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, 10–12 April 2019

Documentation related to Sessions 3 and 4

Wednesday, 10 April 2019			
	Session 3	**Open**	
14:00 – 15:15	Update on the RTS,S Malaria Vaccine Implementation Programme & framework for decision-making Background | Presentation	Dr Mary Hamel Dr David Schellenberg	**For approval**
15:15 – 16:00	Update on drug efficacy and resistance	Dr Pascal Ringwald	**For information**
16:00 – 16:30	*Coffee break*		
	Session 4	**Open**	**For guidance**
16:30 – 17:30	Update on malaria elimination in the Greater Mekong subregion	Dr Hiro Okayasu	
17:30 – 18:00	Update on the Strategic Advisory Group for malaria eradication Background | Presentation	Dr Kim Lindblade	
18:00	*End of day*		

Malaria Policy Advisory Committee Meeting

10–12 April 2019, Geneva, Switzerland
Background document for Session 3

Update on RTS,S Malaria Vaccine Implementation Programme

April 2019, Geneva, Switzerland

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 introduction of the malaria vaccine in selected areas of Ghana, Kenya and Malawi and 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 RTS,S/AS01 malaria vaccine in order to enable a WHO policy decision on the broader use of the vaccine 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 October 2018

Preparations for pilot malaria vaccine implementation in the three pilot countries (expected in late Q1/Q2) have continued at the global, regional and country levels. Key activities by national immunization programmes include the finalization of training and communications materials, adaptation of monitoring and reporting tools, and engagement and sensitization of key stakeholders at national and subnational levels. Training of health workers in the pilot areas was completed in Ghana and started in Malawi. The first vaccine doses arrived in Ghana in January and are expected to be delivered to Malawi and Kenya by the end of March.

Following the selection of evaluation partners in all countries in Q3 2018, country-specific protocols for the pilot evaluations were finalized and submitted for ethical review. Approvals were received for the Ghana-specific protocol and are expected shortly for the other two countries. All countries have successfully completed the randomized selection of areas to receive the vaccine. Sentinel hospitals (18 in total across the three countries) have been identified through country-led processes. With contracts and funding in place since late 2018, evaluation partners have progressed well in planning for and initiating surveillance system strengthening for hospital surveillance and community mortality surveillance. Ghana has initiated the baseline household survey, which it expects to complete by the end of March.

Ensuring appropriate communication about the vaccine and the Programme has continued to be a priority for country teams and partners. National communications plans, including crisis communication preparedness, have been finalized. A tabletop exercise was conducted in March to test and refine the global MVIP crisis communications plan, which complements country-specific

[1] World Health Organization. Malaria vaccine: WHO position paper – January 2016. Wkly Epidemiol Rec. 2016;91(4);33–51. http://www.who.int/wer/2016/wer9104.pdf

WHO/CDS/GMP/MPAC/2019.01

plans. This was a first-of-its-kind experience with strong participation from all levels of WHO and partners, providing useful takeaways with which to improve the plan.

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

As suggested by SAGE and MPAC, a working group with representatives from both advisory groups and other experts was established to develop a Framework for Policy Decision on RTS,S/AS01. The Framework aims to describe how and when data collected through the MVIP will be used to inform a WHO policy recommendation on the use of the vaccine beyond the pilots. The working group finalized its recommendations, and the proposed Framework has been submitted to SAGE and MPAC for review and endorsement during their meetings in April 2019. MPAC members have been invited to join (via web/teleconference) the SAGE meeting session on 3 April 2019 when the Framework will be discussed. Attendance is encouraged in order to foster exchange and alignment among SAGE and MPAC members on the expected use of MVIP data for a future policy recommendation.

In February 2019, the MVIP team submitted a proposal to the Global Fund to seek additional resources for the completion of the pilots. Current funding commitments by the Global Fund, GAVI Alliance and Unitaid will cover MVIP activities to the end of 2020.

Priorities for the next six months

Key priorities in the coming weeks and months include supporting the EPI Programmes in their final preparations for the successful introduction of the vaccine (targeted for late Q1/Q2 2019); supporting and supervising evaluation partners to ensure that hospital- and community-based surveillance systems are fit for purpose and the first household surveys are conducted as planned; coordinating and managing communication activities around the launches; and finally, continuing resource mobilization efforts for MVIP post-2020.

Contact

For more information, please contact:

Mary Hamel, MVIP lead, WHO HQ, Immunization, Vaccines & Biologicals, hamelm@who.int
David Schellenberg, Scientific Adviser, WHO HQ, Global Malaria Programme, schellenbergd@who.int

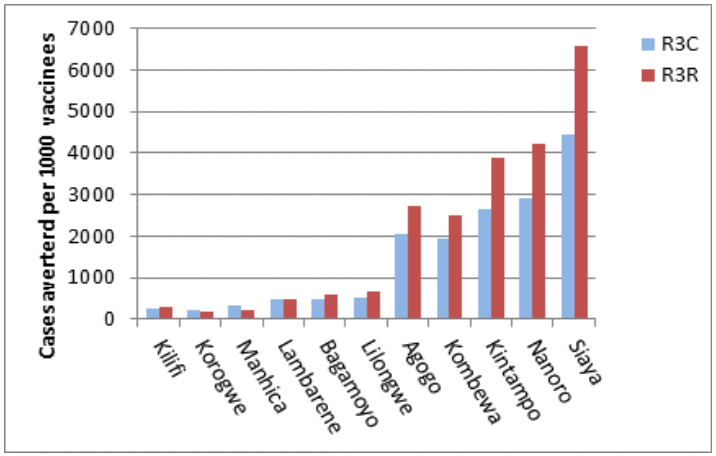
Proposed Framework for Policy Decision on RTS,S/AS01 Malaria Vaccine

Presentation to MPAC

10 Apr 2019

Results from RTS,S Phase 3 Trial, 2009-2014

- RTS,S/AS01 Phase 3 trial
  - 15,459 children, 11 sites, 7 African countries
  - 6-12 weeks or 5-17 months at first vaccination
- Children 5-17 months, 4 doses over 4 years
  - 39% reduction in clinical malaria
  - 29% reduction in severe malaria
  - **62% reduction severe malaria anaemia**
  - 29% reduction blood transfusions
- 4 doses provided optimal benefit;
  - 3 dose group had efficacy against clinical malaria, but not against severe malaria
- High impact
- Modeling: 1 life saved/200 vaccinated; highly cost-effective



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

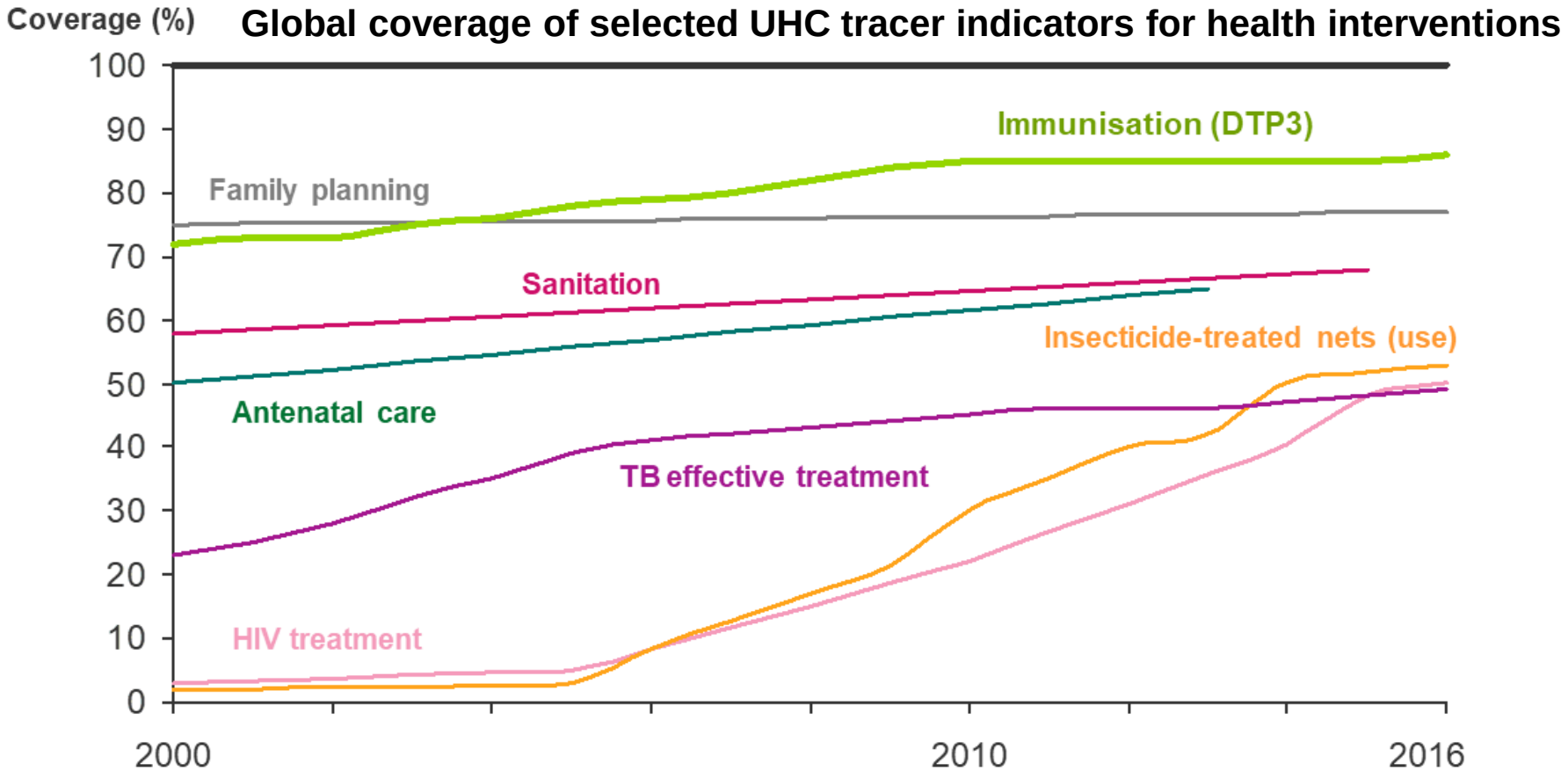
World Health Organization

Results from RTS,S Phase 3 Trial: Safety

- No vaccine-associated deaths
- Febrile convulsions, no sequellae
- Potential safety signals, with causality not established
  - In the 5-17 month age-category only
    - Imbalance in meningitis cases (10:1)
    - *Post hoc* analysis: numerically increased cerebral malaria cases (2:1, algorithmically derived)
  - In combined age-categories *post hoc* analysis: increased number of female deaths in those who received RTS,S vs. comparator vaccine 2:1
- Potential safety signals not observed in:
  - Pooled Phase II trials (n=2981)[1]
  - Large ongoing Phase 3 trial in Mali and Burkina Faso (n=4000 vaccinated children; followed for >18 months)[2]

1. Vekemans et al, Human Vaccines, 2011
2. Personal communication, Greenwood

Potential value of RTS,S/AS01: Immunization programmes tend to have higher reach than other health interventions



 Source: Graph courtesy of Gavi, based on Tracking Universal Health Coverage 2017 Global Monitoring Report

World Health Organization

WHO position & pilot implementations

- Jul 2015: EMA positive scientific opinion under Article 58
- Oct 2015: SAGE/MPAC recommended **pilot implementation** to address outstanding questions:
  - **Feasibility** of reaching children with 4 doses
  - **Safety** in the context of routine use, emphasis on meningitis and cerebral malaria
  - **Impact** on mortality (including gender specific) and severe malaria
- Apr 2017: Kenya, Malawi, Ghana selected
- May 2018: NRAs authorized malaria vaccine for use in pilot areas

The 4 components of the MVIP

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

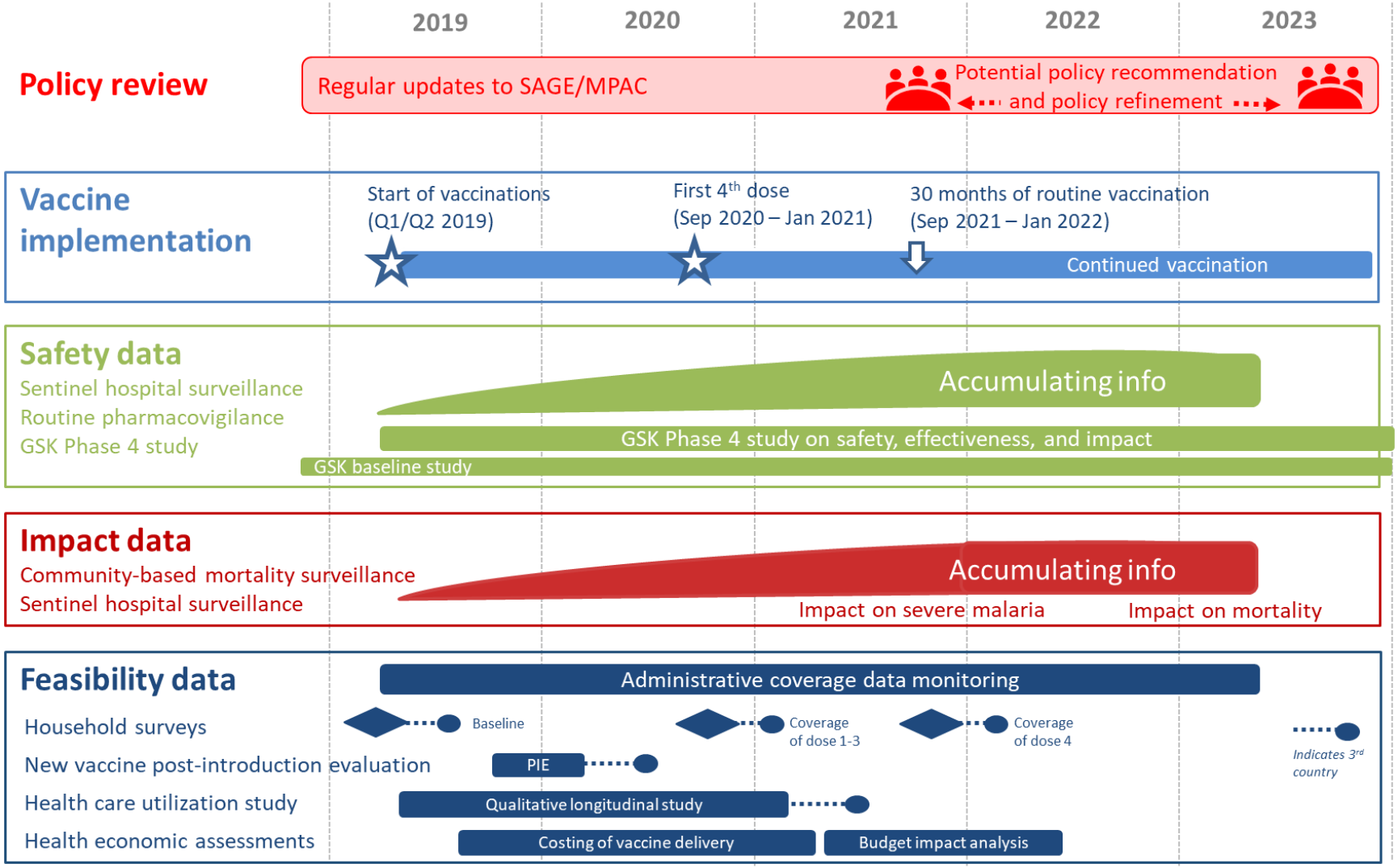
3 **Qualitative assessment (HUS) & economic analyses**

commissioned by PATH

4 **GSK Phase IV study**

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

Timeline of MVIP evidence generation and review

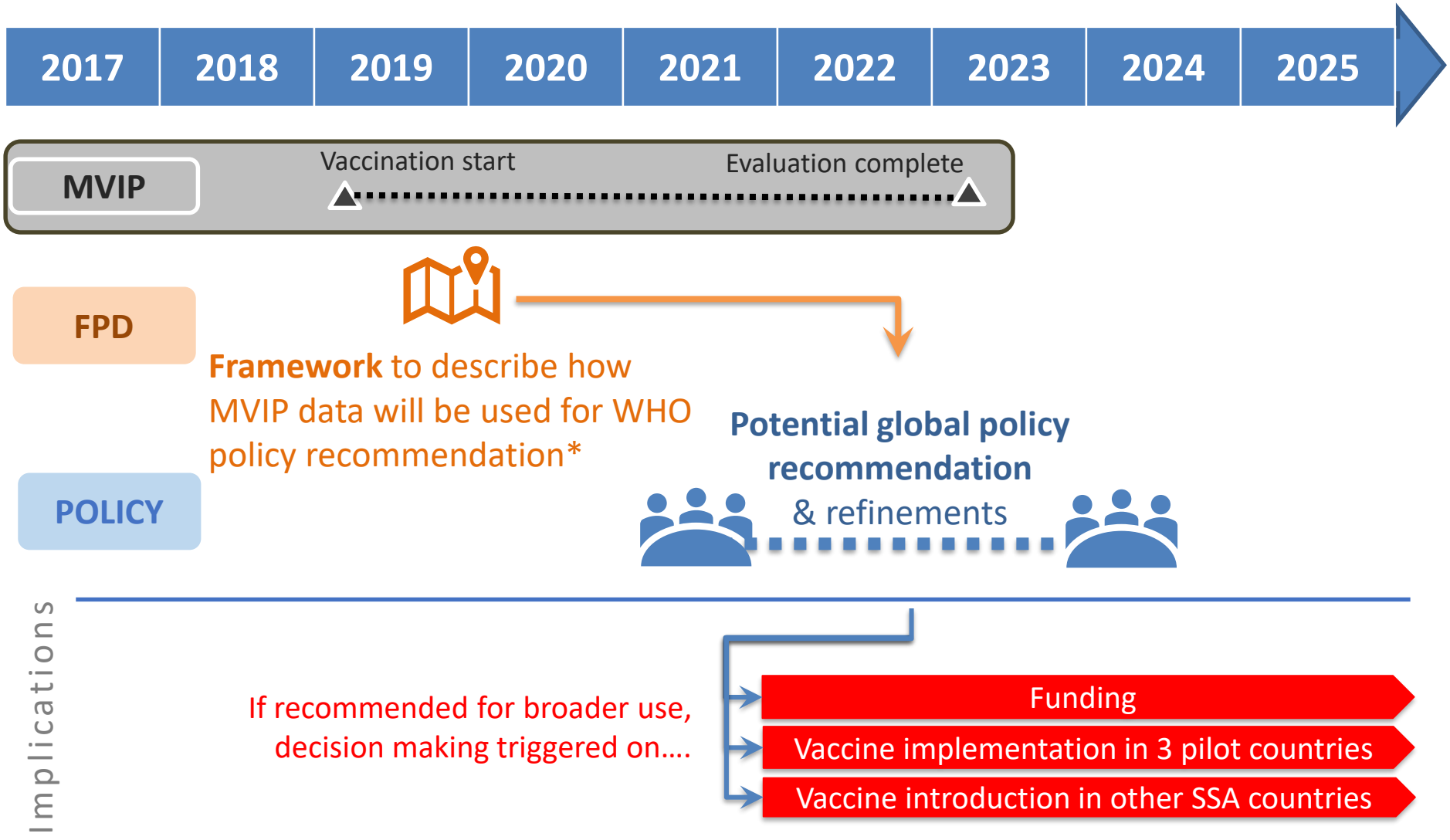


Framework for Policy Decision for RTS,S/AS01

- Framework designed to guide how data collected through the MVIP will be used to inform a WHO policy recommendation on use of the RTS,S/AS01 malaria vaccine

Framework of Policy Decision (FPD) on RTS,S/AS01 Malaria Vaccine

Potential role in context of overall MVIP timelines and policy process



*For endorsement by SAGE and MPAC

World Health Organization

Working Group membership and representation

	Working group member	Representation
1	Fred Were	SAGE
2	Terry Nolan	SAGE member until Oct 2018
3	Gabriel Carrasquilla	MPAC
4	Umberto D'Alessandro	MPAC
5	Eusebio Macete	MVIP Programme Advisory Group (PAG)
6	Kim Mulholland	MVIP Programme Advisory Group
7	Peter Smith (Chair)	MVIP Programme Advisory Group
8	Quique Bassat	IVIR-AC
9	Melissa Penny	Modelers

Informing WG discussion: reviewed data and information to develop framework

- Prior policy decisions
- Timeframe from vaccine introduction (years)
- MAL 076, long term follow up study results
  - Clinical malaria: 4 doses: 24% (95% CI:16, 31); 3 doses: 19% (95% CI: 11, 27)
  - Severe malaria: 4 doses: 37% (95% CI: 15, 53); 3 doses: 10% (95% CI: -18, 32)
  - Any rebound was time limited, few cases severe malaria after 4 years
  - No imbalance in safety signals or deaths during long term follow-up
- Updated results from mathematical models by Imperial College / SwissTPH
  - Suggest fourth dose provides minimal added benefit
  - Impact dependent on parasite prevalence, coverage with first 3 vaccine doses
  - Additional analysis of data from the Phase 3 trial (not shown)
- Timeline estimating when data on RTS,S/AS01 safety, feasibility, impact will be available based on assumptions used for statistical analysis

Expected **safety** data availability 24 months* after first pilot country begins vaccinations

1. Meningitis (assume 0.4/1000/year):
   - 80% power to rule out a 3-fold or greater increased rate of meningitis associated with introduction of RTSS vaccine
   - Phase 3 trial results: 8-fold increase
2. Cerebral malaria (assume 2/1000/year):
   - 90% power to rule out a 2-fold or greater increase in risk of cerebral malaria
   - Phase 3 trial: 2-fold increase
3. Sex-specific mortality (assume mortality rate 8.5/1000/year):
   - 90% power to exclude female:male mortality ratio being 1.2-fold higher in the RTSS arm than in the control arm
   - Phase 3 trial: 1.9-fold increase

*Timing may be updated if actual event rates deviate from assumptions

Expected **impact** data availability 24 months* after first pilot country begins vaccinations

1. Severe malaria (assume incidence rate 2/1000/year):
   - >80% power to detect a 30% reduction in severe malaria by month 24 (data for all sentinel hospitals, all countries combined)
   - Phase 3 trial results: 29% reduction over 48 months with 4 dose schedule
2. Mortality (assume mortality rate 8.5/1000/year):
   - >80% power to detect a reduction in mortality by month 24 if the true reduction is 10%, (for all analyses, data for all countries combined)
   - Phase 3 trial results: no reduction/ not designed to measure impact on mortality

*Timing may be updated if actual event rates deviate from assumptions

Recommendations of the SAGE/MPAC Working Group (WG) on the Framework for Policy Decision on RTS,S/AS01

