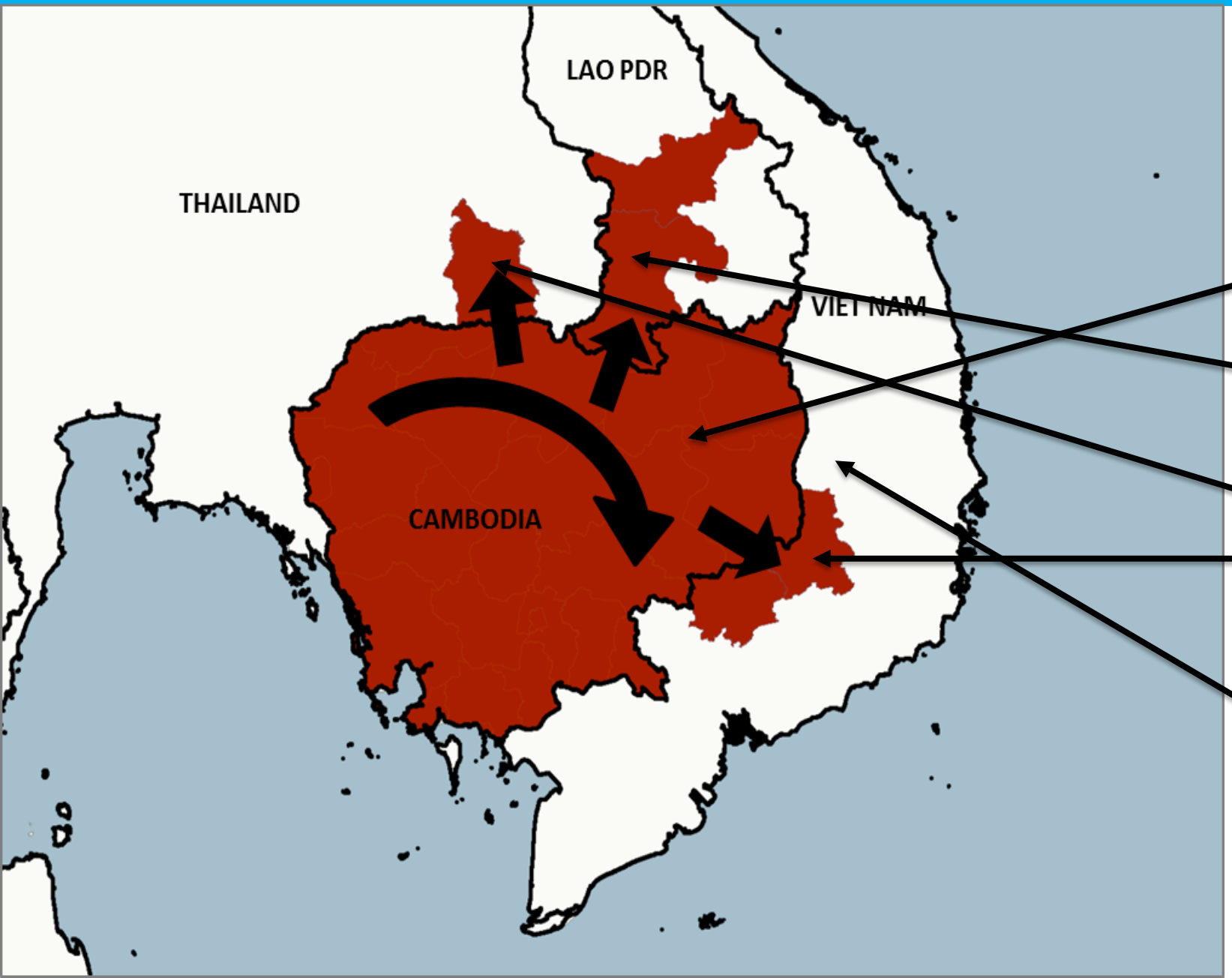
See Articles page 943

Summary

Background The emergence and spread of resistance in *Plasmodium falciparum* malaria to artemisinin combination therapies in the Greater Mekong subregion poses a major threat to malaria control and elimination. The current study is part of a multi-country, open-label, randomised clinical trial (TRACII, 2015–18) evaluating the efficacy, safety, and tolerability of triple artemisinin combination therapies. A very high rate of treatment failure after treatment with dihydroartemisinin-piperaquine