Umberto D'Alessandro

Working Group Member

Working Group approach – hierarchy of data

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

Working Group approach – thought experiment

- Data on RTS,S/AS01, including Phase 3 trial results, were assessed by the EMA in 2015 and vaccine was given a "positive scientific opinion"
- Safety signals from Phase 3 trial were extensively discussed by SAGE/MPAC. It is possible that the SAGE/MPAC would have recommended the vaccine in 2016 had it not been for these signals
- WG took position that if data accumulate in MVIP to provide reassurance the safety signals observed in Phase 3 trial were likely due to chance, and impact on severe malaria or impact on mortality data trends were assessed as consistent with a beneficial impact of the vaccine-- it might be possible to make an initial recommendation for broader use before end of the MVIP
- Option would remain to refine the policy recommendation, if appropriate, when the full MVIP data set becomes available
- This strategy could accelerate the availability of a potentially life-saving vaccine

Recommendation 1: **SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging pilot data**

1

Step 1: Recommendation on use of RTS,S/AS01 beyond pilot countries could be made if:

i. concerns regarding **safety signals** observed in Phase 3 trial (meningitis, cerebral malaria and sex-specific mortality) are satisfactorily resolved, by demonstrating either the absence of a risk of an important size, or an assessment of a positive risk-benefit profile despite adverse event(s); and

ii. severe malaria trends are assessed as consistent with a beneficial impact; or

iii. mortality data trends are assessed as consistent with beneficial impact

Based on current assumptions related to vaccine introduction timings and expected rate of accumulating events, such data on safety and impact would be available approximately 24 months after RTS,S/AS01 introduction.*

*Timing may be updated if actual event rates deviate from assumptions

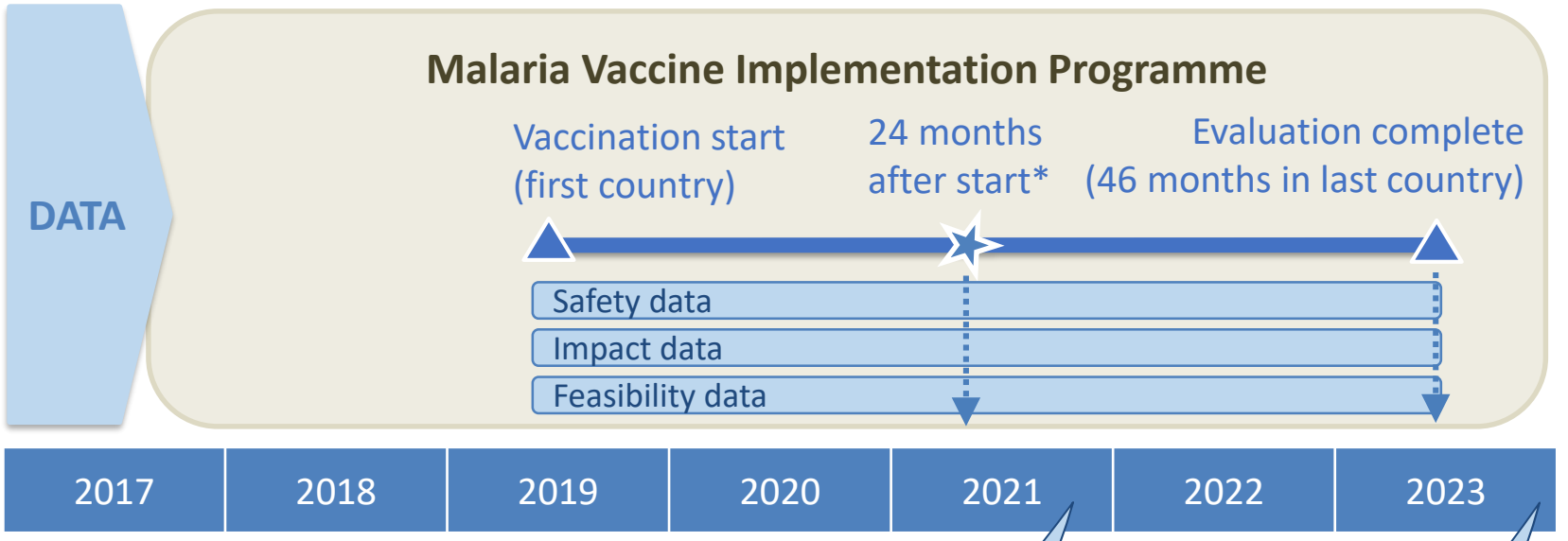
Recommendation 1: **SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging pilot data**

2

Step 2: Adjustments or refinements to policy recommendation for broader use of RTS,S/AS01 based on final MVIP data set, with particular focus on the value of fourth dose

Available approximately 50 months after start of vaccination in 3rd country

Proposed step-wise approach to policy recommendation



*Timing may be updated if actual event rates deviate from assumptions

World Health Organization

Rationale for step-wise approach

- A decision on the broader use of a potentially life-saving vaccine beyond the pilot countries should be made at earliest possible timepoint when robust evidence is available to ascertain a positive risk-benefit profile of the vaccine
- Framework for Policy Decision seeks to reduce some uncertainty around the timing of a policy recommendation, which will facilitate advanced planning for potential outcomes, including:
  - An advanced signal to the manufacturer, that may be needed to maintain vaccine production and increase the likelihood of uninterrupted supply
  - A trigger for financing mechanisms to be in place should there be a recommendation for broader use of RTS,S/AS01

Recommendation 2: **There is a need to resolve safety concerns on meningitis, cerebral malaria, and sex-specific mortality to establish the risk-benefit profile of the vaccine, as reassuring safety data are required for a policy recommendation.**

- **Mechanism to resolve safety concerns:**
  - Data from sentinel hospitals in MVIP
  - GSK Phase 4 study (set up following EMA favourable assessment)
  - Routine pharmacovigilance reporting of AEFI and pre-specified AESI
  - All subject to ongoing review by DSMB
- **Estimated data availability:**
  - Assuming no true excess risk of meningitis, cerebral malaria or female mortality, relative risks of specified magnitude could be ruled out approximately 24 months after vaccine introduction
- **Other considerations:**
  - If any excess risks observed, risk-benefit assessments necessary
  - Benchmarking against other vaccines with known risks (e.g. rotavirus vaccine risk of intussusception) would be useful

Recommendation 3: **The policy recommendation for broader use could be made in the absence of data showing vaccine impact on mortality.** Impact on severe malaria is an acceptable surrogate indicator for impact on mortality, and could support a policy recommendation if assessed as consistent with a beneficial impact.

- WG recommendations on impact on severe malaria and mortality align with MPAC recommendations made in Oct 2018, based on MAL 076
  - Concern regarding a potential excess risk of severe malaria in long-term follow-up of children who miss 4th dose has been reduced
- **Estimated data availability:** Data on the impact on severe malaria may be available approximately 24 months after vaccine introduction
  - Unlikely that a 10% country-specific impact on mortality demonstrable before pilot evaluations end
- **Policy precedence:** SAGE has not required demonstration of mortality impact for other vaccines prior to making initial recommendation for vaccine use. Data on mortality impact have resulted in modifications of recommendations.
- **Other considerations:** Impact of vaccine on severe malaria would not necessarily be the same in programmatic implementation as in the Phase 3 trial

Recommendation 4: **A policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose)**.

- MAL-076 long-term follow up data indicate
  - rebound in severe malaria among children who received only 3 doses of RTS,S/AS01 was time limited
  - absence of rebound after 4th dose
- **Policy precedence:**
  - Implementation data are rarely available at time of initial vaccine policy recommendation, rather findings from post-marketing studies are incorporated later
- Target threshold for vaccine coverage (incl. 4th dose) should not be defined to inform a policy decision.
  - Vaccine coverage attained, and methods used to increase coverage, can be used to guide future strategies for improved vaccine implementation

Recommendation 5: **Barring substantial adverse impact on coverage of other vaccines or malaria control interventions, effect of RTS,S/AS01 introduction on coverage of these interventions should not influence policy recommendation.** Rather these indicators should inform strategies for implementation, including areas to call attention or provide opportunities for improvement.

- RTS,S/AS01 is proposed as complementary to other malaria interventions
- RTS,S/AS01 immunization regimen provides new contacts for children in 2YOL*, providing opportunities to increase coverage of other childhood vaccines and enhance delivery of other malaria interventions
- MVIP includes interviews of parents and health workers to understand the obstacles and opportunities for vaccine delivery
- Reduction in health intervention uptake, coverage or use associated with vaccine introduction could be addressed with targeted action and/or messaging

*2YOL=second year of life

Recommendation 6: **Cost-effectiveness estimates should be regularly refined, as data become available for increasingly precise calculations, and presented at appropriate time points.**

- Cost-effectiveness of RTS,S/AS01 was assessed as favourable compared to that of several other vaccines
  - RTS,S/AS01 is expected to be highly cost-effective in moderate to high malaria transmission settings alongside other malaria interventions
- **Policy precedence:** Cost-effectiveness is rarely incorporated into an initial vaccine policy recommendation for broader use
- Need to validate and/or update existing modelled estimates on public health impact and cost-effectiveness
- Cost-effectiveness estimates for SAGE/MPAC should be refined as more data become available from MVIP

Recommendation 7: **Expansion within MVIP countries should be synchronized with recommendation for broader use across sub-Saharan Africa.**

- In MVIP, vaccine deployment for 30 months (minimum):
  - MVIP countries could decide **to continue vaccinations**, as any pause is detrimental to programme operations and community mobilization
  - **Vaccination in comparison areas** advised by the WHO Ethics Committee
- There should be regular SAGE/MPAC briefings on plans for vaccine expansion
- Provided there is sufficient vaccine supply, NRAs are in agreement, and a positive risk/benefit profile is maintained, vaccine should not be withheld from comparison areas until after MVIP end
- Important to address risk of vaccination interruption in advance, due to time required for decision making, financing, vaccine availability, and implementation planning
  - Creative mechanisms should be considered to ensure supply and funding are available

Recommendation 8: **In the context of step-wise approach to policy recommendations, the pilots should continue through to completion of data collection to establish the public health value of the fourth dose, including assessment of the vaccine's impact on mortality.**

- The MVIP should continue to generate data through end of evaluation (expected to be 46 months in each country)
  - Regardless of whether an earlier policy recommendation is provided (barring a safety concern resulting in stopping MVIP)
- If it is found upon completion of the Programme that the 4th dose provides little incremental benefit, the initial recommendation could be modified (e.g. to a 3-dose regimen)

Recommendation 9: **Conflicting data among MVIP countries would require careful investigation into the reasons for differences.** Continue forward with plans for analysis even if data are delayed or not available in all countries.

Recommendation 10: **Criteria are suggested that could result in WHO not making a recommendation for use of vaccine in routine immunization programmes or deferring a policy decision to a later time point.**

- To *not make a recommendation* if:
  - there is a clear safety risk (e.g. an excess of meningitis among those vaccinated) assessed to be unfavourable in context of risk-benefit profile, or
  - there is something in the risk-benefit profile that could critically undermine the confidence and trust in national immunization programmes
- To *defer a decision* to the end of the pilot evaluations if:
  - there is significant uncertainty about safety issues (meningitis, cerebral malaria, sex-specific mortality), or
  - much less than expected impact on hospitalized malaria

Conclusion

- Value of Framework as future reference depends on joint support from SAGE/MPAC
  - SAGE endorsed the Framework on 3-Apr; SAGE chair and SAGE Working Group members invited to join MPAC session today
  - MPAC requested to consider formal endorsement of Framework in its closed session
- SAGE/MPAC endorsement of the proposed Framework would imply
  - Once data described for step 1 is available, SAGE/MPAC would be requested to consider a policy recommendation for broader use of RTS,S/AS01 in sub-Saharan Africa
  - Regular update on MVIP progress will continue to be provided
  - Regional and country consultation in lead up to policy decision

Thank you

World Health Organization

Expert review: Treatment assignment *per* study period for all "Confirmed" cases of cerebral malaria (n=23)

Study period (Month)	R3R+R3C	R3R	R3C	C3C
M0-20	--	2	6	4
M21-SE	--	3	6	2

23/340 (6.8%) cases where at least one expert felt that it was a case of cerebral malaria (*i.e.* the **18** cases where both experts agreed/assessed as "Confirmed" plus **5** cases where there was disagreement but at least one assessor felt that it was a case of cerebral malaria).

Expert Review: Treatment assignment *per* study period for all "Possible" cases of cerebral malaria (*i.e.* n=37)

Study period (Month)	R3R+R3C	R3R	R3C	C3C
M0-20	--	3	10	7
M21-SE	--	7	8	2

37/340 (10.9%) cases where either both experts agreed that they were cases of cerebral malaria (*n=18*) **<u>or</u>** both experts were uncertain/could not rule-out whether it was a case of cerebral malaria or not (*n=13*) **or** both experts disagreed but at least one expert felt that it was a case of cerebral malaria or was uncertain/could not rule it out (*n=6*).

Imbalance in 3 and 4 dose group prior to 4th dose provided

Source: JTEG Background paper (Sept 2015)

Serious Adverse Events: Meningitis 5-17 Months Group

5-17 month age group	4 dose schedule N=2976		3-dose schedule N=2972		Controls N=2974	
	n	%	n	%	n	%
At least one SAE	**720**	24.2	**752**	25.3	**846**	28.4
At lease one SAE excluding malaria	**673**	22.6	**704**	23.7	**784**	26.4
Fatal SAE	**61**	2.0	**51**	1.7	**46**	1.5
At least one related SAE	**8**	0.3	**4**	0.1	**1**	0.0
Meningitis (any pathogen)	**11**	0.4	**10**	0.3	**1**	0.0

Low number of meningitis cases in control arm of 5-17 month olds age-category

Models indicate RTS,S is cost-effectiveness

- At **a hypothetical** vaccine price of $5 a dose median incremental vaccine cost effectiveness ratio is
  - **$87 (range $48-$244) per DALY averted**
  - $25 ($16-$222) per clinical case averted.
- **RTS,S compares favourably relative to global cost effectiveness estimates of several other vaccines.**

Penny MA et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. 2015, Lancet, Vol. 15, pp. 0140-6736

RTS,S schedule

WHO position : A 4-dose schedule is required, with the first dose given as soon as possible after 5 months of age, doses 2 and 3 given at monthly intervals, and the fourth dose given 15–18 months after the third dose .

Example: Ghana vaccination schedule

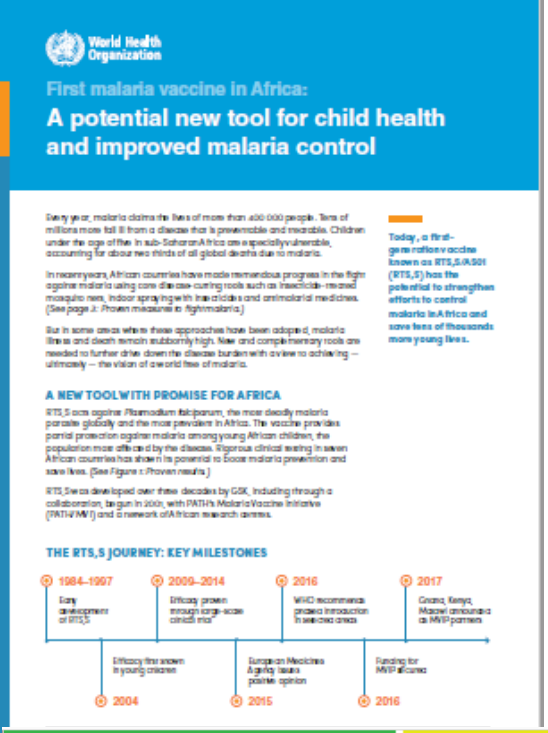
Age / Vaccine	Birth	6 weeks	10 weeks	14 weeks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22mo	24 mo
BCG	X											
OPV	X											
DPT-HepB-Hib (penta)		X	X	X								
PCV		X	X	X								
Rota		X	X									
IPV				X								
MenA										X		
MR								X		X		
YF								X				
RTS,S Ghana						X	X	X				X
RTS,S Kenya						X	X	X				X
RTS,S Malawi					X	X	X				X	
VitA						X			X	X		X

Programme Advisory Group members

Nick Andrews	Statistics, vaccine safety, GACVS
Dominique A. Caugant	Meningitis, vaccine impact evaluation
Corine Karema	Malaria in Africa, programme implementation, impact evaluation
Eusebio Macete	Clinical trials of RTS,S and other malaria control interventions, child health
Kim Mulholland	Vaccine evaluation, child health, meningitis
Graham Brown	Malaria research, Immunology, vaccines, MPAC
Adelaide Eleanor Shearley	Immunization programme management, child health, IPAC
Peter Smith	Implementation research, epidemiology, statistics
Fredrick Were	Vaccine and immunization research, child health, SAGE

DSMB members

Alex Dodoo	Pharmacovigilance, GACVS, Malaria
Cynthia Whitney	Epidemiology, Meningitis,
Esperança Sevene	Pharmacovigilance, Regional PV systems
Kate O'Brien	Epidemiology, SAGE, Meningitis, Vaccine Safety
Charles Newton	Paediatric neurology, Epidemiology, Cerebral Malaria, Meningitis
Larry Moulton	Statistics, Epidemiology
Jane Achan	Epidemiology, Child health, Malaria


World Health Organization

First malaria vaccine in Africa:

A potential new tool for child health and improved malaria control

Every year, malaria claims the lives of more than 400 000 people. Tens of millions more fall ill from a disease that is preventable and treatable. Children under the age of five in sub-Saharan Africa are especially vulnerable, accounting for about two thirds of all global deaths due to malaria.

In recent years, African countries have made tremendous progress in the fight against malaria using core disease-curbing tools such as insecticide-treated mosquito nets, indoor spraying with insecticides and antimalarial medicines. (See page 3: Proven measures in fight against malaria.)

But in some areas where these approaches have been adopted, malaria illness and death remain stubbornly high. New and complementary tools are needed to further drive down the disease burden with a view to achieving – ultimately – the vision of a world free of malaria.

Today, a first-generation vaccine known as RTS,S/AS01 (RTS,S) has the potential to strengthen efforts to control malaria in Africa and save tens of thousands more young lives.

A NEW TOOL WITH PROMISE FOR AFRICA

RTS,S acts against Plasmodium falciparum, the most deadly malaria parasite globally and the most prevalent in Africa. The vaccine provides partial protection against malaria among young African children, the population most affected by the disease. Rigorous clinical testing in seven African countries has shown its potential to boost malaria prevention and save lives. (See Figure 1: Proven results.)

RTS,S was developed over three decades by GSK, including through a collaboration, begun in 2001, with PATH's Malaria Vaccine Initiative (PATH MVI) and a network of African research centres.

THE RTS,S JOURNEY: KEY MILESTONES

1984–1997 Early development of RTS,S

2004 Efficacy first shown in young children

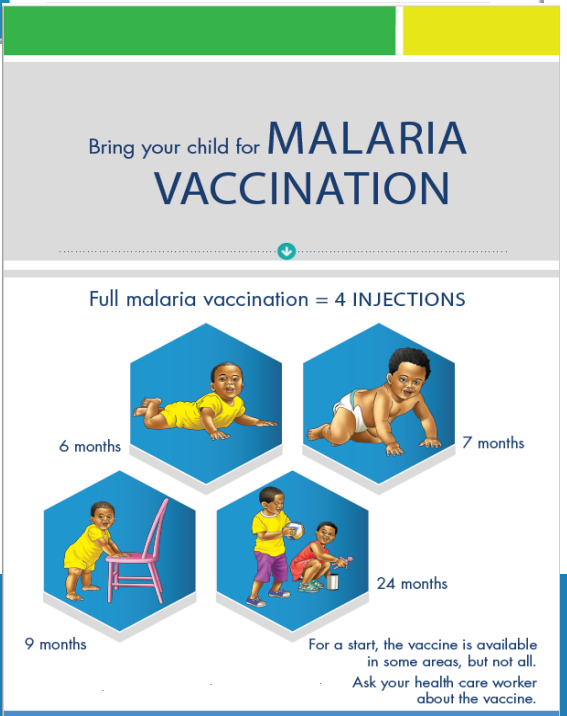
2009–2014 Efficacy proven through large-scale clinical trials

2015 European Medicines Agency issues positive opinion

2016 WHO recommends phased introduction in selected areas

2016 Funding for MVIP scale-up

2017 Ghana, Kenya, Malawi announced as MVIP partners



Status: Global, regional, country communications

- General information about the MVIP on the WHO website
- Brochure on the MVIP
- FAQ about the MVIP
- FAQ about the RTS,S/AS01 Phase 3 trial results

Global and country level

- Crisis communication plan, table top exercise
- Launch plans, media engagement, spokesperson training
- Country level engagement with policy makers, including parliamentarian, opinion leaders, religious and community leaders, medical community
- Information, Education and Communication materials and training materials

World Health Organization

Informing WG discussion: reviewed data and information to develop framework

- Existing data and information
  - Results from Phase 3 trial
  - JTEG report, SAGE/MPAC recommendation and WHO position paper
  - Prior vaccine policy decisions: Rotavirus, pneumococcal conjugate, and dengue vaccines case studies
  - Prior malaria intervention policy decisions: Insecticide treated nets (ITN), Intermittent preventive treatment in infants (IPTi)/pregnancy (IPTp)

New data reviewed by the Working Group Mal 076, Long term follow-up

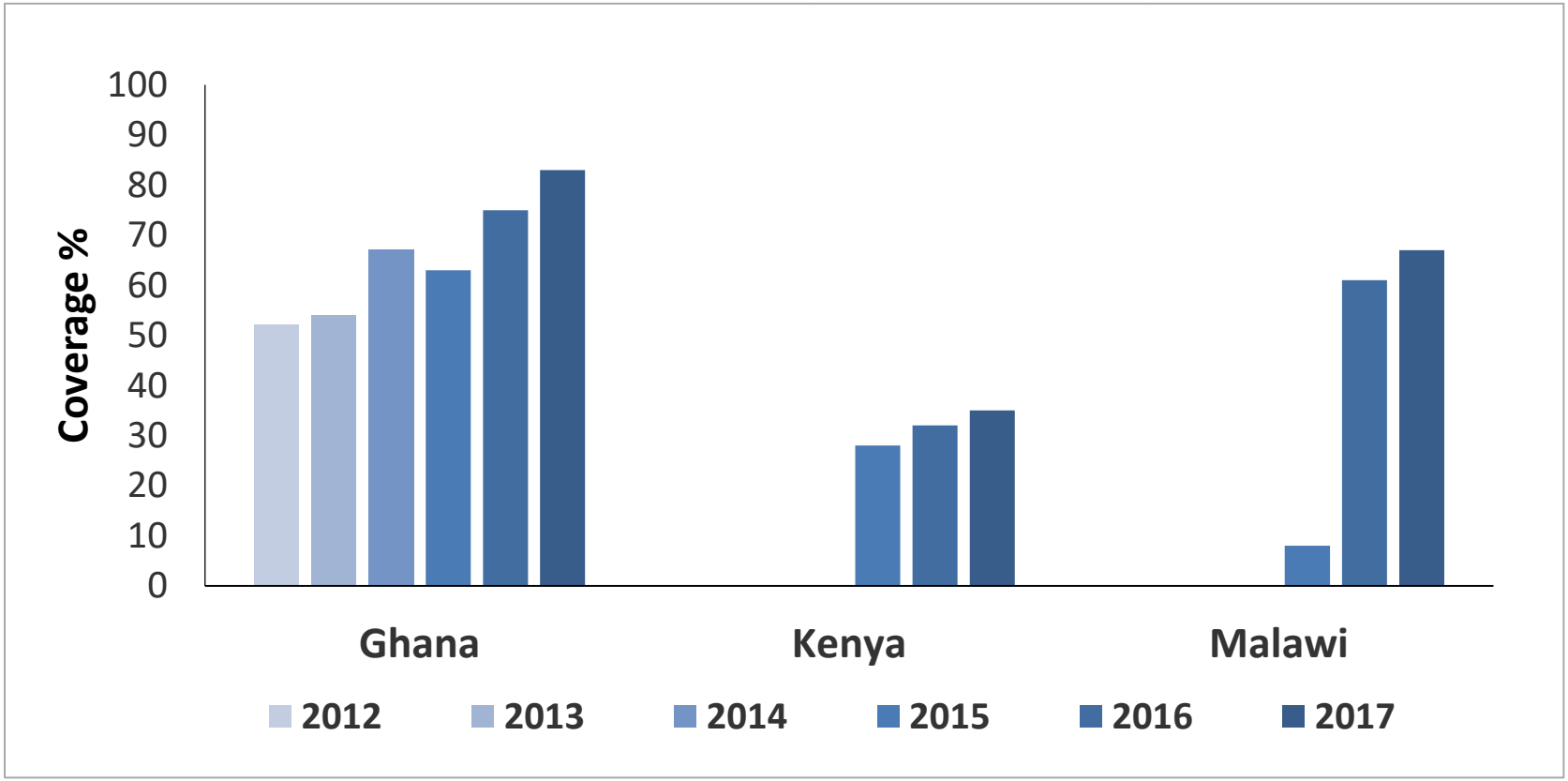
- Additional 3 years at 3/11 Phase 3 sites* (7 years total)
- Open label
- Data collection: mix of retrospective and prospective
- Overall vaccine efficacy during 7 year follow-up
  - Clinical malaria: 4 doses: 24% (95% CI:16, 31); 3 doses: 19% (95% CI: 11, 27)
  - Severe malaria: 4 doses: 37% (95% CI: 15, 53); 3 doses: 10% (95% CI: -18, 32)
- No excess cases of severe malaria (rebound) in any group
  - Any rebound in severe malaria that may have occurred in 3-dose group was time-limited
  - No rebound after 4th dose
- Very few severe malaria cases after 4 years follow-up in any arm
- No imbalance in safety signals or deaths during long term follow-up

 *Korogwe (Tanzania), Kombewa (Kenya), Nanoro (Burkina Faso)

Operational feasibility:

Expected new vaccine coverage & trajectory over time

MCV2 WHO/UNICEF estimated coverage* in Ghana, Kenya and Malawi, 2012-2017



*according to WHO/UNICEF coverage estimates, as of 15 July 2018

Situation of antimalarial drug efficacy and resistance: focus on special cases

P. Ringwald
Drug Efficacy and Response Unit

Global **Malaria** Programme

World Health Organization

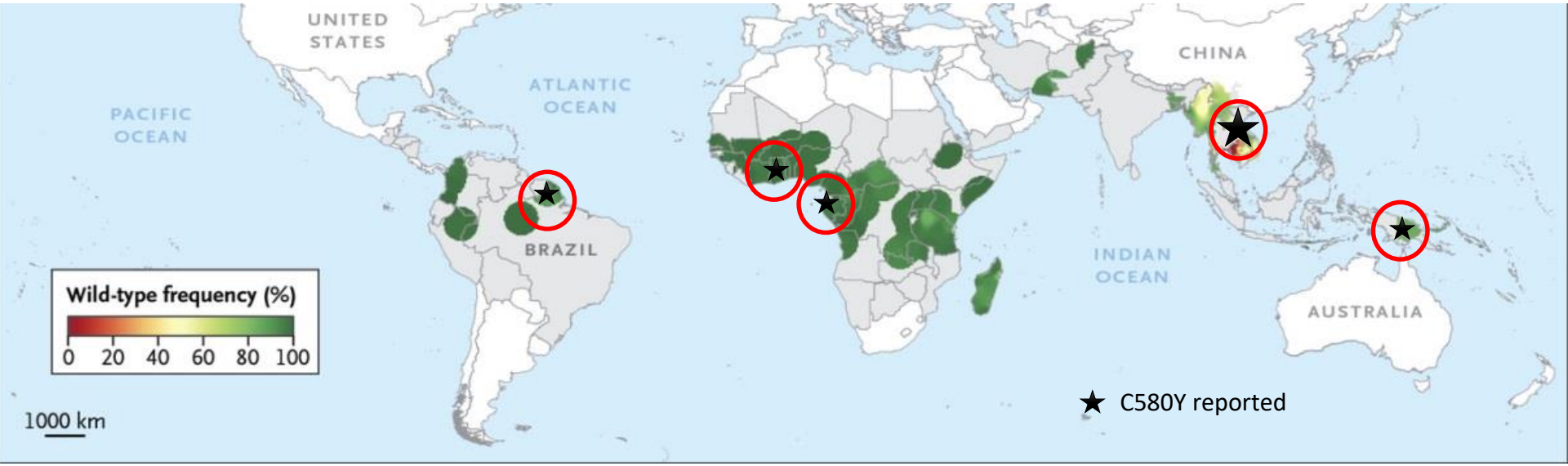
Outline

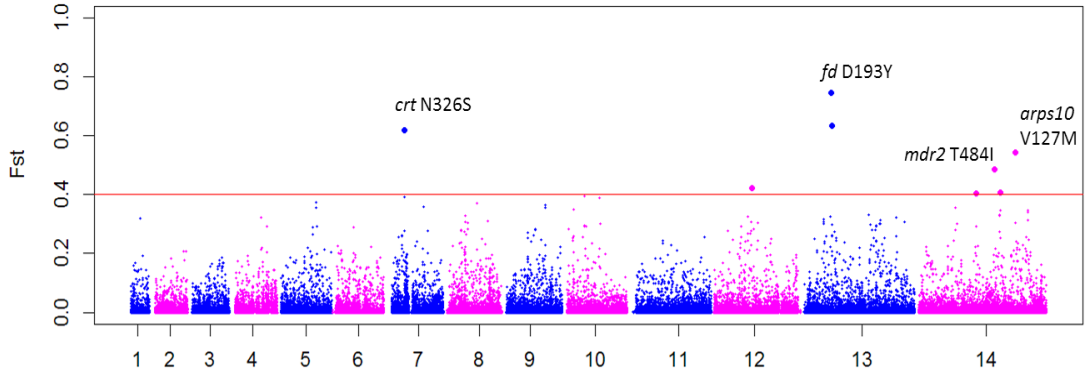
- **Definitions**
- **Artemisinin partial resistance(s)**
- **Case reports**
- **Piperaquine resistance in Africa**
- **Advice on data sharing, methods to assess origin of parasites and QC of circulating DHAPIP**

Definitions

- ***Antimalarial resistance*** is defined as 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)** is resistance to more than 2 antimalarial compounds of different chemical classes. This term usually refers to *P. falciparum* resistance to chloroquine, sulfadoxine-pyrimethamine, and a third antimalarial compound;
- ***Artemisinin resistance*** is defined as delayed parasite clearance following treatment with an artesunate monotherapy or with an ACT – partial resistance would be more appropriate wording;

Distribution of C580Y mutations worldwide





Possible “permissive” or compensatory background mutations

Miotto *et al.*, *Nature Genetics* 2015

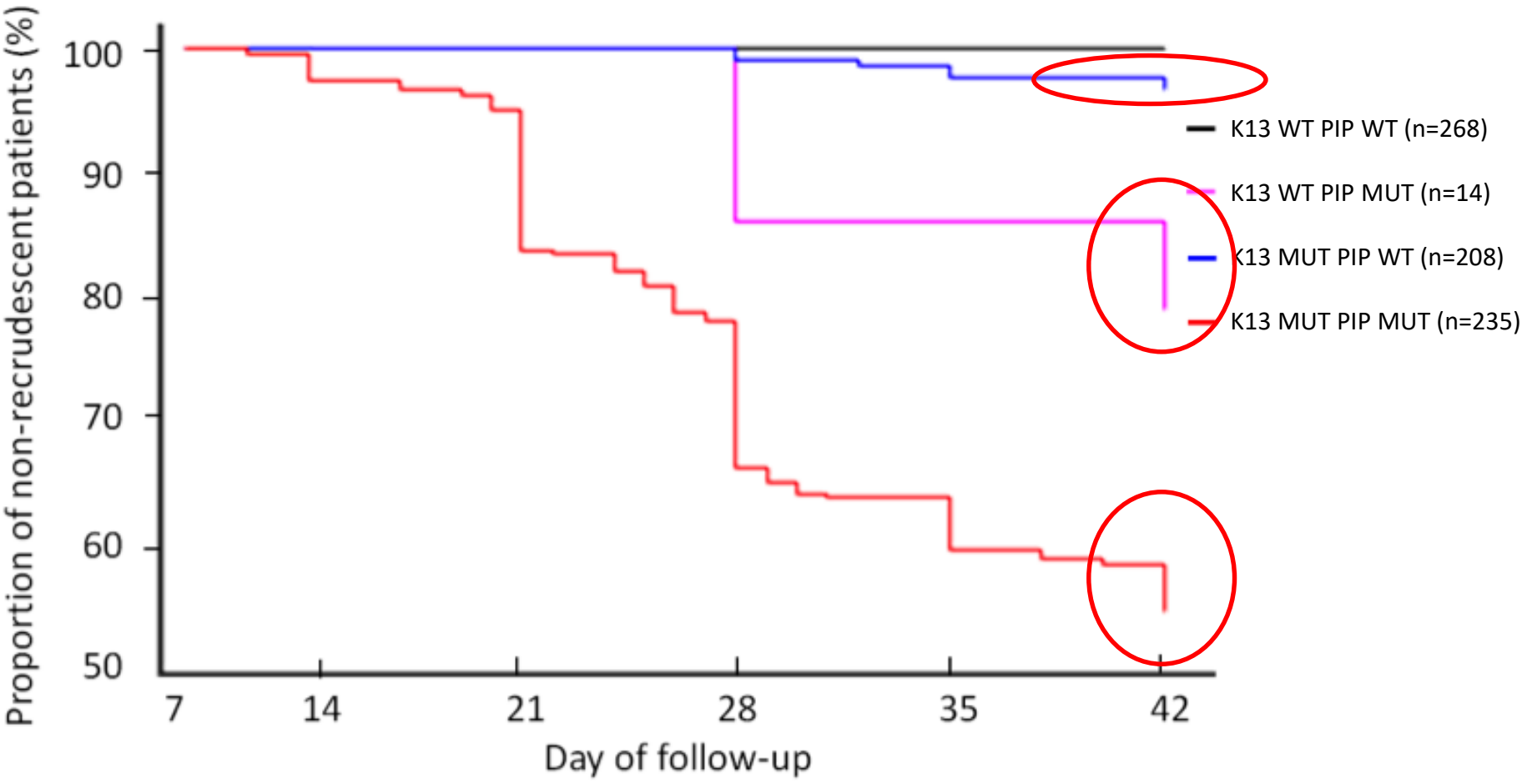
Relation between partner drug efficacy and K13 mutations

Year	Site	ACT	N	Efficacy 28/42 days (%)	K13 mutant (%)
2016	Kampong Speu, Kratie	Artesunate-mefloquine	69	100	95.6 (C580Y)
2017	Kampong Speu, Pursat, Stungtreng	Artesunate-mefloquine	170	99.5	78.2 (C580Y, R539T, Y493H)
2017	Ratanakiri, Mondulkiri	Artesunate-pyronaridine	123	97.6	72.4 (C580Y)
2017	Kachin, N. Shan	Artemether-lumefantrine	71	97.2	43.7 (F446I, R561H)

Even if delayed clearance doesn't directly lead to treatment failure, it puts more pressure on partner drugs to succeed in mopping up lingering parasites, says Nicholas White, a professor of tropical medicine at Mahidol University and the University of Oxford.

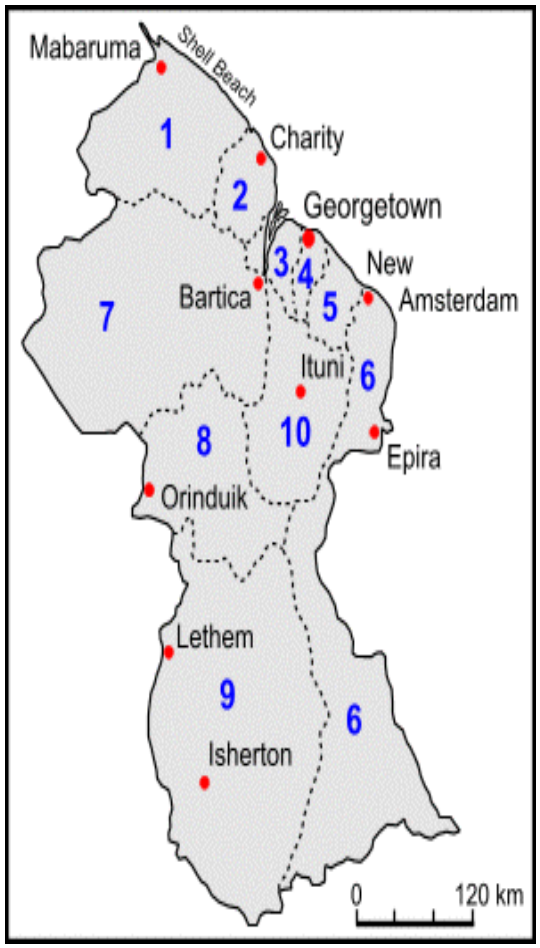
Are We Headed for a New Era of Malaria Drug Resistance?
https://www.the-scientist.com/features/are-we-headed-for-a-new-era-of-malaria-drug-resistance--65496

Role of each markers in DHA-PIP efficacy in Cambodia (N = 725)



Witkowski et al., *Lancet Inf. Disease* 2016

Artemisinin partial resistance : Guyana



Articles:

- Chenet SM et al. Independent Emergence of the *Plasmodium falciparum* Kelch Propeller Domain Mutant Allele C580Y in Guyana. J Infect Dis. 2016, May;2013(9):1472-5.
- Chenet SM et. Molecular Profile of Malaria Drug Resistance Markers of Plasmodium falciparum in Suriname. Antimicrob Agents Chemother. 2017 Jun 27;61(7).
- Rahman R et al. Continued Sensitivity of *Plasmodium falciparum* to Artemisinin in Guyana, With Absence of Kelch Propeller Domain Mutant Alleles. Open Forum Infect Dis. 2016 Aug 30;3(3).

Summary:

- Samples collected in 2010 for *Pfhrp2* survey;
- 5/98 samples carried the mutant C580Y (4/5 from zone 7 and 1/5 zone 1).
- All five samples had similar *Pfkelch 13* flanking microsatellite profiles and were different to the ones observed in Southeast Asia;

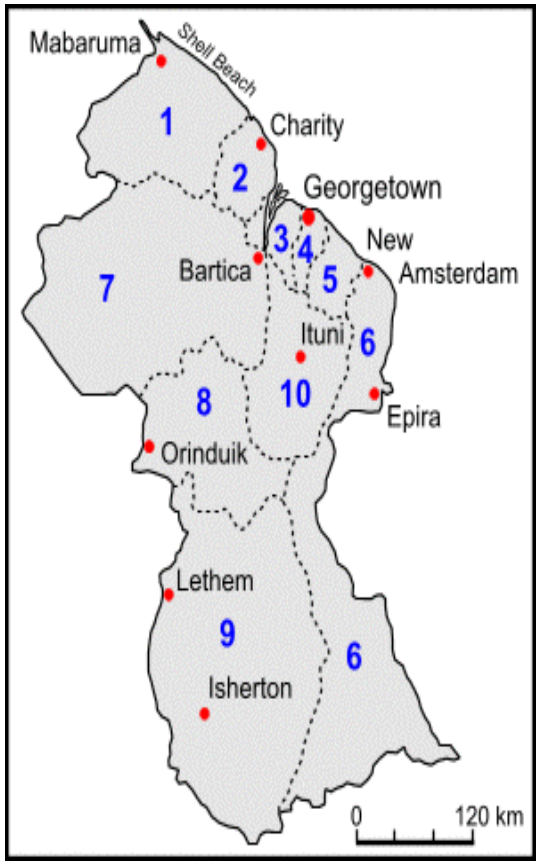
Artemisinin partial resistance: Guyana

Actions taken:

- TES between June-Nov 2014:
  - 7-day artesunate trial (4 mg/kg/day) + primaquine single dose;
  - n = 50 (26% from zone 1; 54% zone 7; 16% zone 8);
  - day3+ rate = 2%; 100% efficacy and 100% *Pfkelch 13* wild type.

- Survey conducted between 2016-2017 whole country (n = 877)
  - presence of C580Y mainly in zone 1;
  - declining trend over time.

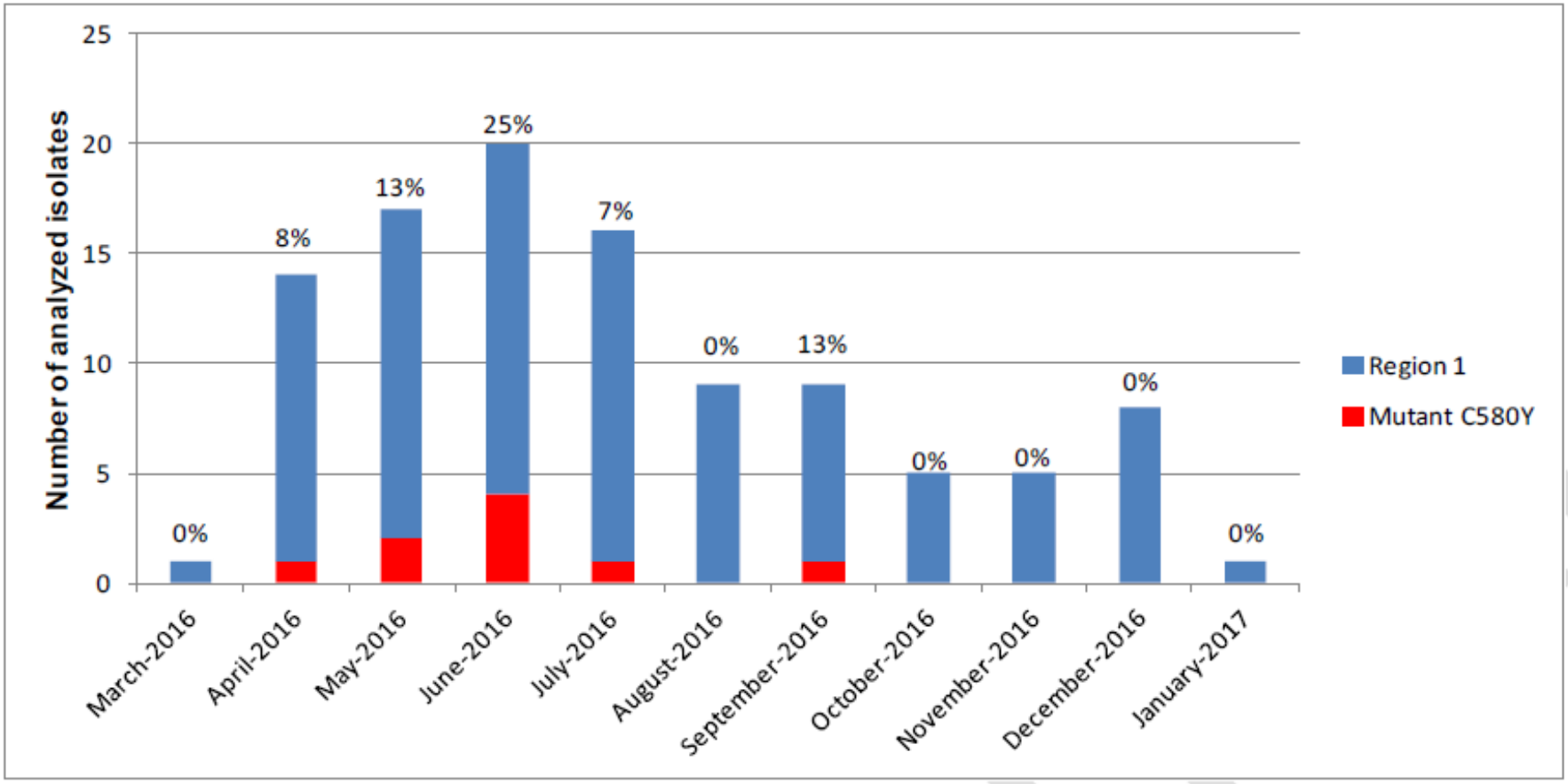
Artemisinin partial resistance: Guyana



	N	C580Y	% mutant
Region 1	114	10	**8.8**
Region 2	2	0	0
Region 3	10	0	0
Region 7	572	3	**0.5**
Region 8	150	1	**0.7**
Region 9	4	0	0
Region 10	2	0	0
Venezuela	21	0	0
Unspecified	2	0	0
Total	**877**	**14**	**1.6**

Prevalence of *Pfkelch13* C580Y by region in Guyana

Artemisinin partial resistance: Guyana



Trend over time of *PfKelch 13* C580Y in Guyana

Artemisinin partial resistance: Guyana

Actions taken cont'd:

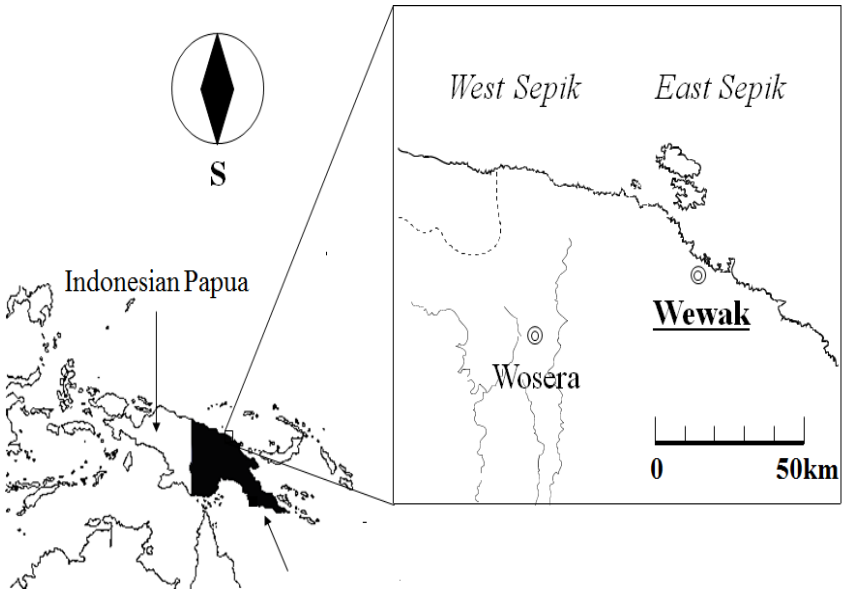
- To understand origin of those mutants:
  - nine microsatellite loci flanking the *Pfkelch 13* gene, whole genome sequencing (WGS) and selective whole genome amplification (SWGA) were performed;
  - confirm that the *Pfkelch 13* C580Y variant arose on a single Guyanese haplotypic background, and was not imported from South-East Asia.