was observed in Thailand, Cambodia, and Vietnam. The immediate public health importance of our findings prompted us to report the efficacy data on dihydroartemisinin-piperaquine and its determinants ahead of the results of the overall trial, which will be published later this year.

World Health Organization

Spread of DHA-piperaquine in GMS



Reported by WHO since 2011

Reported by WHO in 2017

Reported by VBDB to WHO in 2018

Reported by WHO 2015 (Binh Phuc) and 2016 (Dak Nong)

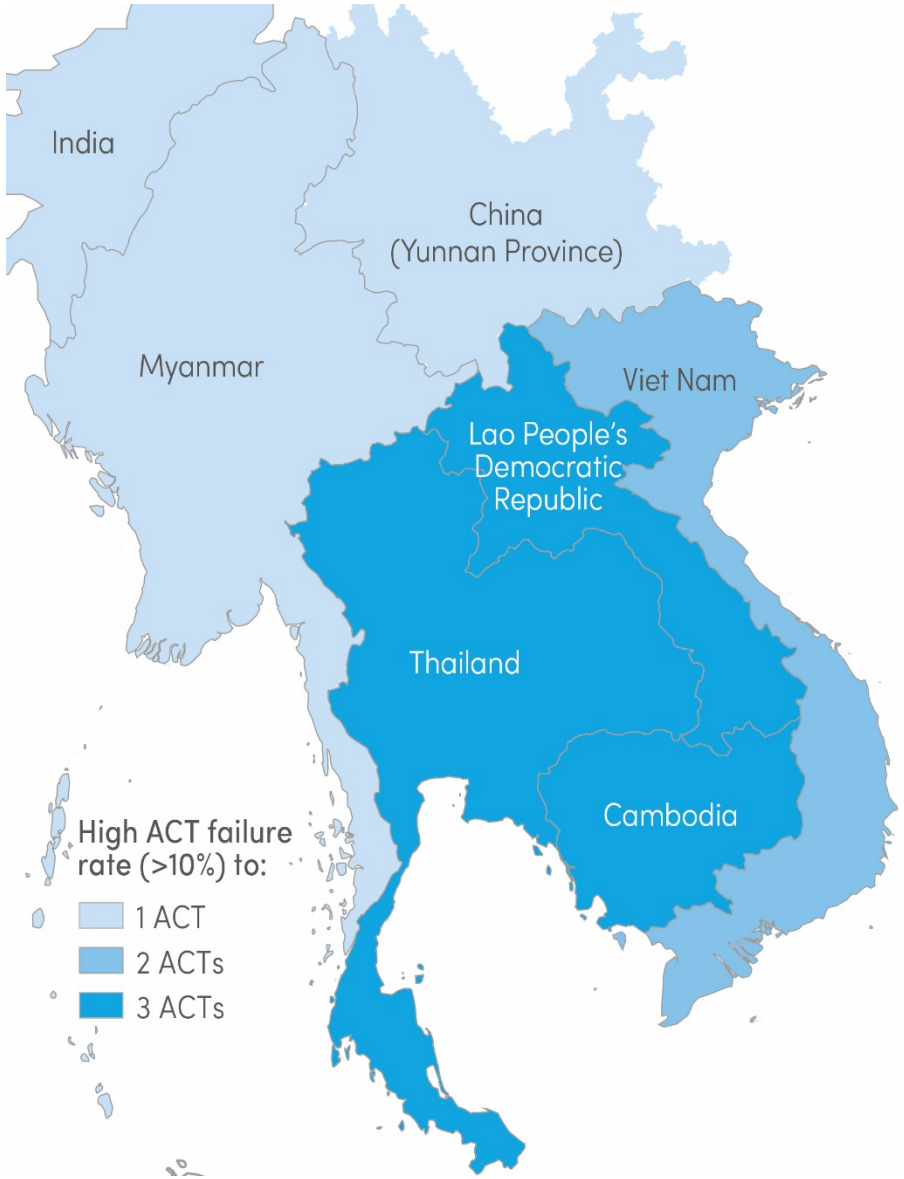
Reported by WHO in 2019 (Dak Lak)