- TES in June-Oct 2018 in Georgetown and zone 1:
  - Georgetown: completed (n = 84); microscopy QC needed; *Pfkelch 13* absent in Georgetown (n = 99);
  - Zone 1: on-going.

Artemisinin partial resistance: Papua New Guinea

Articles:

- Sekihara et. Al. Emergence of *Plasmodium falciparum* parasites with *K13* mutant allele C580Y in Papua New Guinea. Submitted.
- Prosser C et al. Resistance screening and trend analysis of imported falciparum malaria in NSW, Australia (2010 to 2016). PLoS One. 2018, 13:e0197369.



Summary:

- Sampling periods: 11-30 January 2016 (n = 112) and 23 January-11 February 2017 (n = 132);
- Symptomatic patients > 2 years with *P. falciparum* confirmed by RDT or microscopy;
- In 2017, 3/132 patients carried C580Y vs 0/112 in 2016;

Artemisinin partial resistance: India

Articles:

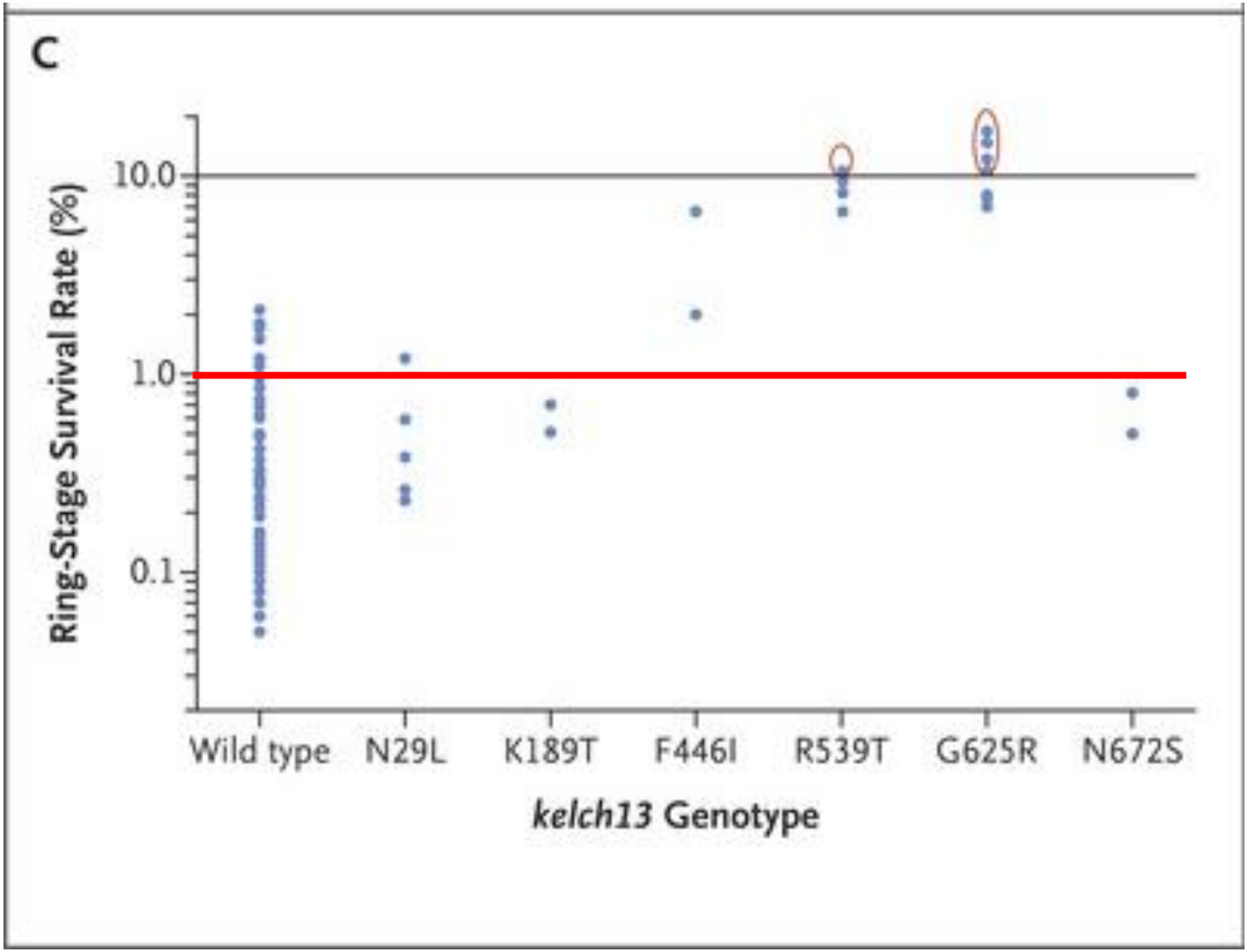
- Das S et. Al. Evidence of Artemisinin-Resistant *Plasmodium falciparum* Malaria in Eastern India. N Engl J Med. 2018 Nov 15;379(20):1962-1964.

- Das S et. Novel pfkelch13 gene polymorphism associates with artemisinin resistance in eastern India. Clin Infect Dis. 2019 in press.

Summary:

- TES in West Bengal (4 sites) between **2014-2016**, n = 226;
- ASSP failure rate = 15.9% (7.9% ETF) and all treatment failures cured with AL;
- Parasite clearance time > 5.0 h = 11.9%; based on the analysis of *Pfkelch 13* and *pfmdr1* 184F + 1042D which role is unclear;
- *Pfkelch 13* F446I (n = 2), R539T (n = 7), G625R (n = 21), and N672S (n = 4) were identifdied in 34/226 (15%) isolates;
- Among 7 patients with R539T allele, 5 patients were working in Cambodia during the past 15 days.

Artemisinin partial resistance: India



Das S et. Al. N Engl J Med. 2018

Artemisinin partial resistance: India

Comments:

Several issues challenge the conclusion:

- Inadequate definitions used:
  - ETF ≠ artemisinin resistance; extremely high parasitemia at day 3;
  - confusion between candidate/validated *Pfkelch 13* mutant and suspected/confirmed artemisinin resistance;
  - in vitro threshold (1% not 10%);
  - parasite clearance half-life threshold (5.5 h not 5.0 h);
- G625R is neither validated nor a candidate marker for artemisinin partial resistance; only reported once in Gabon;
- Data contrast with other available data: ASSP efficacy between 2010-2017 (n = 52) is on average 99.3% (93.8-100%) and 100% in West Bengal in 2014;
- Survey in India (2014-2016) (n = 832) *PfKelch13* mutations = 1.4% (different from 15% reported);
- R539T has almost disappeared in Cambodia after 2014 (2.1% in 11 studies in 2014).

Actions taken:

- QC (slides, DNA, sequencing) and re-analysis requested but rejected by the authors;
- G625R genome editing and $RSA_{0\text{-}3h}$ studies;
- TES studies in West Bengal with parasites clearance and *Pfkelch 13* analysis.

Artemisinin partial resistance: Equatorial Guinea

Article:

- Lu F et al. Emergence of Indigenous Artemisinin-Resistant *Plasmodium falciparum* in Africa. *N Engl J Med.* 2017 Mar 9;376(10):991-993.

Summary:

- 43-year-old man Chinese worker returning from Equatorial Guinea in **2013** and developing a malaria attack in China **treated successfully** with DHA-piperaquine. Day 3 parasitaemia: 40/ml (1/200 WBC); RSA0-3h survival rate ≈ 2%, PfKelch13: M579I (confirmed by IPC).

- Origin confirmation led to controversy;
  - The analysis was based on 26,918 SNPs spanning the entire genome. The SNP/REF were extracted from the 26,918 positions that differentiate 245 *Plasmodium* samples into their respective geographical origins ;
  - CWX sample had a total of 559 SNPs predicted by samtools mpileup;
  - Geographic origin was also independently confirmed based on a 23-SNP barcode within the apicoplast and mitochondrial genomes.

Artemisinin partial resistance: Equatorial Guinea

Comments:

- Period of 8 weeks between return from Africa;
- only 1 case of M579I was previously reported in Myanmar;
- *PfKelch 13* mutations frequently appear and disappear due to fitness cost. A single case cannot lead to the statement that resistance has emerged in a country or continent (ref. WHO definition on artemisinin resistance);
- Two studies conducted in 2005 and 2013-2014 (n = 98 + 144) in Equatorial Guinea did not report M579I.

Actions taken:

- $RSA_{0\text{-}3h}$ after gene editing M579I ≈ 10%
- TES in 3 sites with 2 arms (AL & ASAQ) in 2017-2018: n = 438; day 3 positivity rate = 0%;
- *PfKelch 13* on-going (final results expected soon; 100 samples absence of M579I).

Artemisinin partial resistance: Rwanda

Article:

- Uwimanaa A et al. Efficacy of artemether–lumefantrine versus dihydroartemisinin–piperaquine for the treatment of uncomplicated malaria among children in Rwanda: an open-label, randomized controlled trial. Trans R Soc Trop Med Hyg 2019; 00: 1–8.

Summary:

- A total of 534 children were treated with AL (n=267) or DHP (n=267) in 2 sites: Masaka and Ruhaha (2013-15);
- After PCR adjustment, 98.3% ACPR in the AL at day 28 and 98.4% ACPR for DP at day 42;
- Day 3+ rate ranged from 0.8 to 2.5%.

Artemisinin partial resistance: Rwanda

Comments:

- Analysis of K13 was performed on TES samples from 2012-15 (AL in 4 sites Bugarama, Kibirizi, Nyarurema, and Rukara) and 2013-15 samples (Masaka and Ruhaha);
- Total of 927 samples among which 45 had non-synonymous mutations;
- R561H was found in 20 samples: 19 in Masaka (7.3%) and 1 in Rukara;
- No correlation between R561H and day3+ and not correlation between 561 and treatment failure (among the 9 treatment failures 8 were reinfection and 1 ETF = low parasitemia at day3 + fever) (data to be confirmed).

Actions taken:

- Whole genome sequencing on the parasite to evaluate a clonal expansion;
- Requested individual patient data from country;
- TES conducted in 2018 with support of CDC and PMI; data not shared so far but CDC confirmed presence of R561H.

Artemisinin partial resistance: Horn of Africa

Article:

- Bayih AG et al. A Unique *Plasmodium falciparum* K13 Gene Mutation in Northwest Ethiopia. *Am J Trop Med Hyg.* 2016 Jan;94(1):132-5.

Summary:

- Patients (N = 148) in five districts of northwest Ethiopia were enrolled in a 28-day AL TES.
- A unique *Pfkelch 13* mutation (R622I) was identified in 3/125 (2.4%) samples.
- The 3 isolates with R622I were from Negade-Bahir and Aykel districts in Amhara region close to the Ethiopia-Sudan border.
- One of three patients with the mutant strain was day3+; however, all patients cleared parasites by day 28.

DHA-pipearquine as a policy for treatment of uncomplicated malaria

- DHA-piperaquine was considered in the WHO treatment guideline when Duo-cotexin® was registered in China;
- Eurartesim® was approved later by EMA and was also pre-qualified by WHO;
- PQ department indicates on its website that this ACT is unstable > 30°C and 75% humidity (tropical conditions);
- DHA is thermally and chemically labile (> artesunate > artemether) (≠ piperaquine)
    - temperature, humidity and contact with partner medicine (Haynes et al., Chem Med Chem, 2007);
- So far no other combination is pre-qualified;
- Eurartesim® is difficult to procure, which leaves the door open to many generic compounds of various quality in Africa.

Prevalence of *Pfplasmepsin 2-3* increased copy number in some African countries

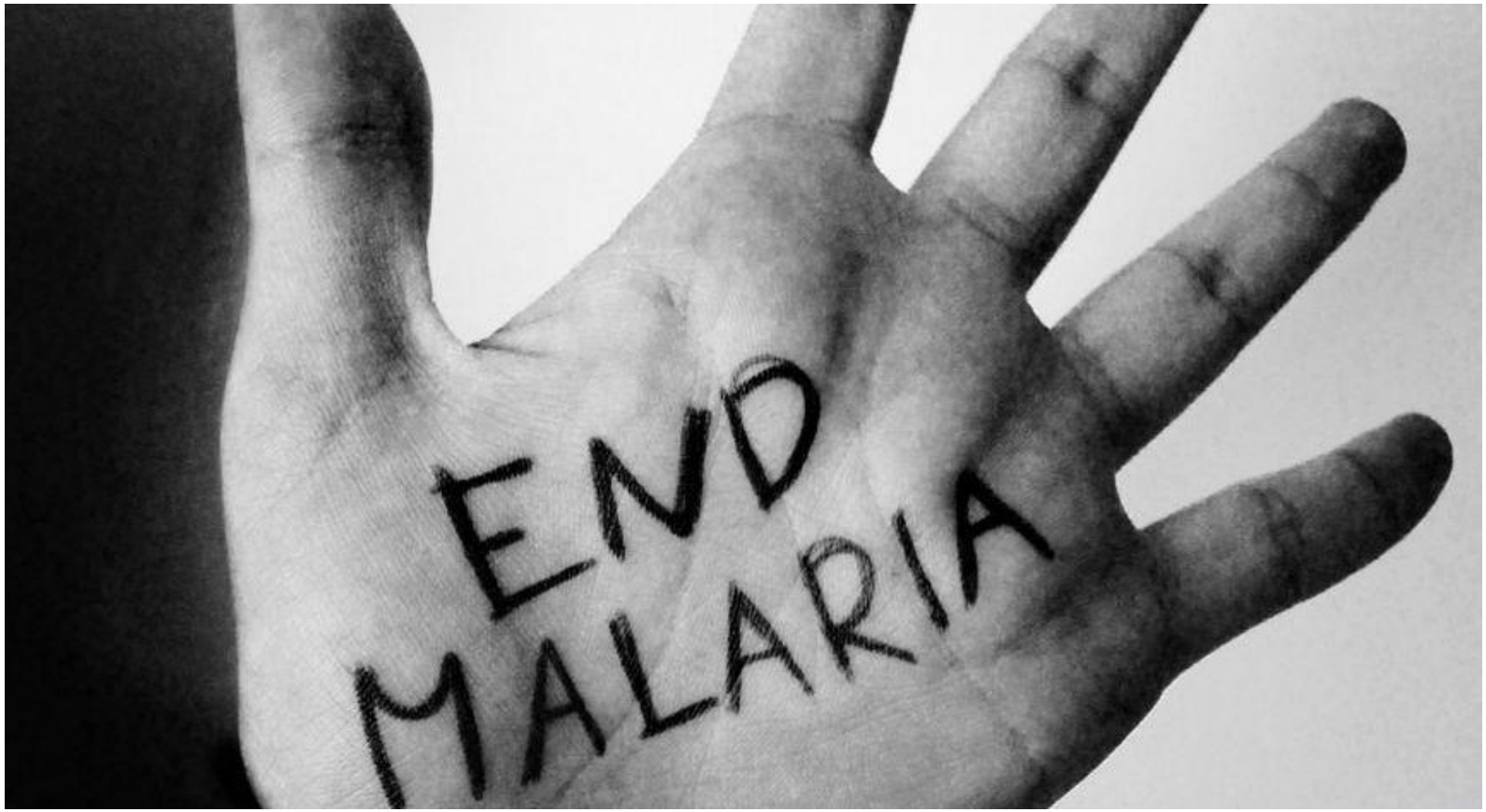
Year	Countries	Prevalence	Study
2012-14	Mali	7/65 (10.8%)	TES
2013	Comoros	3/46 (6.5%)	TES
2013-15	Rwanda	4/130 (3.1%)	TES
2015	Mozambique	0/87 (0%)	TES
2015	Mozambique	1/88 (1.1%)	TES
2015	Mozambique	1/89 (1.1%)	TES
2015	Mozambique	2/87 (2.3%)	TES
2015	Mozambique	3/61 (4.9%)	Pre-MDA
2016	Mozambique	1/19 (5.3%)	Post-MDA
2017	Eritrea	8/42 (19.0%)	TES

Presence of multicopy *Pfplasmepsin 2-3* in Africa is a potential concern in particular with the massive of the uncontrolled use of DHA-PIP of various quality.

Summary

- WHO has a normative and public health role:
  - How can WHO retrieve data from countries or research institutes refusing to share these data when there is a public health concern?
  - Huge delays between evidence generation and publication.
- Several different methodologies are used to assess the origin of a parasites:
  - What would be the minimum/optimal information to confirm the origin of a resistant parasites?
- Use substandard DHA-PIP (mainly as a monotherapy) could pose a public health problem for Africa
  - Urgent need to support/conduct QC of the multiple generic DHA-PIP compounds circulating in Africa.

Thank you for your attention



Malaria Elimination in the Greater Mekong Subregion (GMS)

Malaria Policy Advisory Committee (MPAC)

10-12 April 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

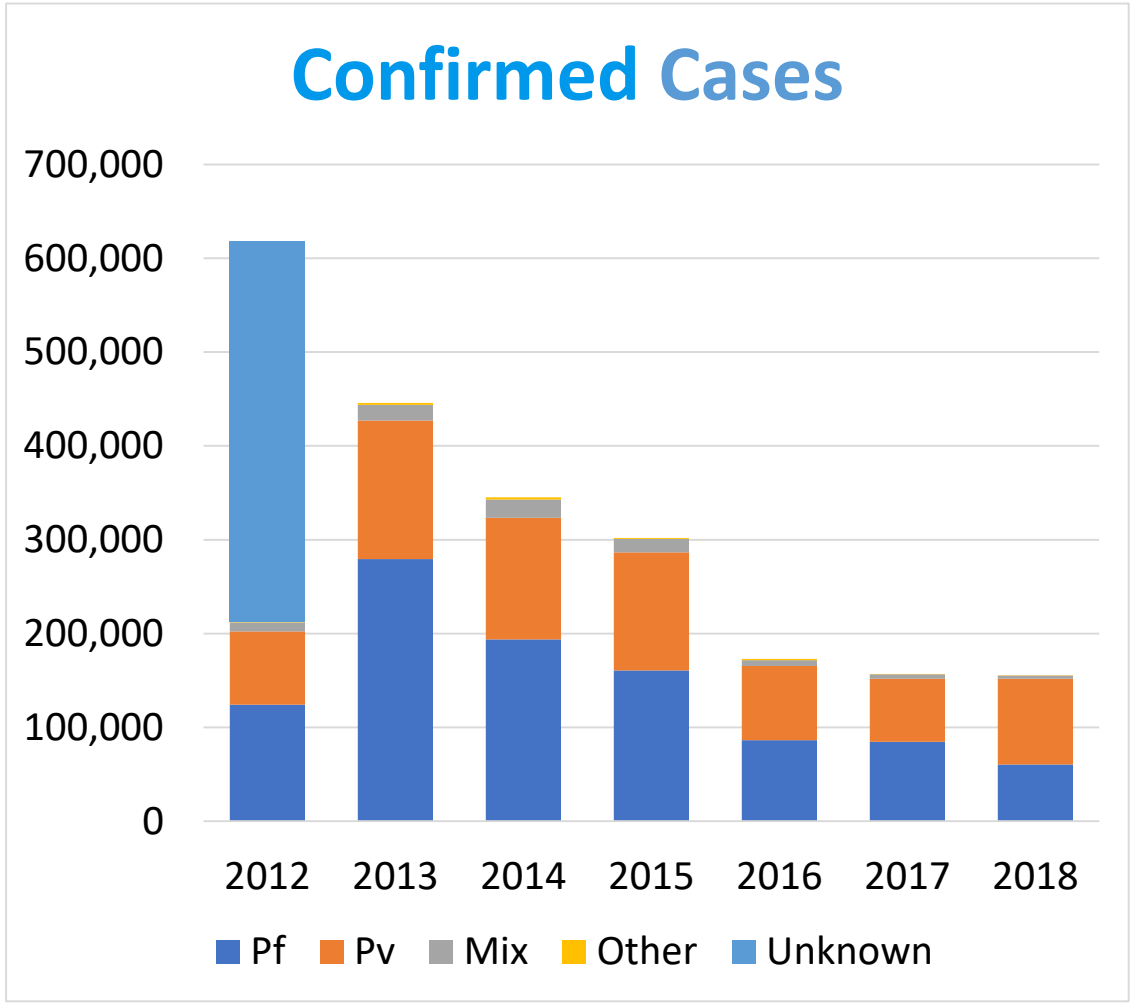
- *P. falciparum* malaria eliminated in all countries of the GMS
- All species of human malaria eliminated in Cambodia and Thailand