World Health Organization

Efficacy of ACTs in GMS (2010-2018)

	Year	N of studies	Tx failures min	Tx failures max
Myanmar				
Artemether-lumefantrine	2010-17	25	0.0	6.0
Artesunate-mefloquine	2011-13	5	0.0	2.2
Artesunate-pyronaridine	2017-18	4	0.0	0.0
DHA-piperaquine	2010-18	21	0.0	4.8
Cambodia				
Artesunate-mefloquine	2011-18	18	0.0	1.8
Artesunate-pyronaridine	2017-18	4	0.0	3.3
Lao PDR				
Artemether-lumefantrine	2010-17	9	0.0	17.2
DHA-piperaquine	2016-17	2	13.3	47.4
Artesunate-pyronaridine	2018-19	1	0.0	0.0
Viet Nam				
DHA-piperaquine	2010-17	42	0.0	46.3
Artesunate-pyronaridine	2017-18	5	0.0	4.8

World Health Organization



World Health Organization

Priorities in GMS

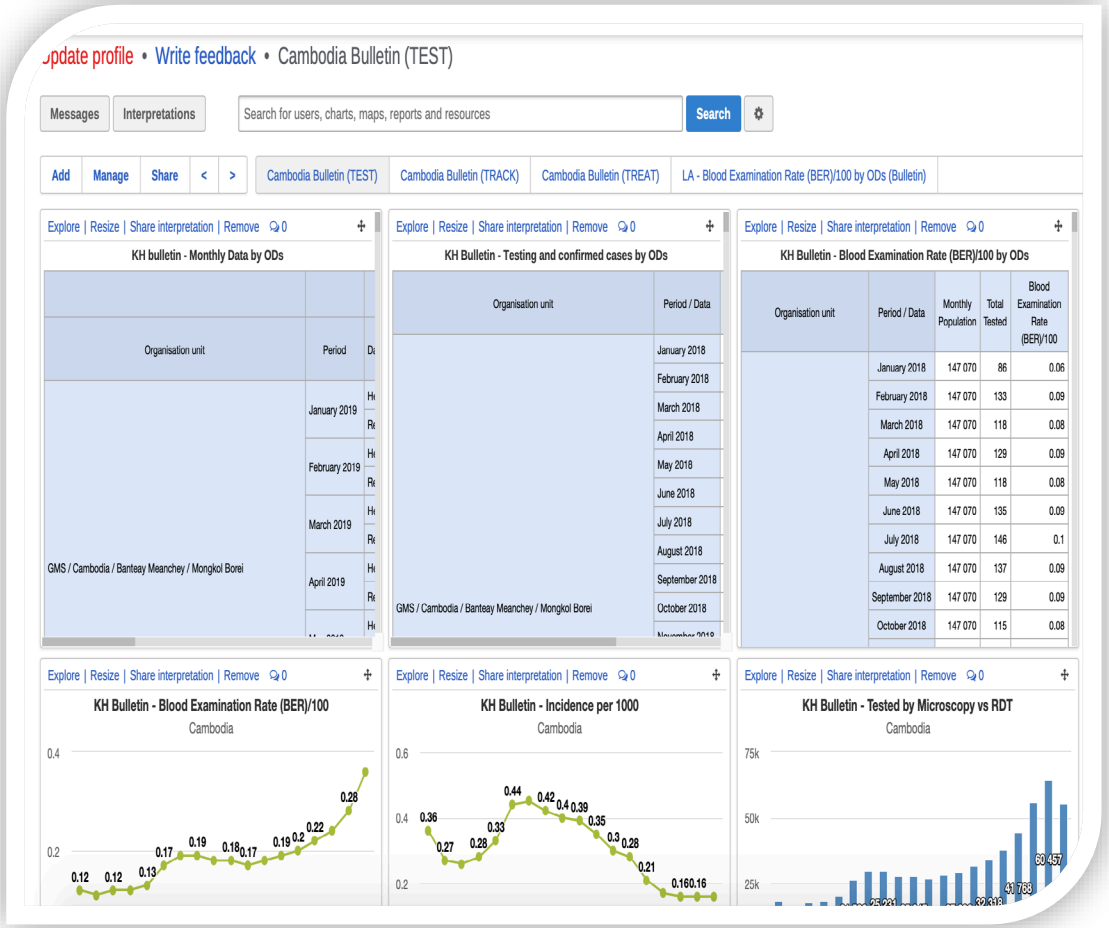
- Targeting high-risk populations, including:
  - → Forest goers in remote areas
  - → Mobile and migrant populations