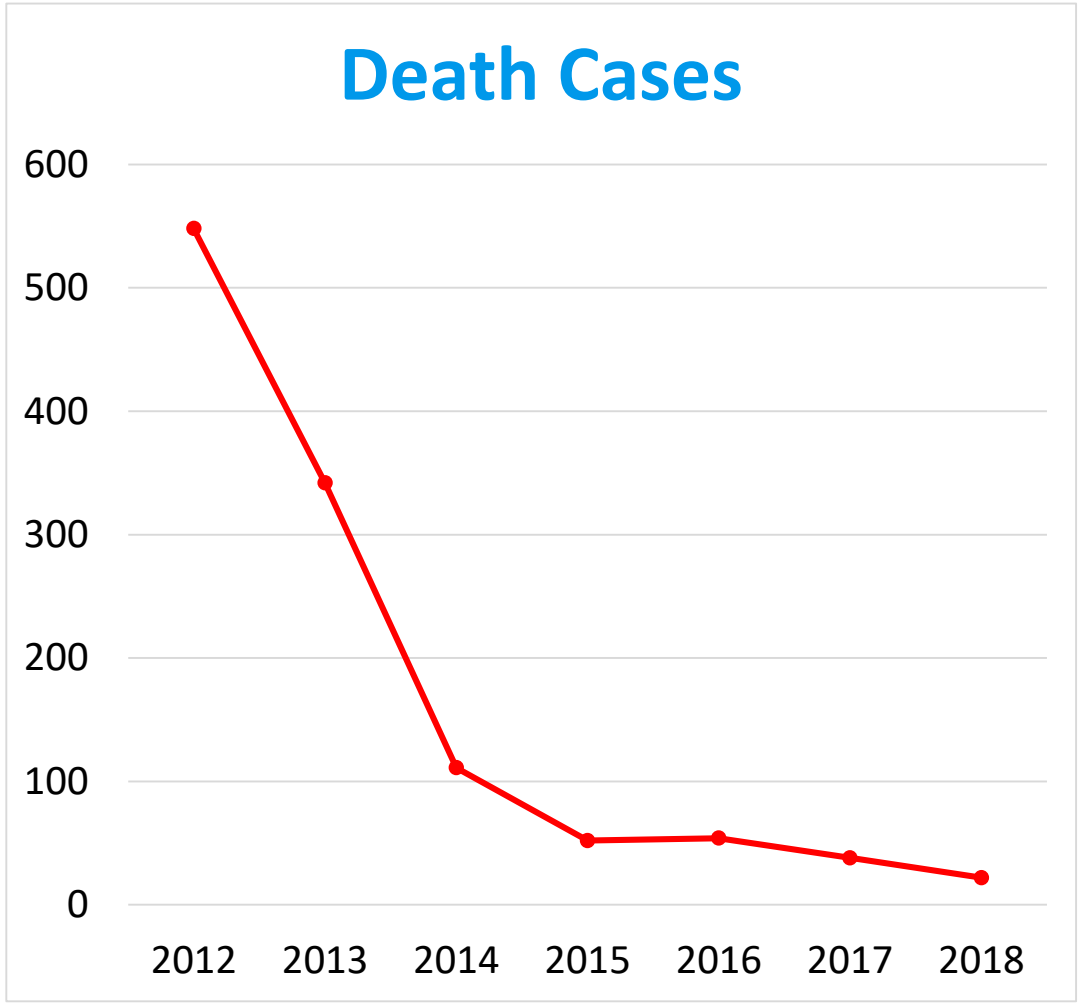
By 2030

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

World Health Organization

Malaria cases in the GMS (2012-2018)

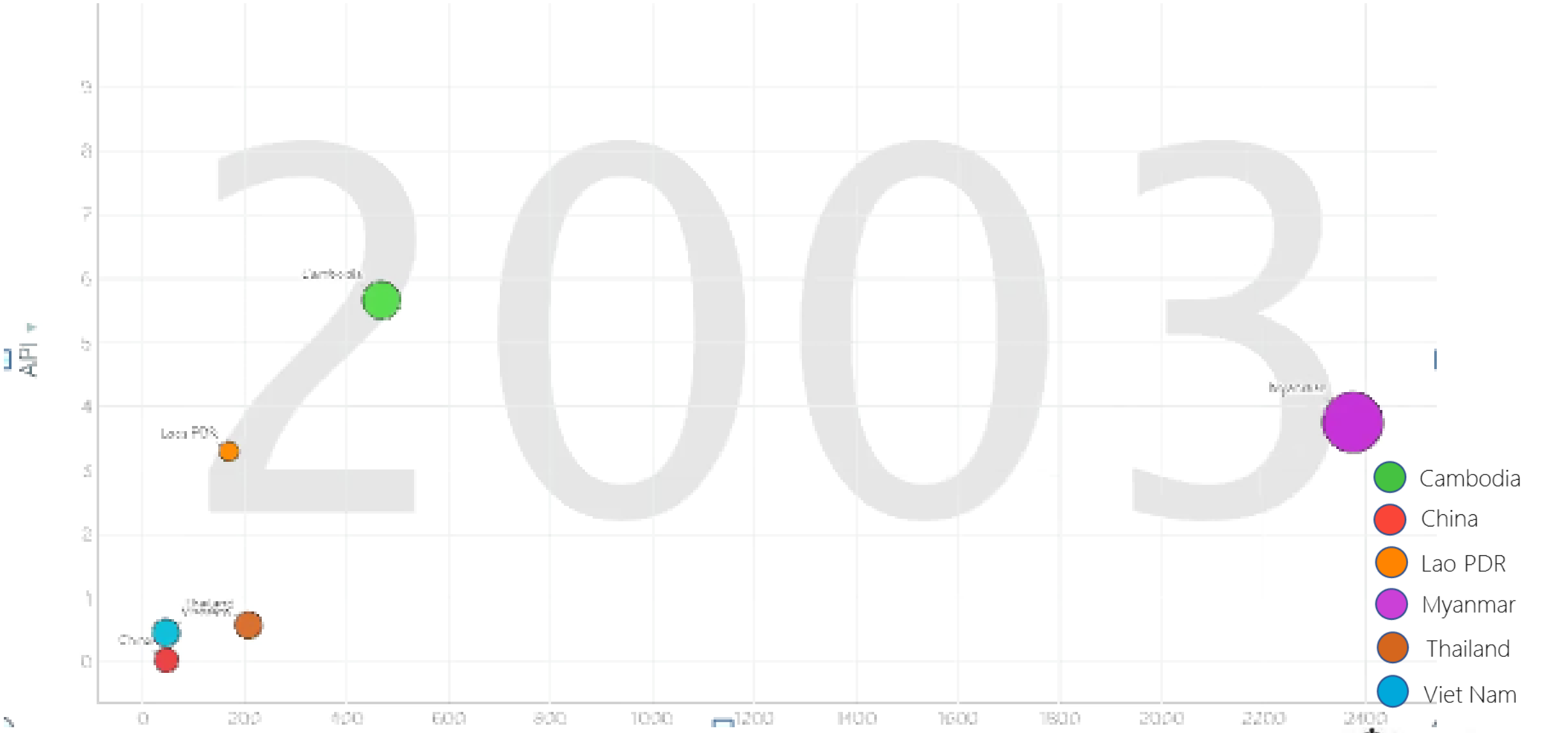




Source: WHO subregional database

World Health Organization

Parasite Incidence and Malaria Death by GMS Countries, 2003-2018



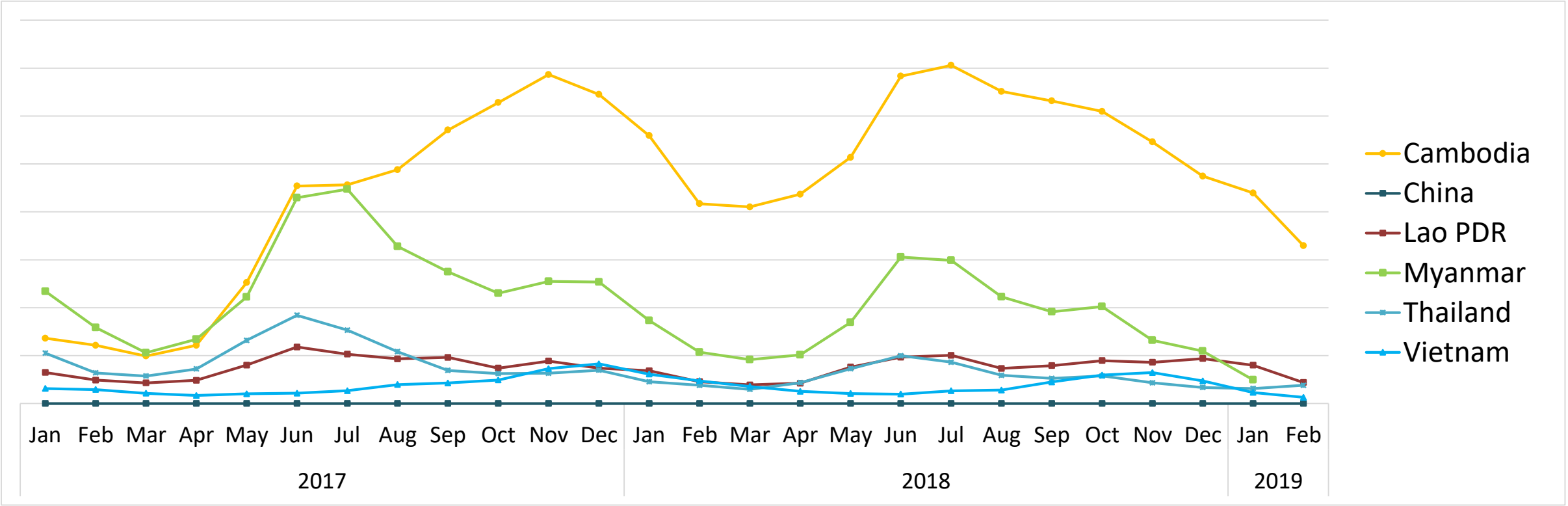
Parasite Incidence and Malaria Death by GMS Countries, 2003-2018

Source: World Malaria Report

World Health Organization

Monthly case trend in the GMS

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



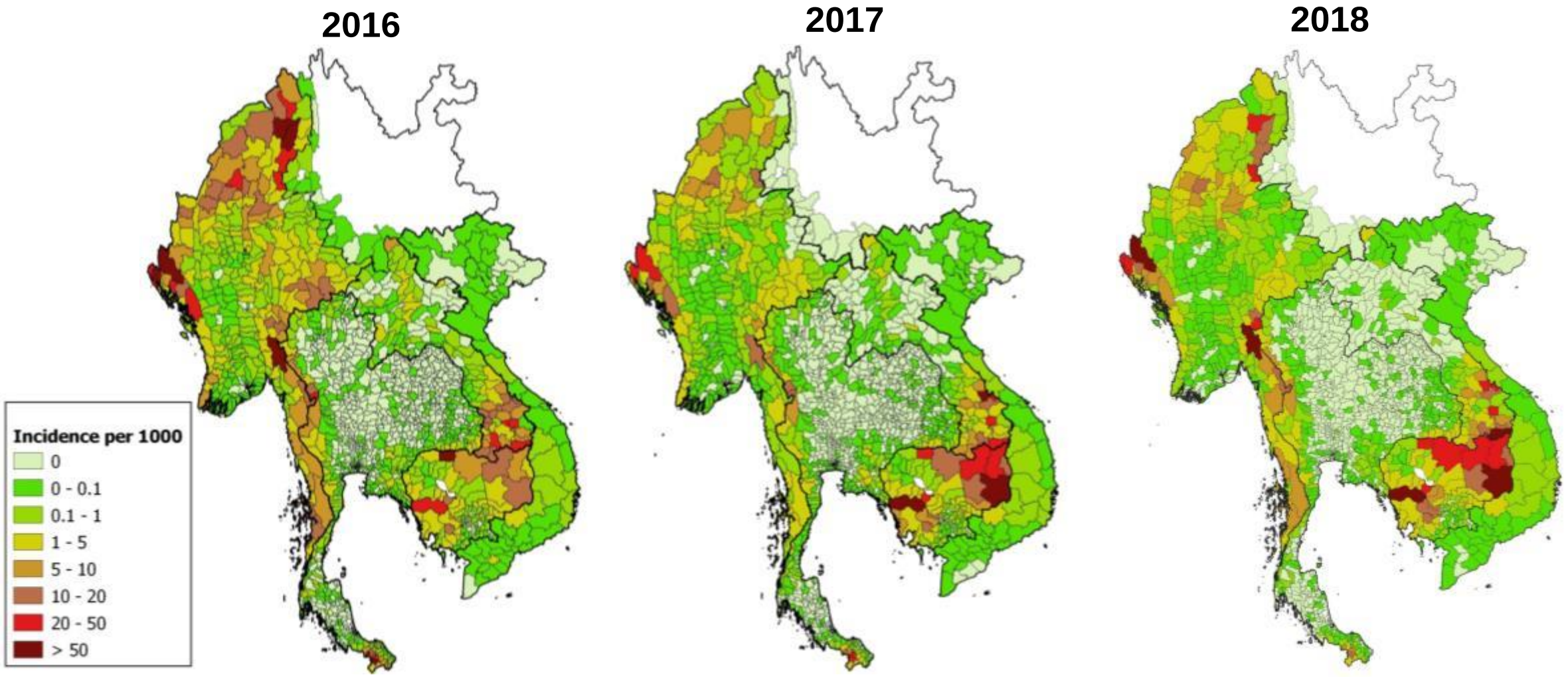
Case burden in Cambodia remains high but has started to decrease in 2H 2018.

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

World Health Organization

Progress: Cases are concentrated

Annual Parasite Incidence (API) by District*

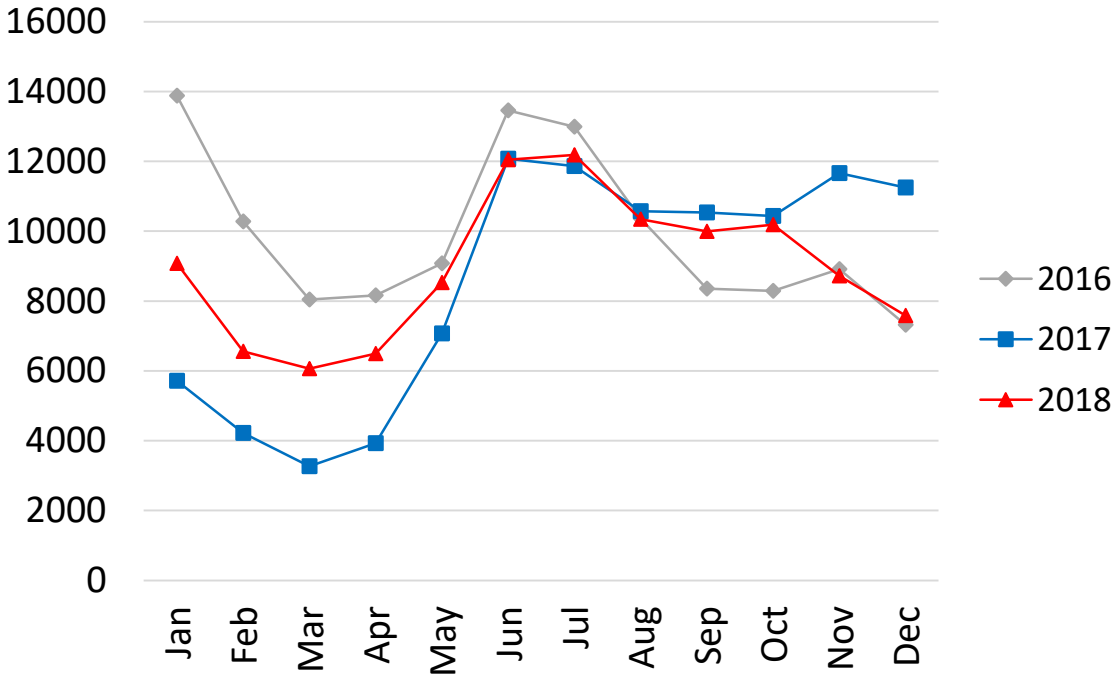


Source: WHO subregional database. *Viet Nam data are provincial level.

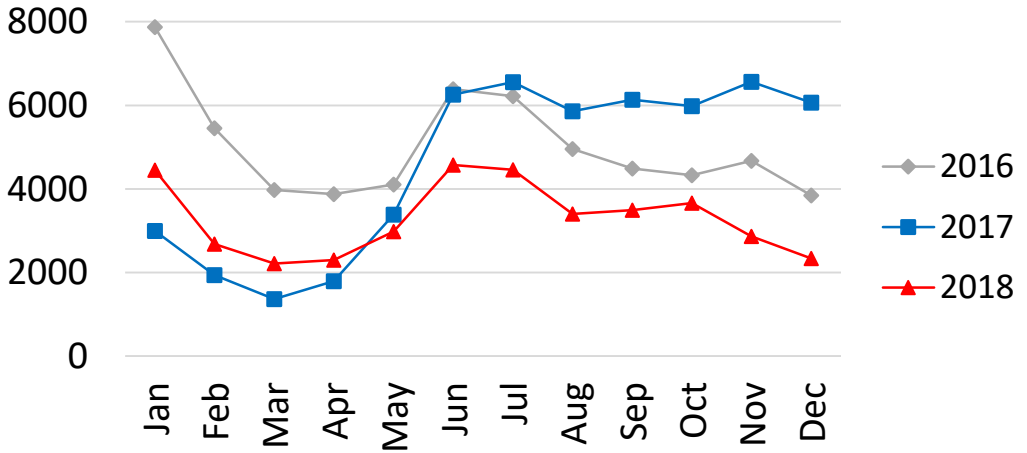
World Health Organization

Monthly case trend in GMS by species

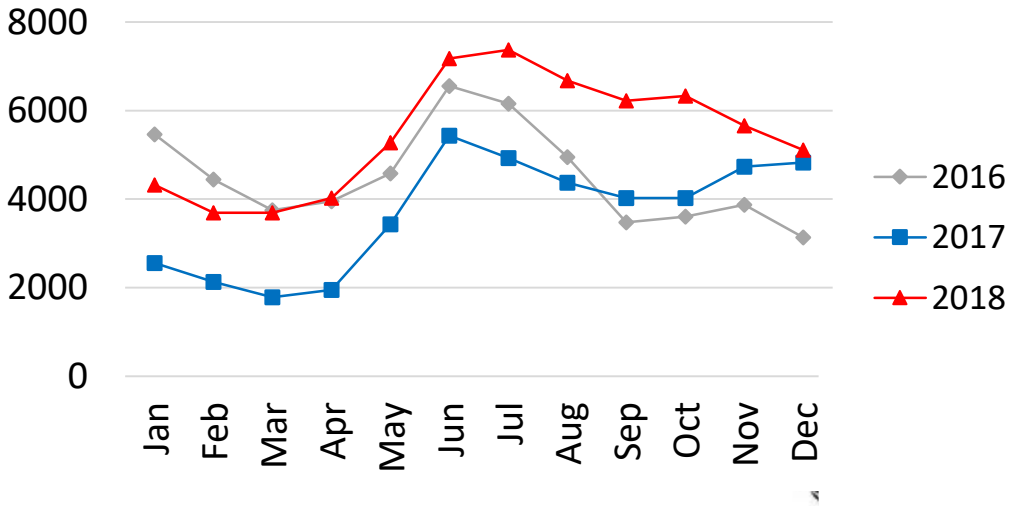
Total confirmed cases (2016-2018)



P. falciparum cases



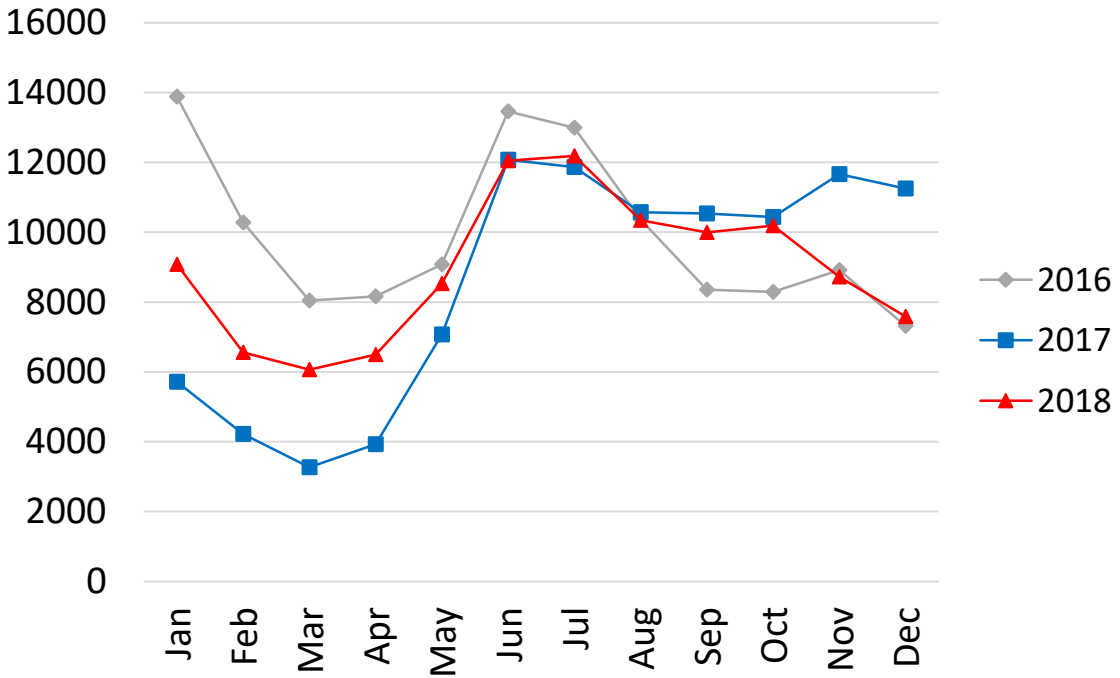
P. vivax cases



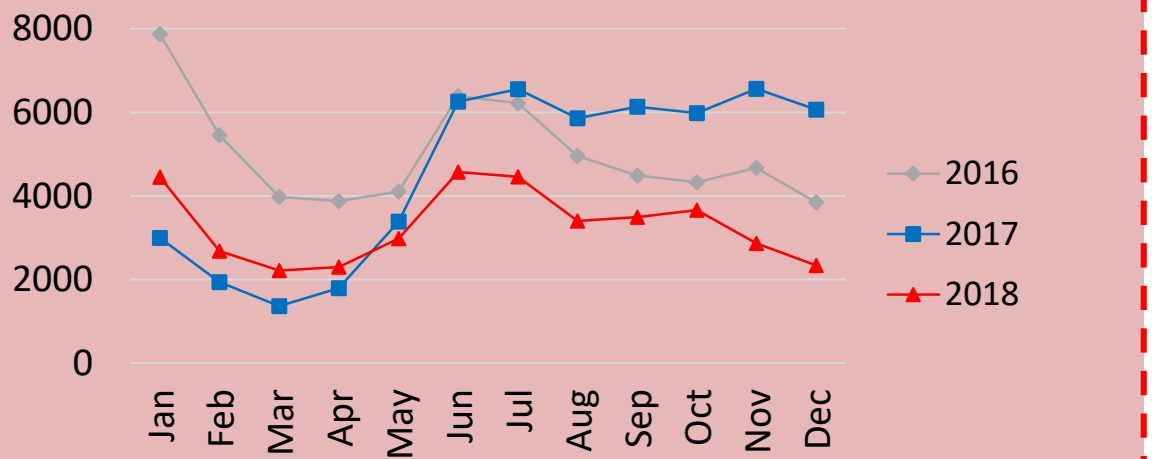
Source: WHO subregional database, excluding mix cases