- Monitoring drug efficacy and updating/implementing national treatment guidelines, including:
  - → Replacing ineffective first-line drugs and identifying second-line drugs
  - → Implementing Pv radical cure

- Cross-border collaboration, including:
  - → Regional data-sharing platform (RDSP)
  - → Partner coordination

World Health Organization

Cross-Country Collaboration: Regional Data Sharing Platform (RDSP)



- All GMS countries are sharing monthly surveillance data to the WHO RDSP
- RDSP enables monitoring toward malaria elimination, detailed data analysis, and sharing data across the Subregion (e.g. cross-border meetings).

World Health Organization

Annual GMS surveillance meeting

WHO hosted an annual GMS surveillance meeting (Nov 2018), with the objectives to:

- Exchange information on surveillance progress and challenges in GMS countries
- Strengthen surveillance in elimination phase (e.g. case and foci-investigation)
- Discuss proposed mechanism to utilize the WHO RDSP for cross-border collaboration
- Brainstorm future priorities for surveillance

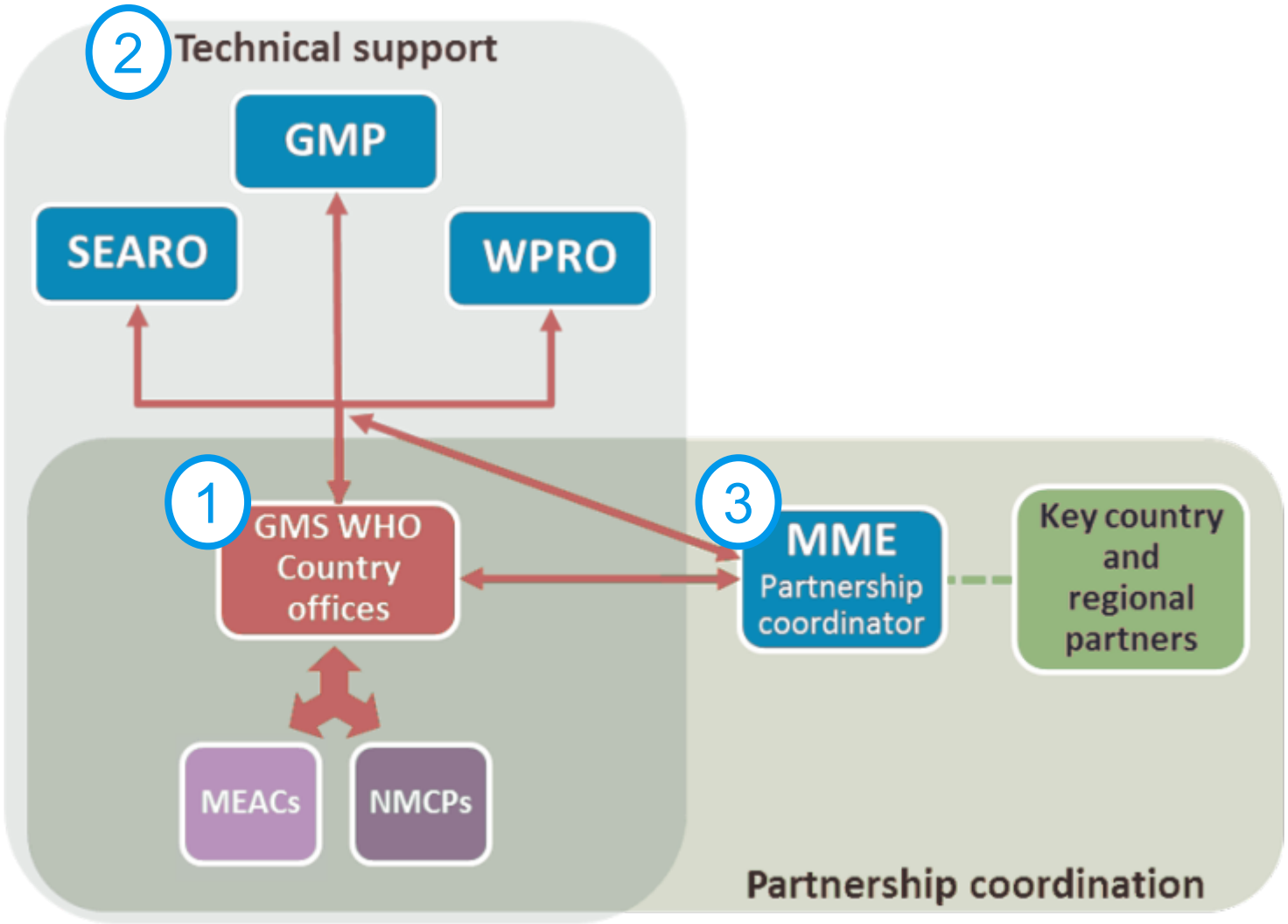
Next surveillance meeting scheduled for Nov 2019

Challenges for surveillance in GMS

Key Areas of Work	Challenges
Data Collection and Reporting	• Include surveillance data from partners and private sector • Timely reporting of aggregated data to the national database • Implement case-based surveillance and iDES
Data Use	• Analyse & share surveillance data especially sub-national levels • Take timely programmatic actions
Validation	• Regular validation of surveillance data • Surveillance assessment

World Health Organization

WHO technical support in GMS



MEAC: Malaria Elimination Advisory Committee; NMCP: National Malaria Control Programmes

Major Objectives

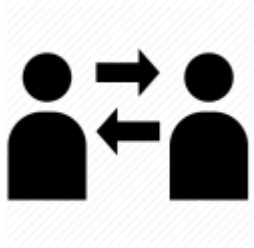
1. **Country Offices** continue support to national malaria elimination programmes

2. **HQ and Regional Offices** ensure timely technical support

3. **Mekong Malaria Elimination** (MME) team addresses partnership coordination and cross-country issues

World Health Organization

WHO supports partner coordination and collaboration



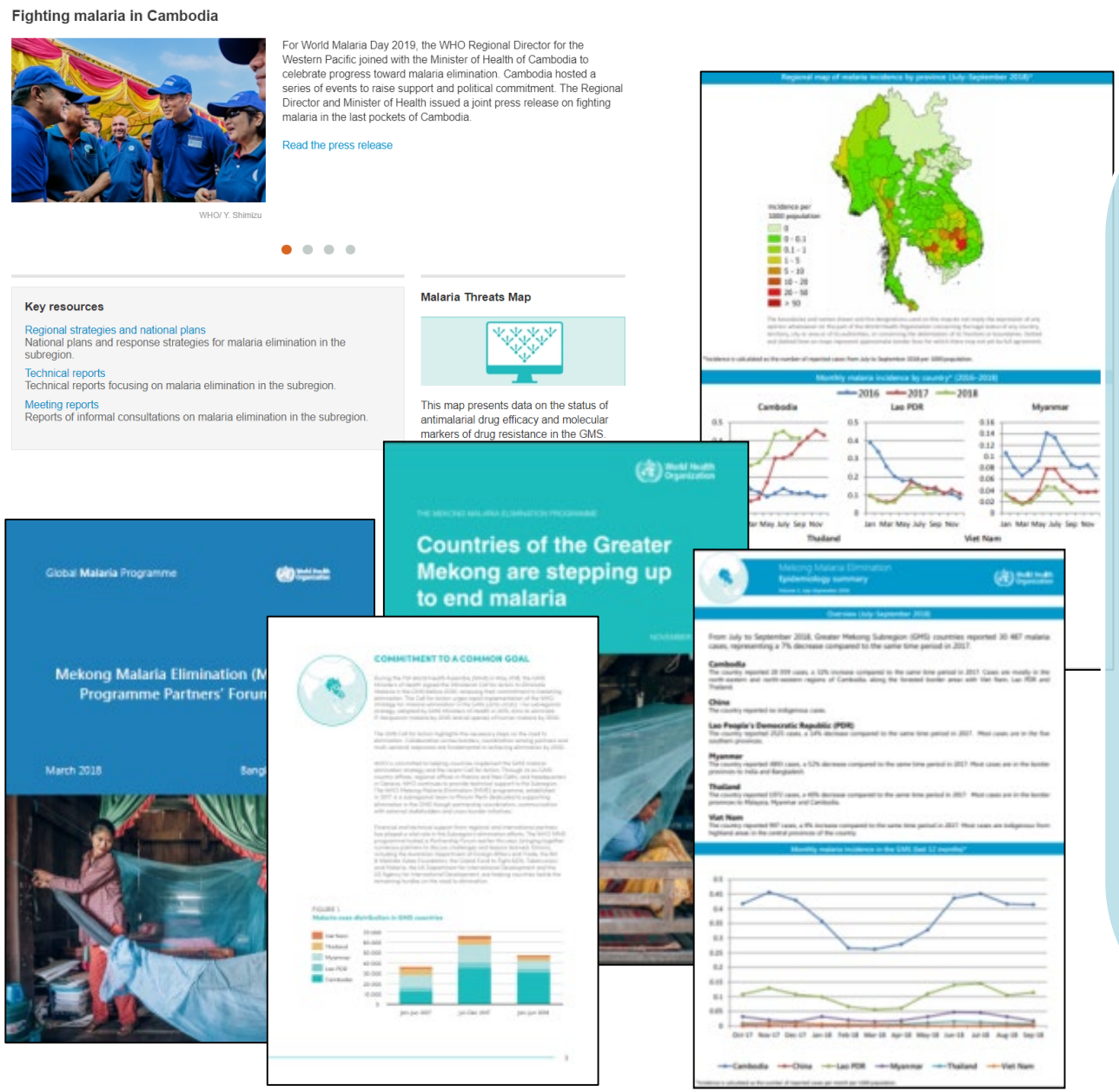
- **Information**: Exchange information on activities. Regularly share key updates (e.g. new project, publication, meeting)

- **Coordination:** Ensure there are neither overlaps nor gaps in our activities. Maintain close contact among partners that operate in the same provinces/districts

- **Collaboration**: Establish joint projects with clear definitions of responsibilities for each partner and NMCP