Progress toward Pf elimination

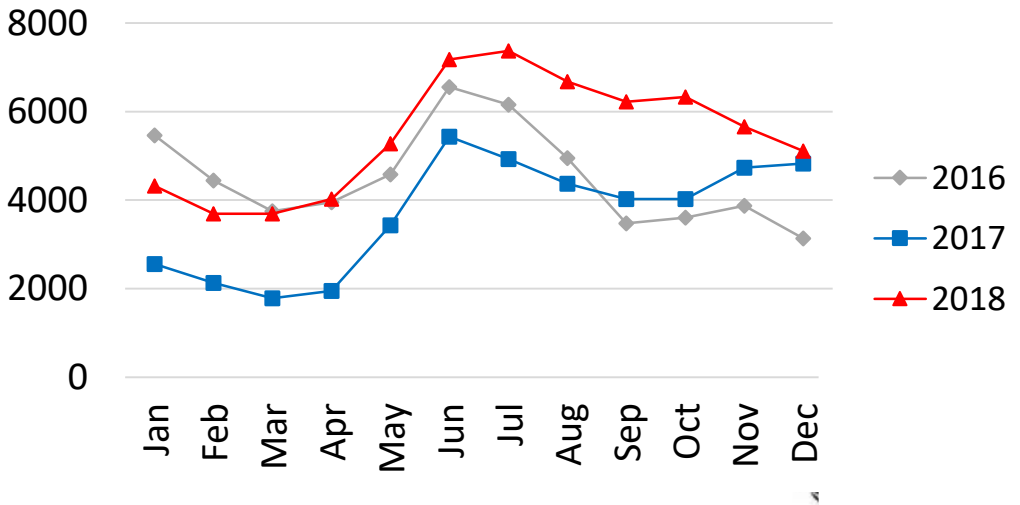
Total confirmed cases (2016-2018)



P. falciparum cases



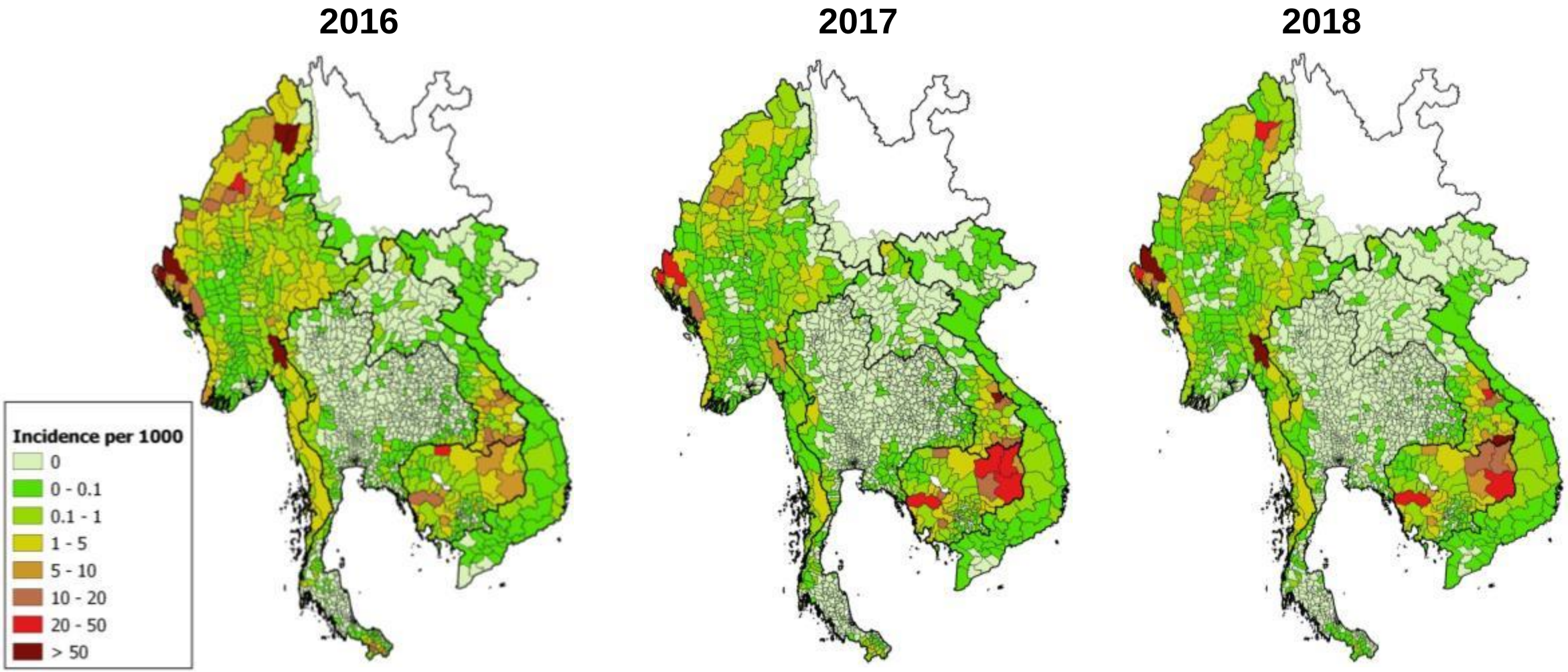
P. vivax cases



Source: WHO subregional database, excluding mix cases

Incidence of Pf in the GMS

Pf+Mix Incidence by District*

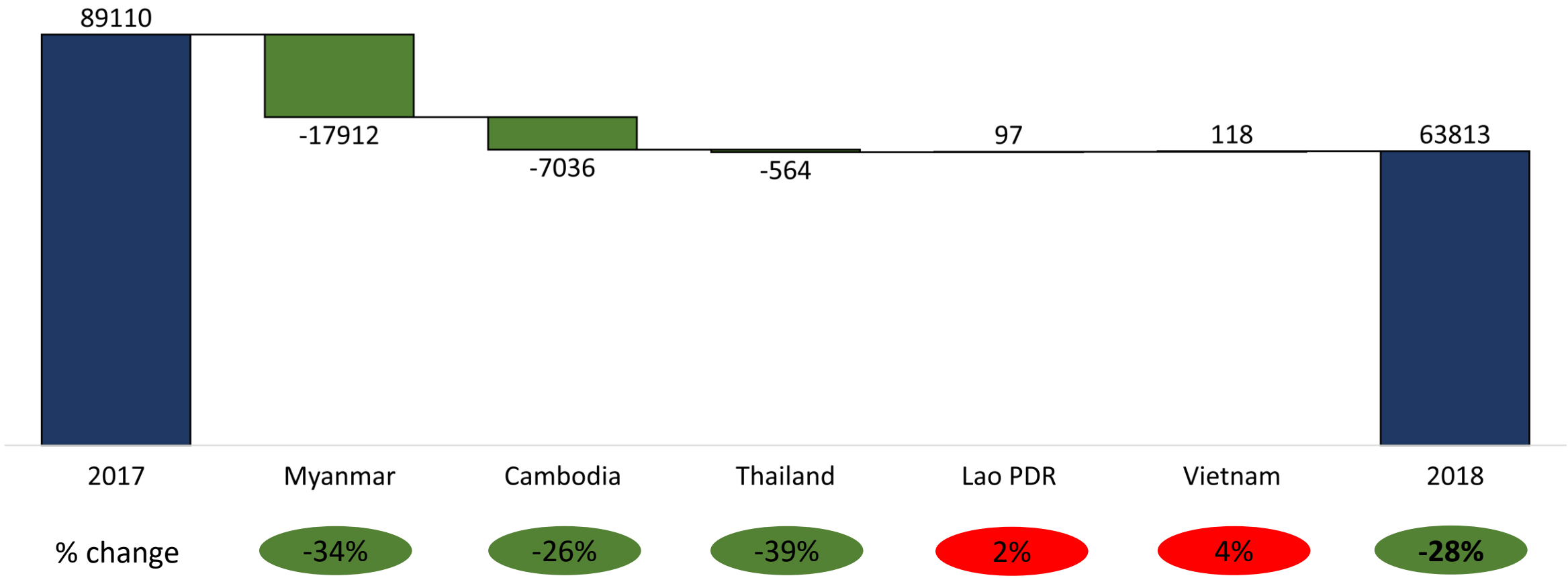


Source: WHO subregional database. *Viet Nam data are provincial level. Myanmar data in 2018 do not include reports from CSOs.

World Health Organization

Progress toward Pf elimination (2017 compared to 2018)

Changes in Pf+Mix Cases from 2017 to 2018

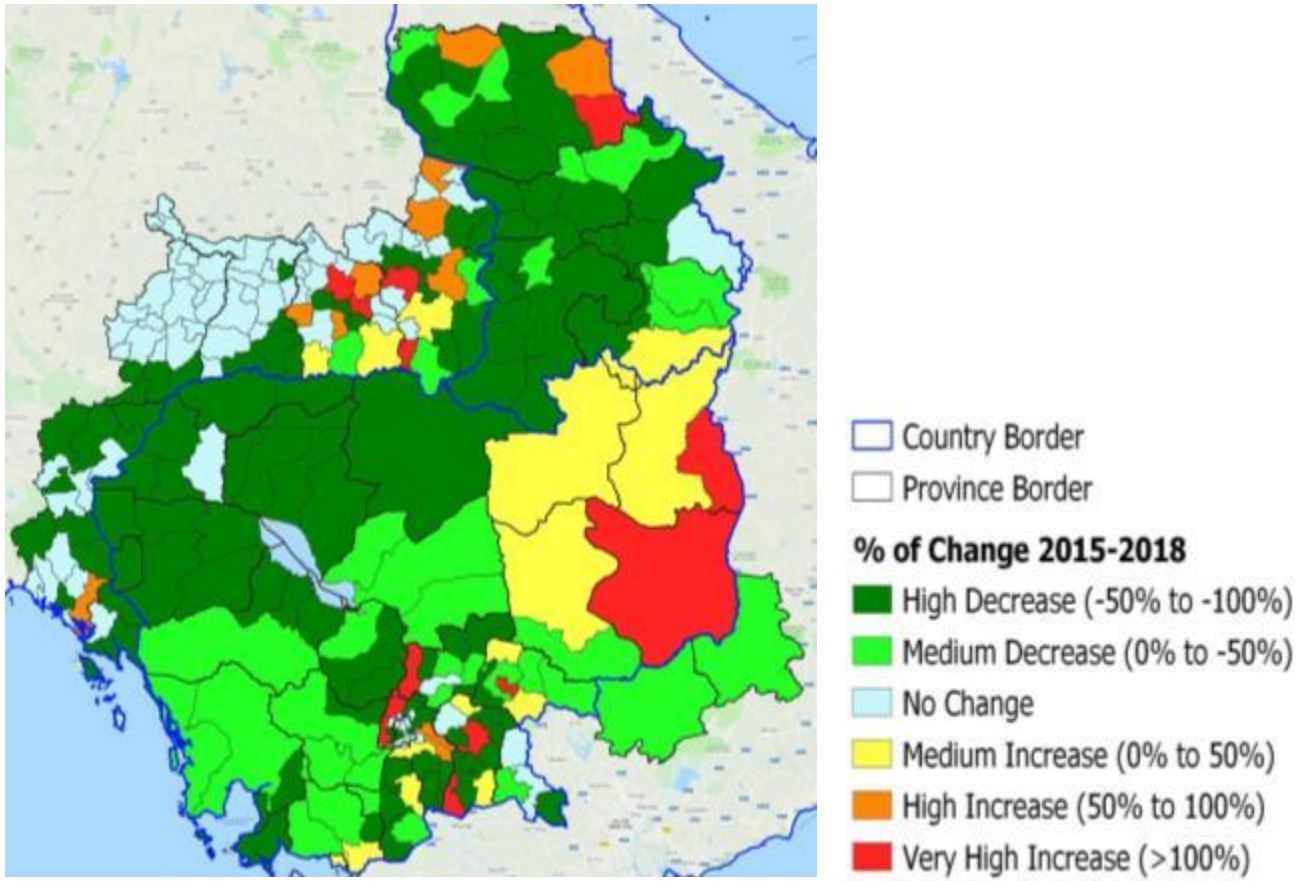


Source: WHO subregional database

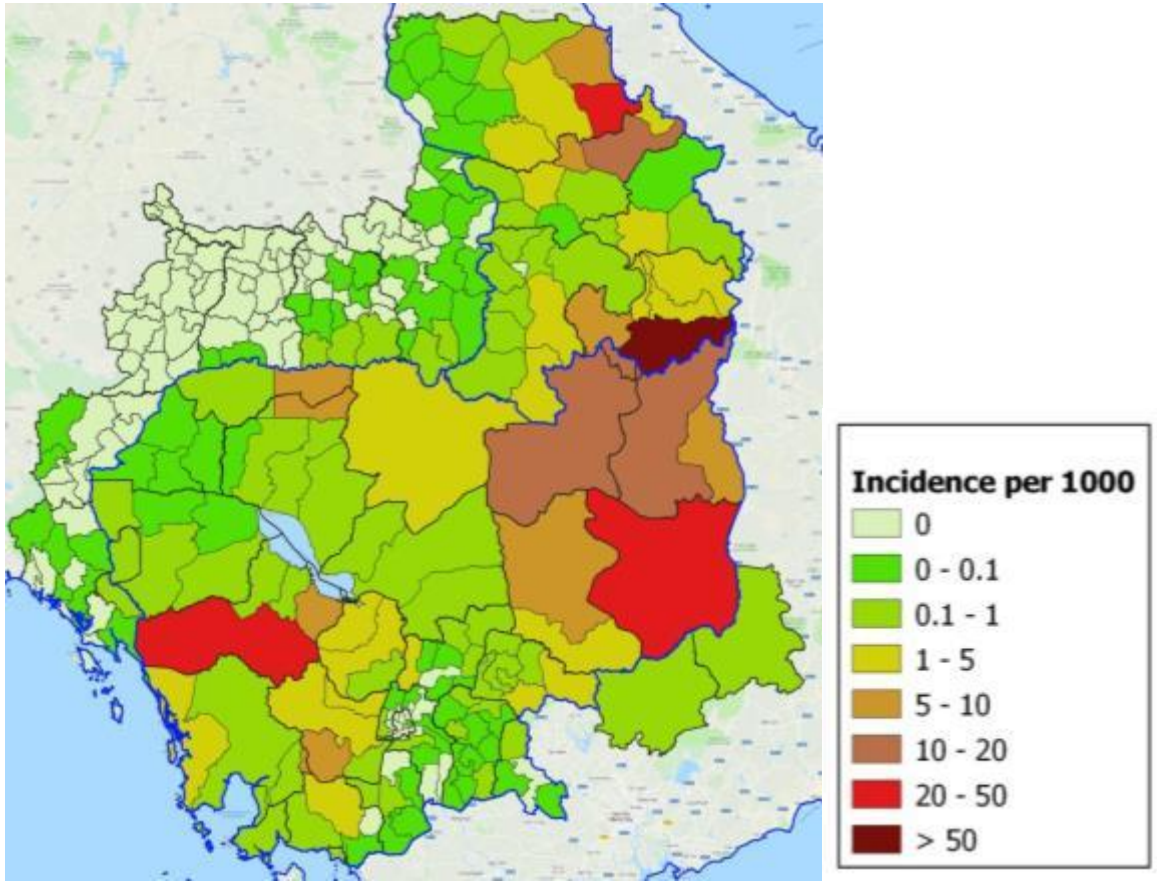
World Health Organization

Significant progress in districts with multidrug resistance

% Change in Pf Cases (2015 vs. 2018)



Pf Incidence (2018)

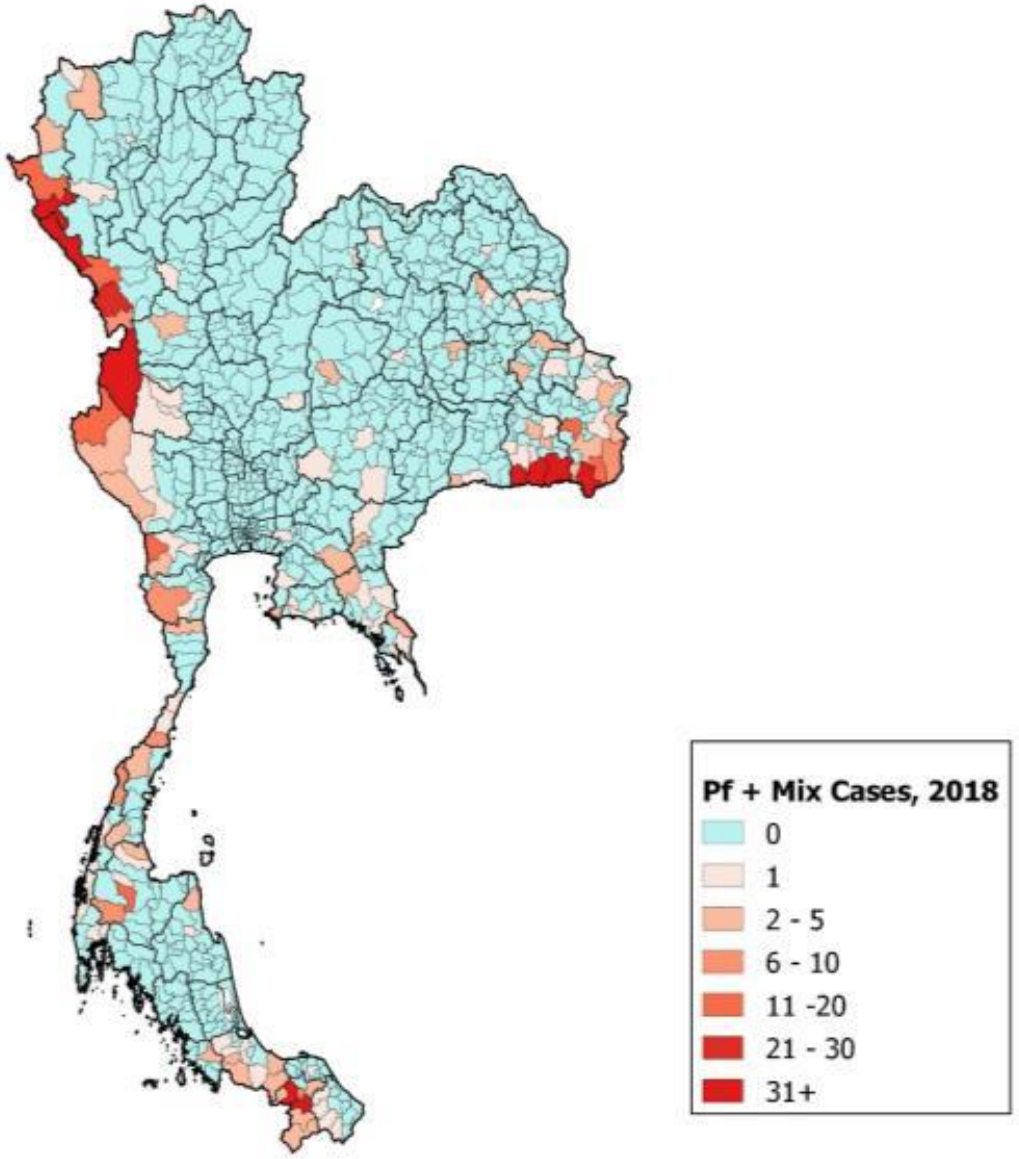


Source: WHO subregional database

World Health Organization

Thailand is nearing Pf elimination

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

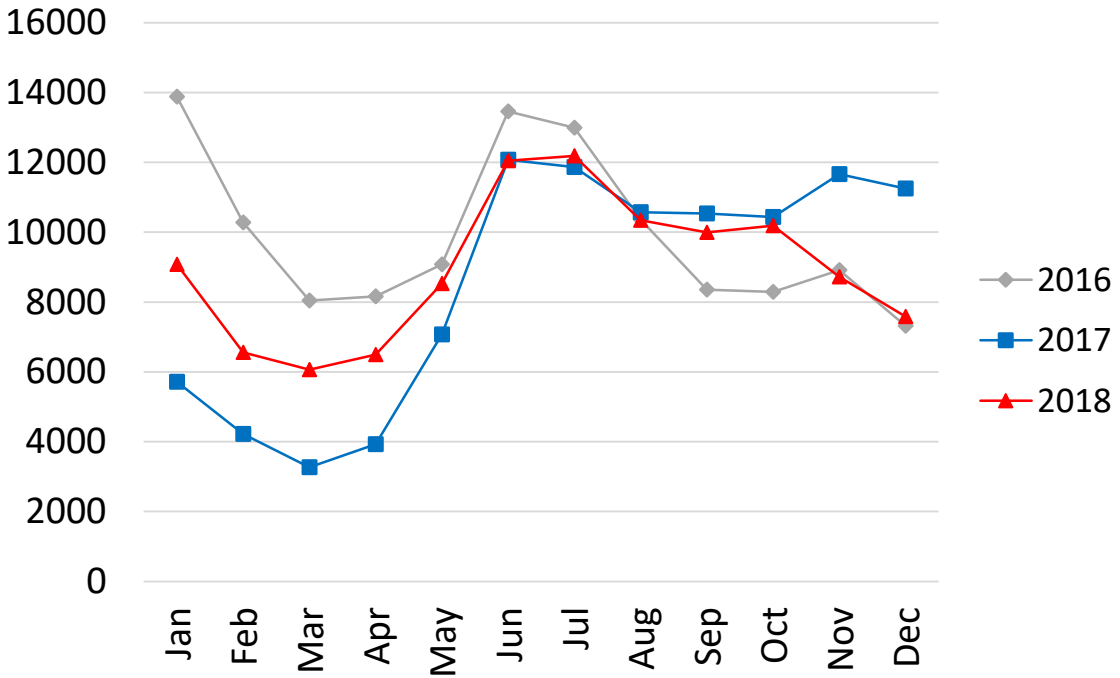


Source: WHO subregional database. Data extracted on 20 March 2019.