World Health Organization

Information exchange

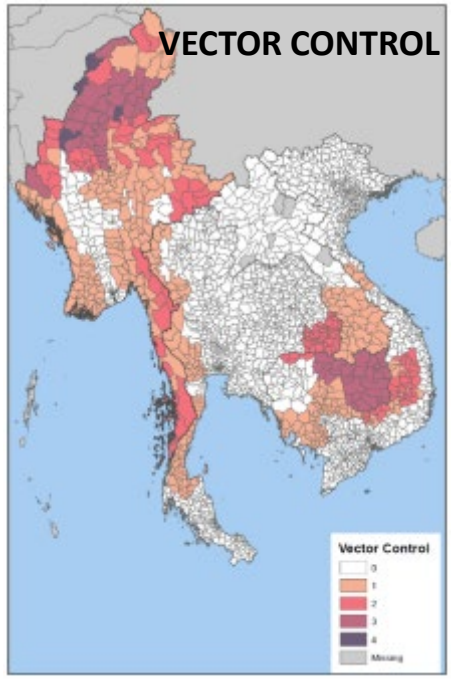


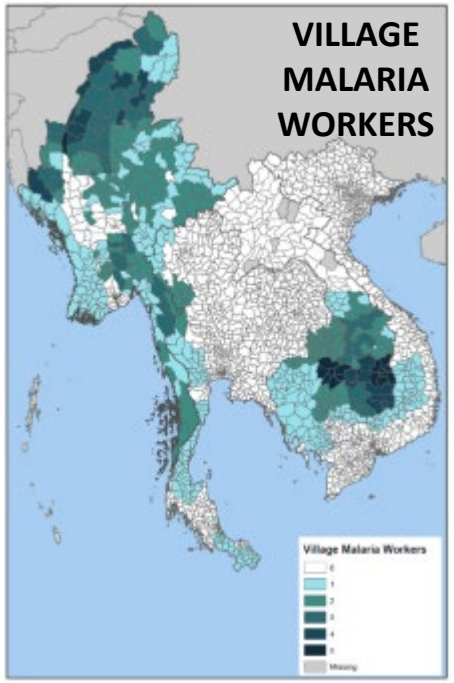
WHO facilitates information exchange among partners through various mechanisms:

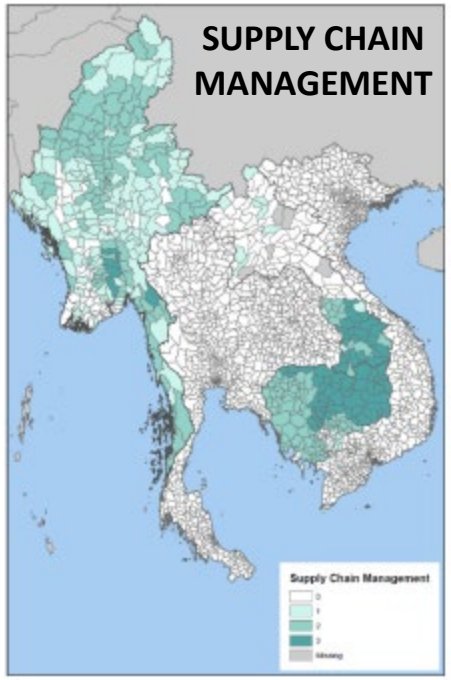
- Publications (e.g. annual publication, quarterly epidemiology summary)
- Partners' mailing list (e.g. quarterly partner activity summary)
- MME website
- Subregional and national meetings

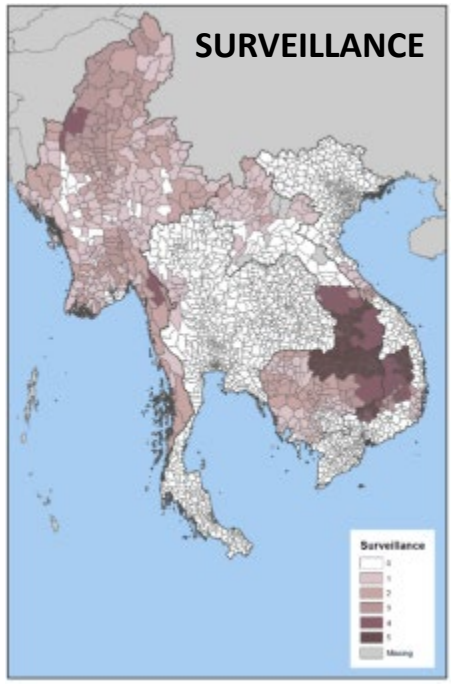
World Health Organization

Partner Mapping with CHAI



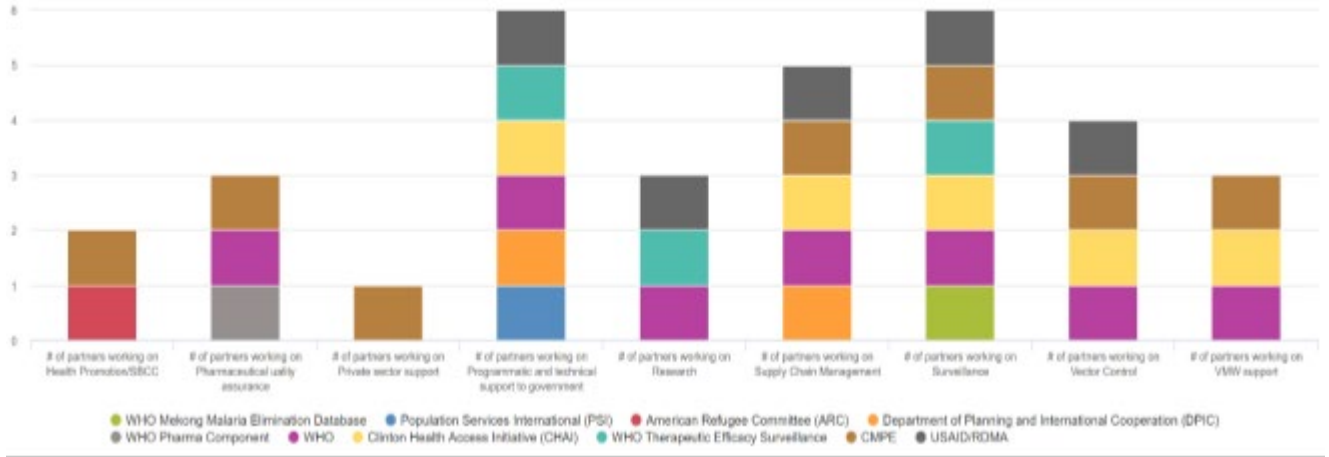






Source: WHO subregional database and CHAI survey

Partners working at national level (Lao PDR)



Examples of results from partner mapping with CHAI

World Health Organization

Summary

- GMS countries have substantially reduced the number of malaria cases from 2012-2018. In 2018 and the first half of 2019, countries have made significant progress towards *Pf* elimination, especially Cambodia, Myanmar and Thailand.

- From January to June 2019, approximately 79% of cases in the GMS were *Pv* or combined cases of *Pv* and *Pf*.

- The remaining cases are concentrated in small geographical areas among forest goers, requiring a focused and tailored strategy for these populations (inc. prophylaxis).

- WHO continues to support National Malaria Control Programmes to address challenges and priorities and the Mekong Malaria Elimination (MME) programme continues to support communication, partner coordination and cross-country activities.

World Health Organization

Thank you

World Health Organization

Back-up

Country	Overall			Pf+Mix		
	# of Cases 2017	# of Cases 2018	% Change	# of Cases 2017	# of Cases 2018	% Change
Cambodia	46590	66386	42%	27077	20041	-26%
Lao PDR	9327	8909	-4%	4736	4833	2%
Myanmar	85014	68752	-19%	52944	35032	-34%
Thailand	11396	6610	-42%	1413	867	-39%
Viet Nam	4542	4813	6%	2922	3040	4%

World Health Organization