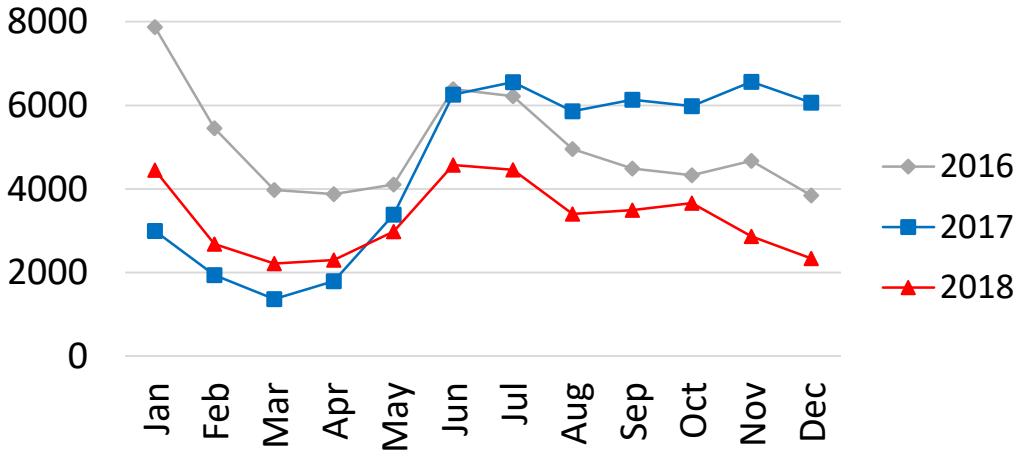
World Health Organization

Progress toward Pv elimination

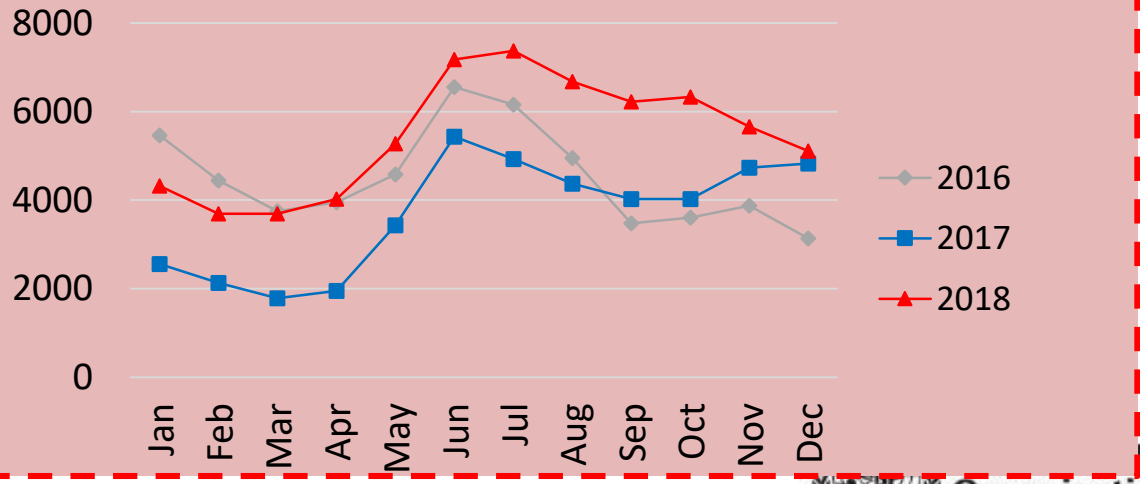
Total confirmed cases (2016-2018)



P. falciparum cases



P. vivax cases

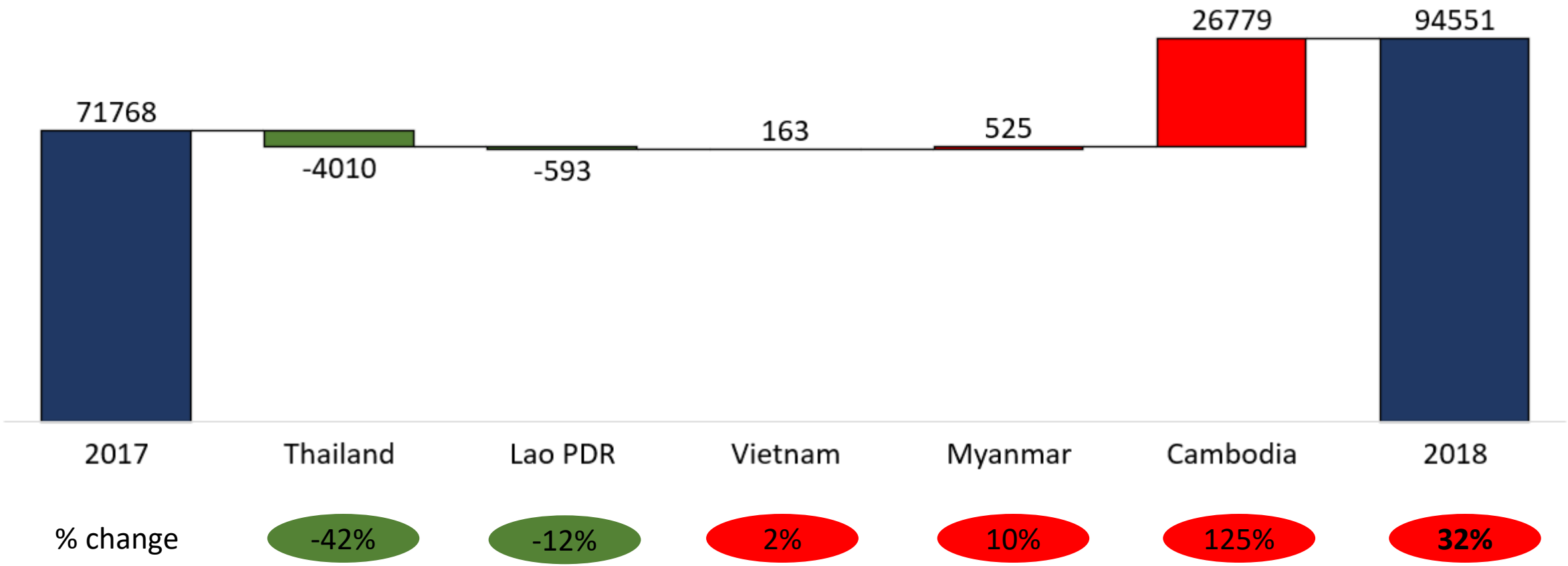


Source: WHO subregional database, excluding mix cases

Organization

Progress toward Pv elimination (2017 compared to 2018)

Changes in Pv+Mix Cases from 2017 to 2018

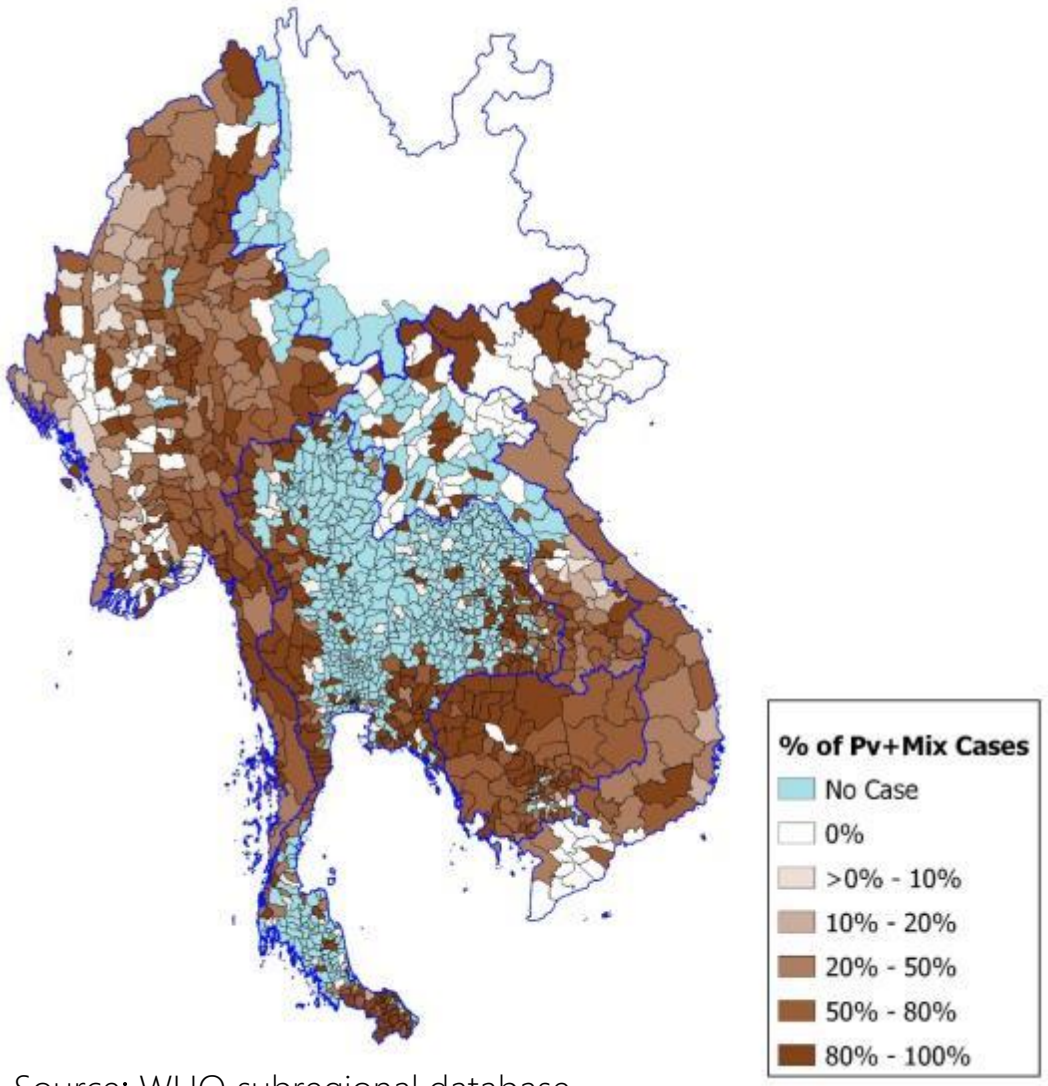


Source: WHO subregional database

World Health Organization

Pv distribution in the GMS

% of Pv+Mix cases by district (2018)



Source: WHO subregional database

- In 2018, more than 60% 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

World Health Organization

Percentage of Pv+mix cases in GMS (2015-2018)

Country	2015	2016	2017	2018
Cambodia	50%	48%	46%	73%
Lao PDR	60%	63%	51%	47%
Myanmar	40%	43%	32%	51%
Thailand	67%	76%	84%	83%
Viet Nam	54%	44%	37%	38%

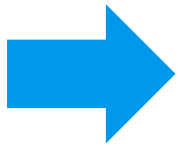
World Health Organization

Common priorities in GMS (MPAC, October 2018)

- Technical support at sub-national levels in highest burden areas to improve implementation and coordination

- Monitor drug efficacy and update/implement national treatment guidelines

- Improve surveillance and scale-up elimination phase activities (e.g. case and foci investigation)



For each category, it is encouraged to explore innovative approaches

World Health Organization

Common priorities in GMS (MPAC, October 2018)

- Technical support at sub-national levels in highest burden areas to improve implementation and coordination

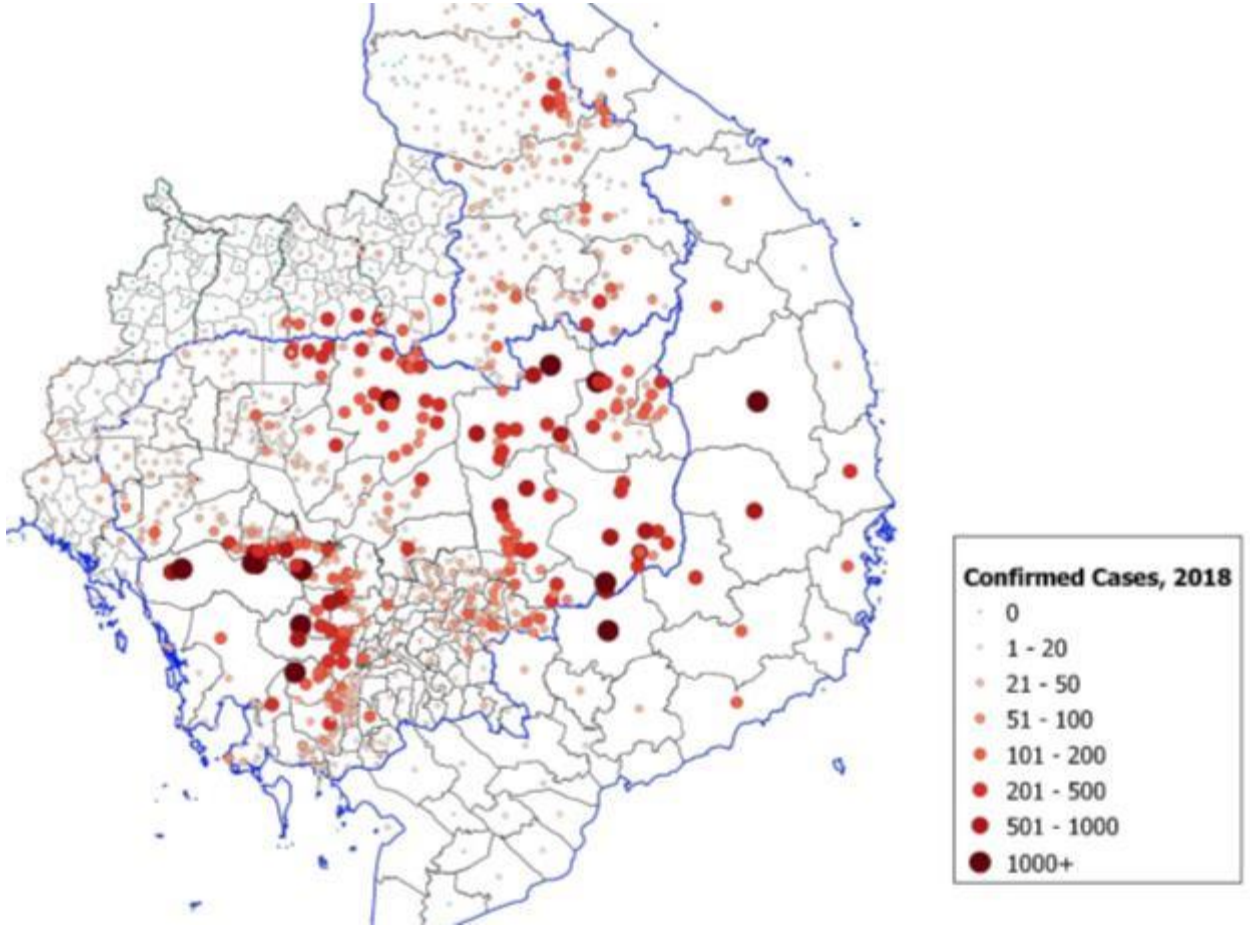
- Monitor drug efficacy and update/implement national treatment guidelines

- Improve surveillance and scale-up elimination phase activities (e.g. case and foci investigation)

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 in 2018

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

World Health Organization

Challenges: Accessibility in remaining endemic areas

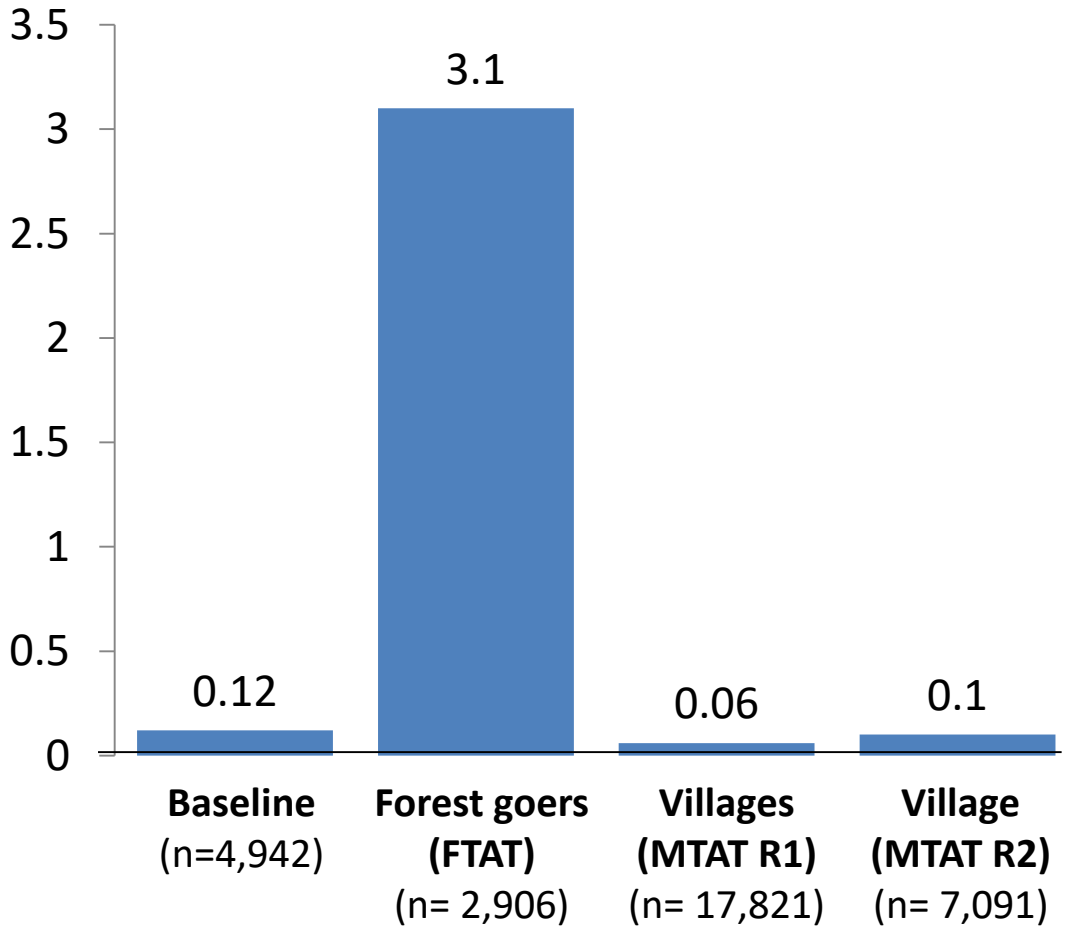




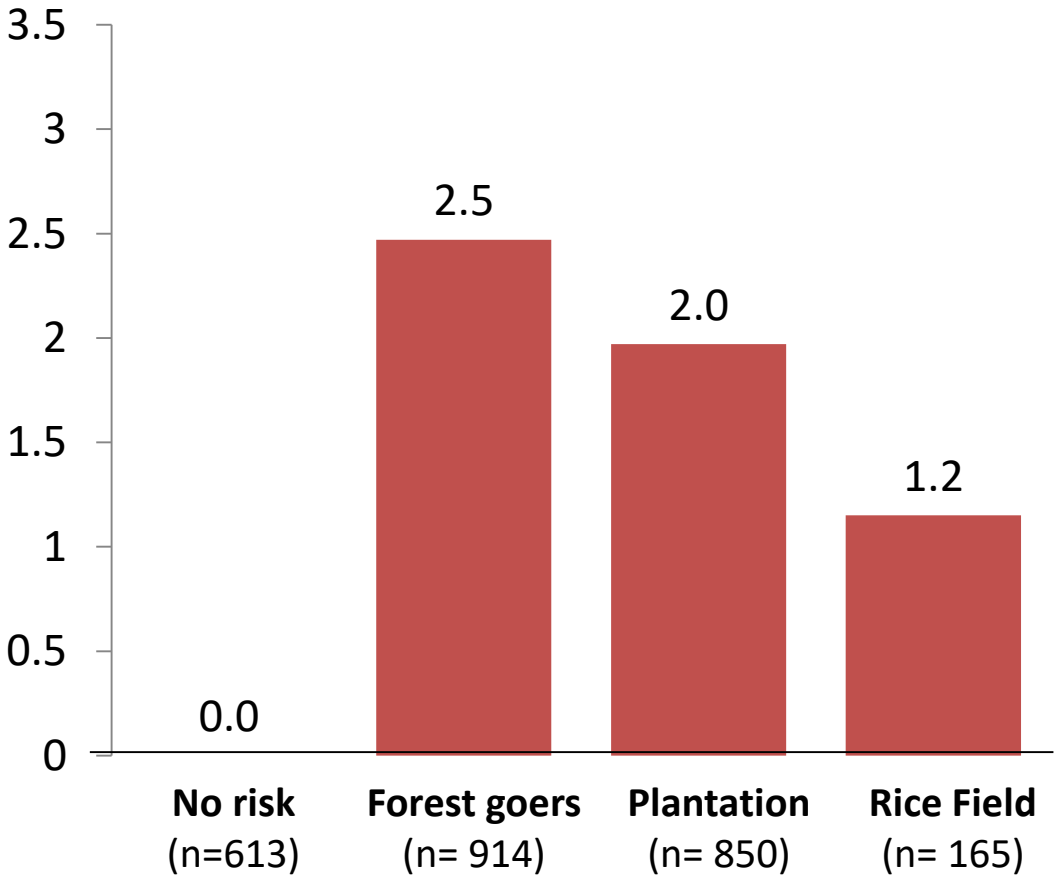

World Health Organization

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

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



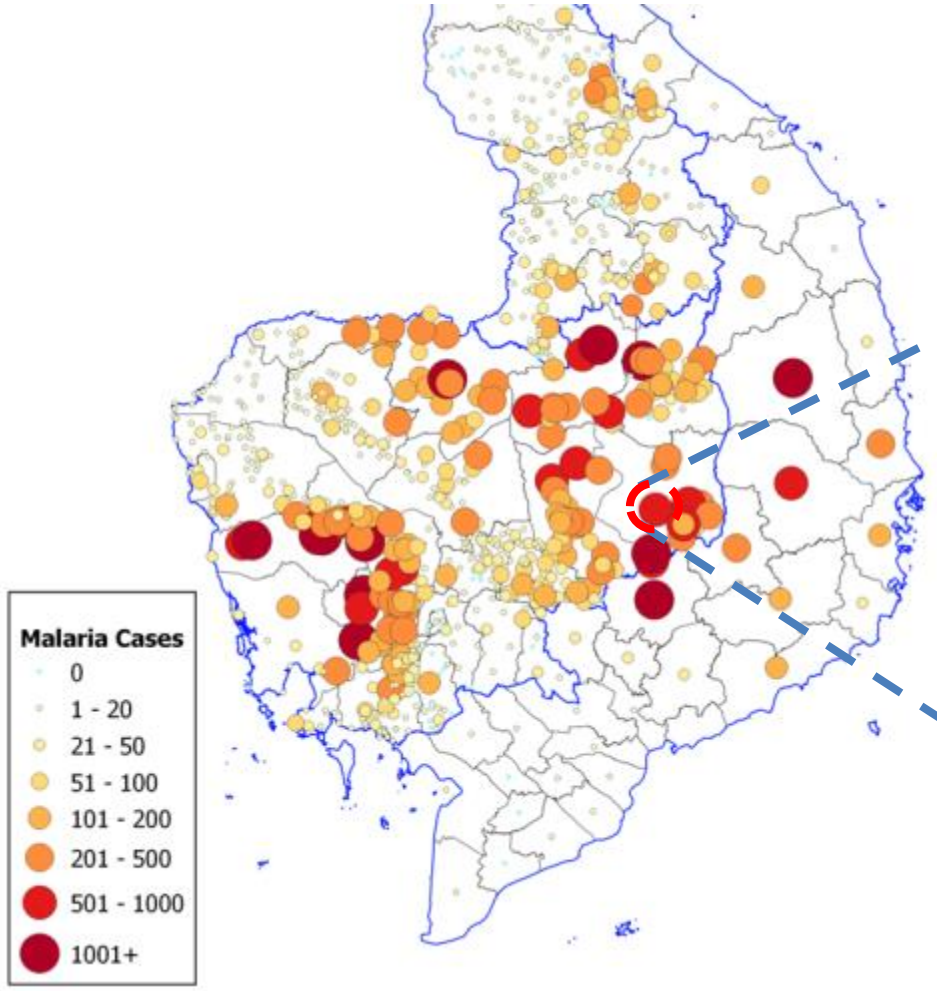
Prevalence in malaria in ACD (PCR)
% of positive Pf case, N= 2772 (Preah Vihear, Cambodia)



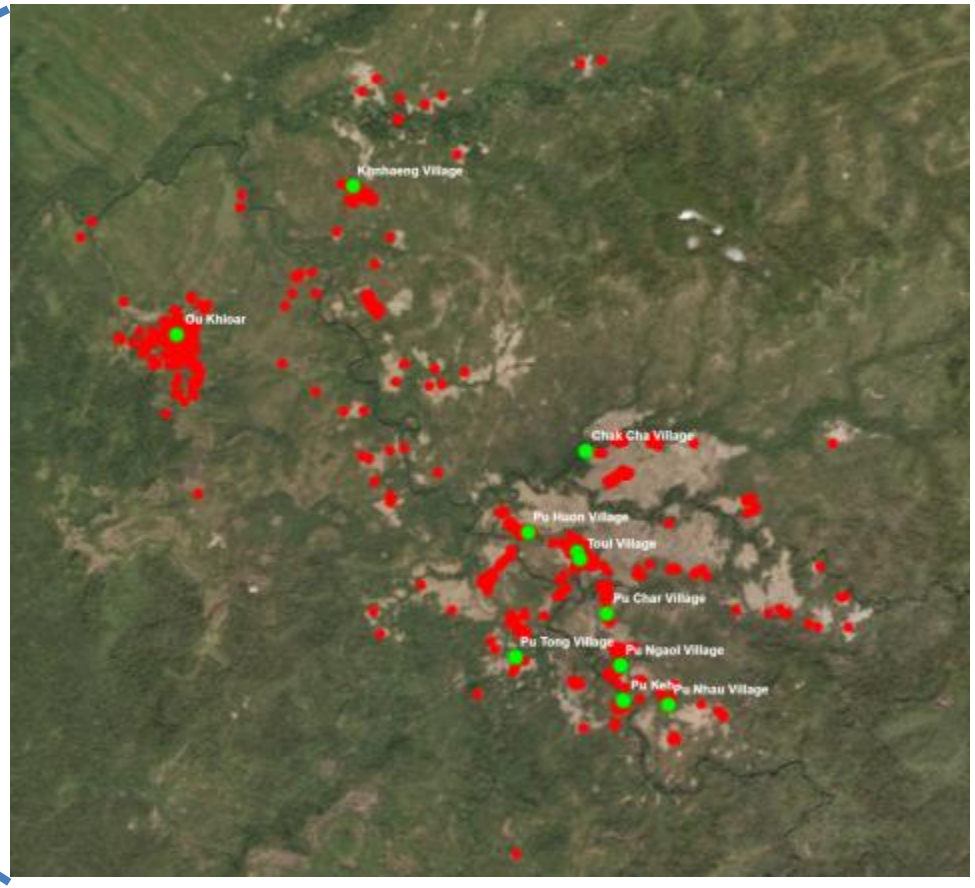
Source: UCSF (Lao PDR) and MSF (Cambodia).

World Health Organization

Forest sites are widely dispersed



Possible Forest Sites in Me Mang, Mondulkiri, Cambodia



Source: WHO subregional database.

World Health Organization

Need for community-owned 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

Remaining challenges in GMS

- Technical support at sub-national levels in highest burden areas to improve implementation and coordination

- Monitor drug efficacy and update/implement national treatment guidelines (e.g. replacing ineffective first-line, identifying second-line ACT and implementing Pv radical cure)

- Improve surveillance and scale-up elimination phase activities (e.g. case and foci investigation)

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	24	0.0	6.0
Artesunate-mefloquine	2011-13	5	0.0	2.2
Artesunate-pyronaridine	2017-17	2	0.0	0.0
DHA-piperaquine	2010-17	15	0.0	4.8
Cambodia				
Artesunate-mefloquine	2010-18	16	0.0	1.7
Artesunate-pyronaridine	2014-18	7	0.0	18.0
Lao PDR				
Artemether-lumefantrine	2010-17	9	0.0	17.2
DHA-piperaquine	2016-17	2	13.3	47.4
Viet Nam				
DHA-piperaquine	2010-17	39	0.0	46.3
Artesunate-pyronaridine	2017-18	5	N = 153; TF = 3.9%	

World Health Organization

Remaining Challenges in GMS Malaria Elimination

- Technical support at sub-national levels in highest burden areas to improve implementation and coordination

- Monitor drug efficacy and update/implement national treatment guidelines

- Improve surveillance and scale-up elimination phase activities (e.g. case and foci investigation)

World Health Organization

Challenge: Issues in Surveillance

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

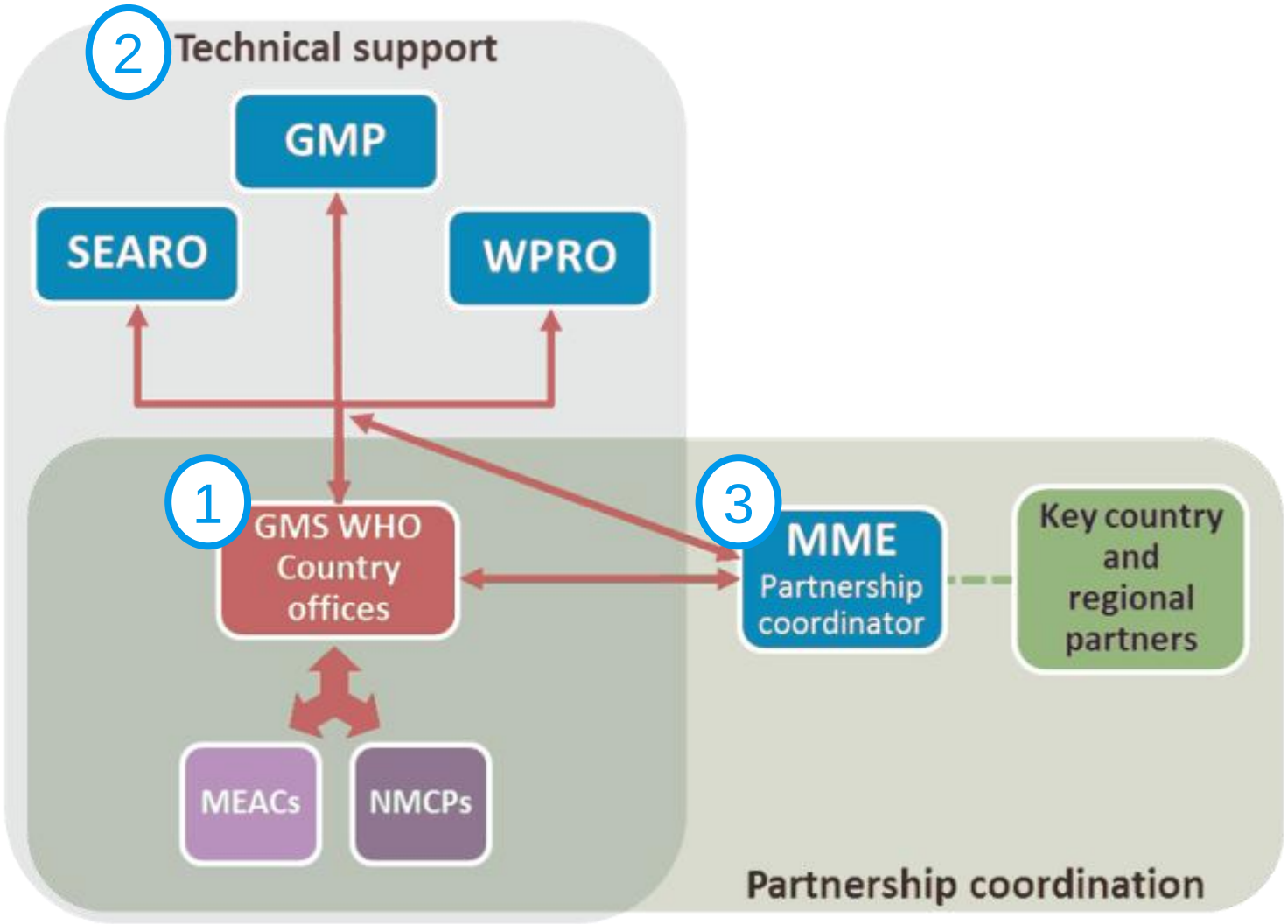
World Health Organization

Coordinating mechanism: Annual surveillance meeting

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

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

Structure of 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

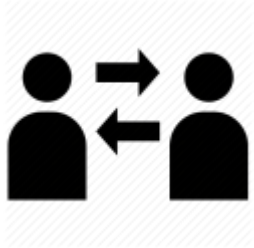
World Health Organization

Partner Coordination: 3 Key Layers

Low

Required interaction

High



- **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

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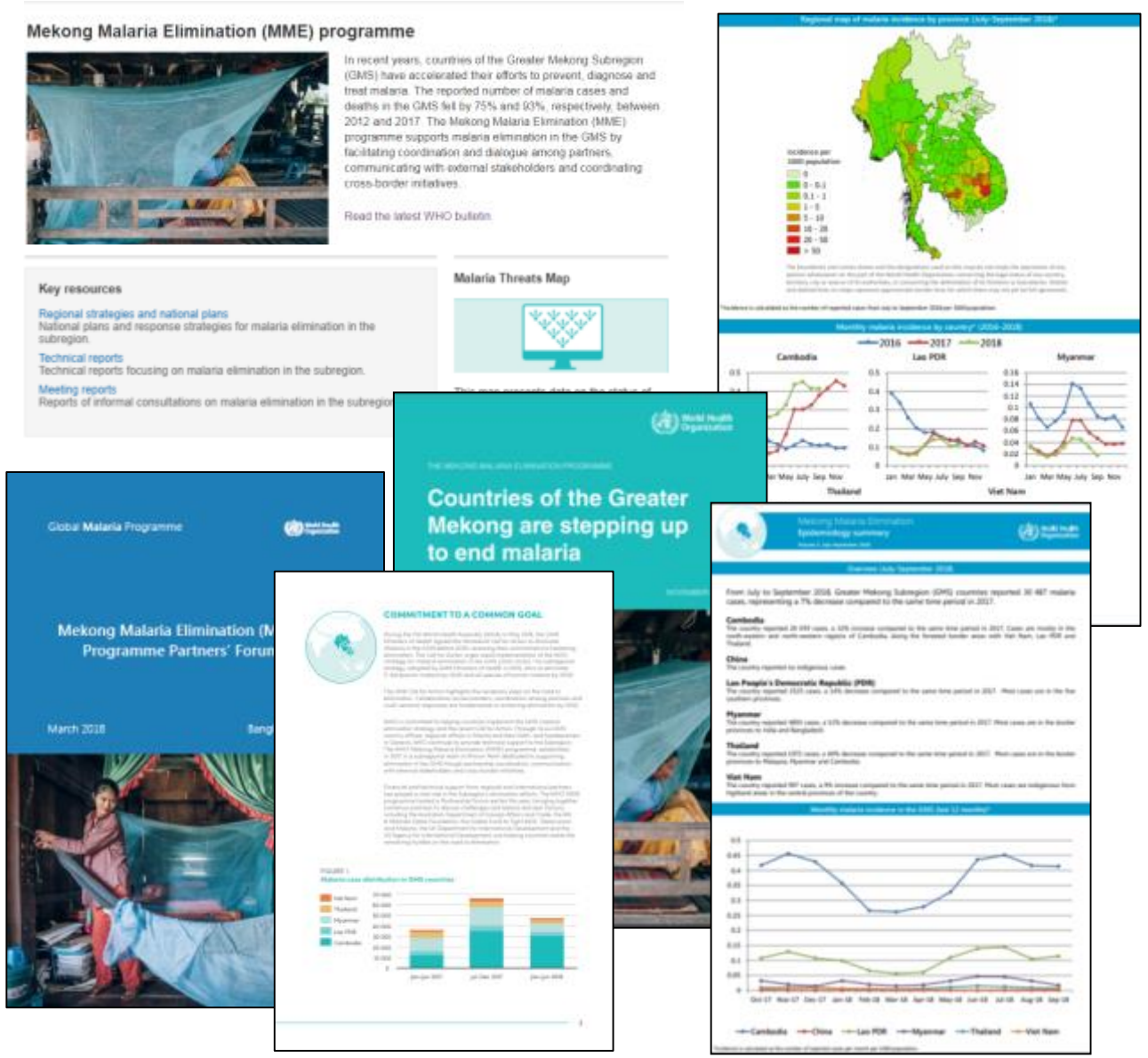
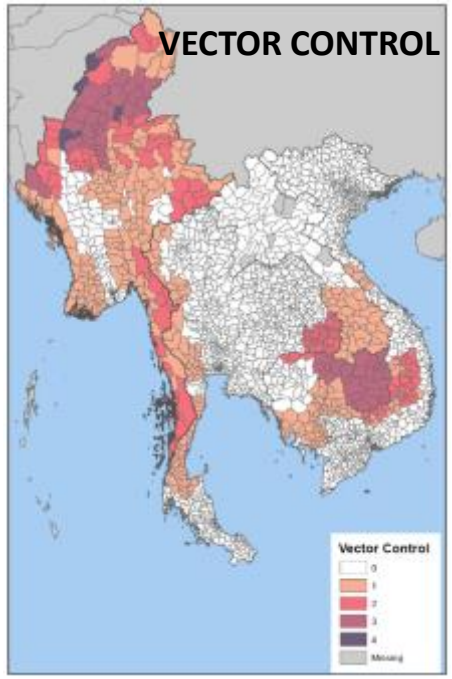
Information exchange

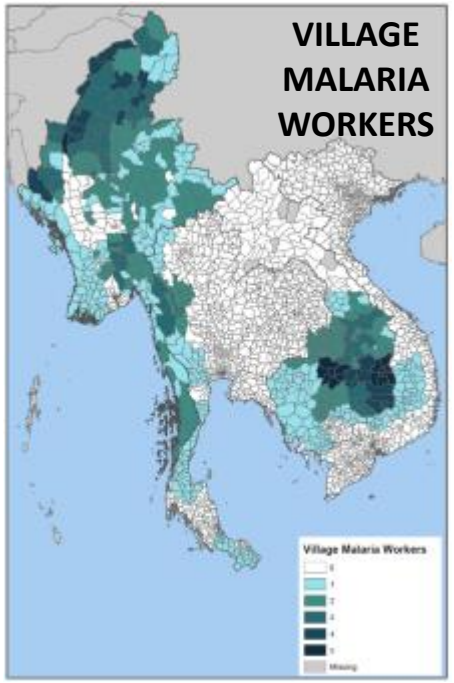


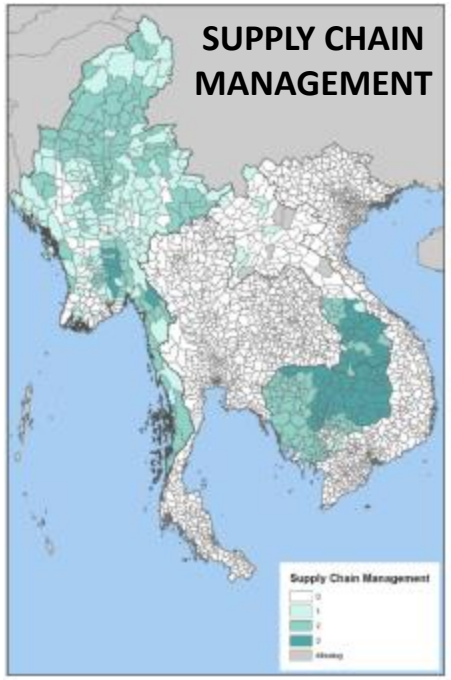
WHO facilitates information exchange (e.g. publications, website, mailing list, sub-regional and national meetings) so that partners are better informed about each other's activities

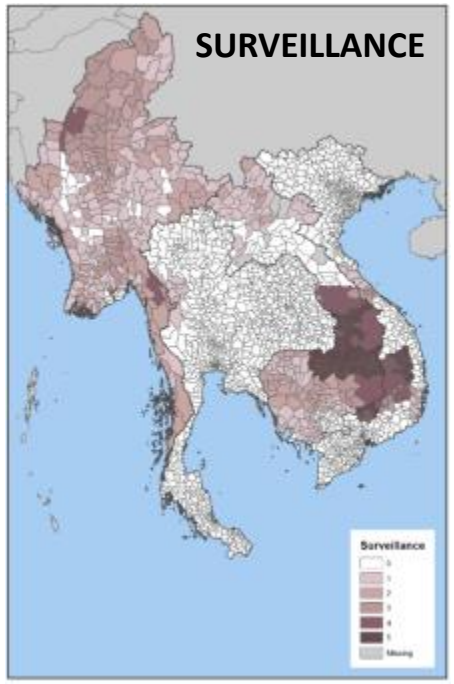
World Health Organization

Coordination and Collaboration - Partner Mapping with CHAI



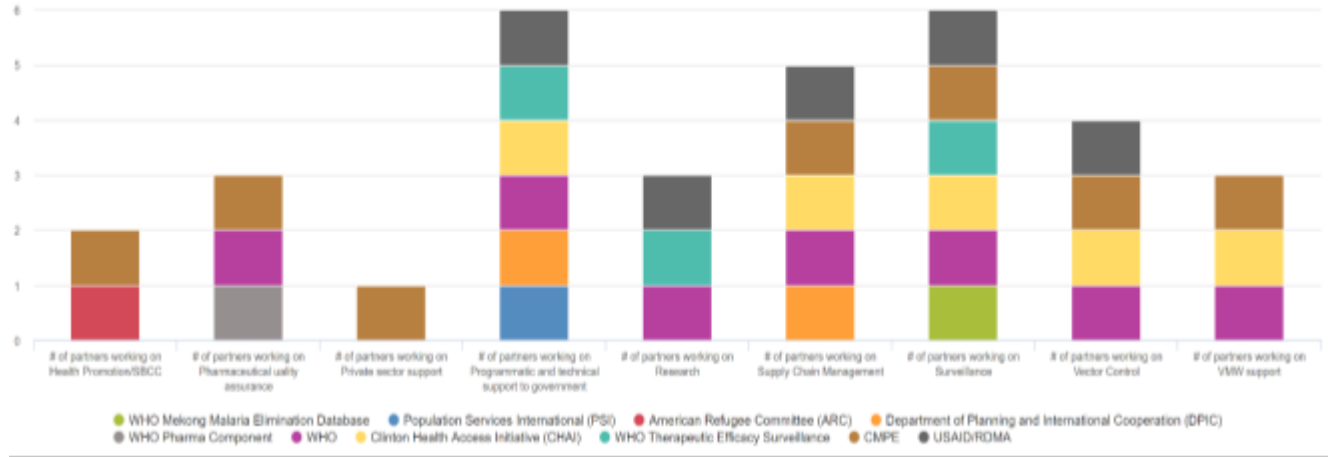






Source: WHO subregional database and CHAI survey

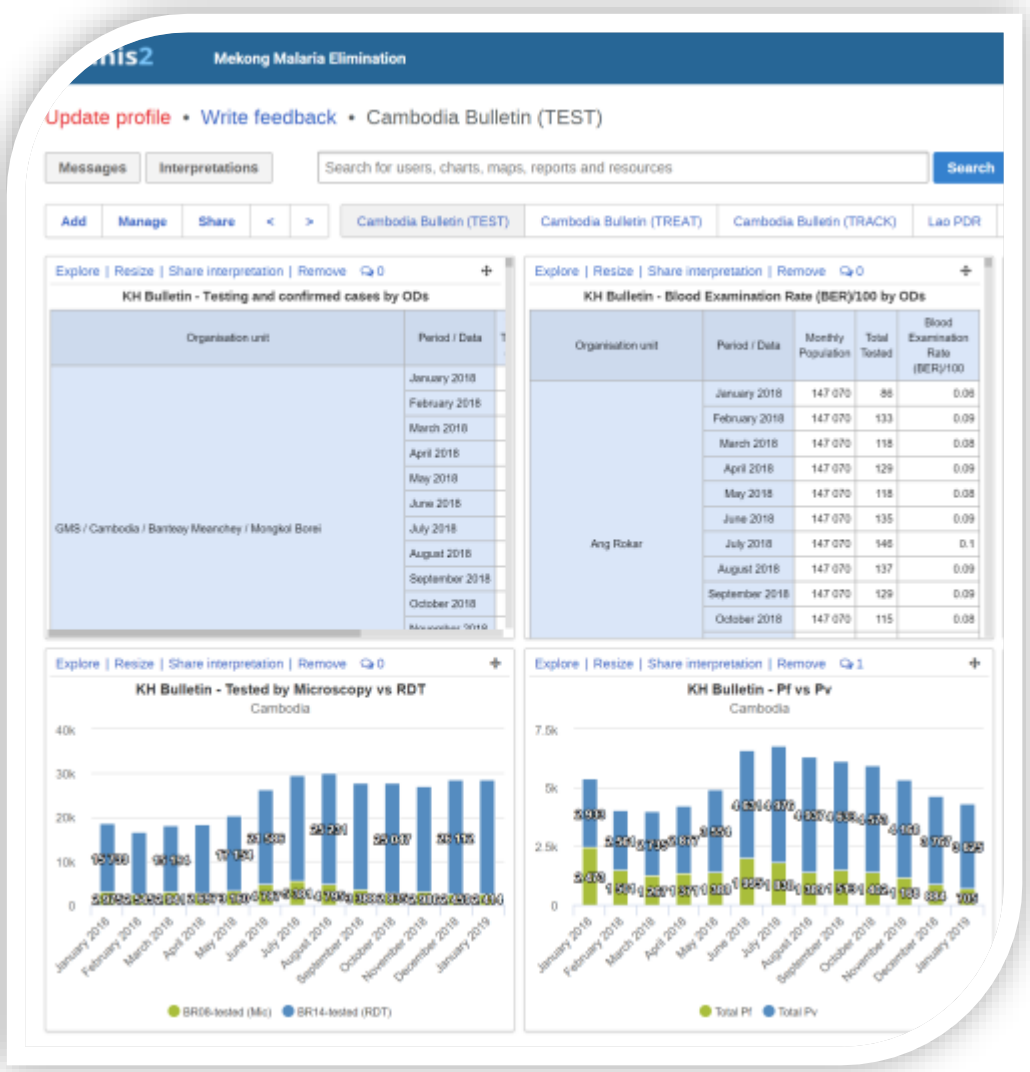
Partners working at national level (Lao PDR)



Examples of results from partner mapping with CHAI

World Health Organization

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



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

World Health Organization

Summary

- GMS countries significantly reduced the number of malaria cases from 2012-2018. In 2018, countries made significant progress towards Pf elimination, especially Cambodia, Myanmar and Thailand.

- Malaria cases are concentrated in small geographical areas among forest goers, requiring a focused and tailored strategy for these population (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

Malaria Policy Advisory Committee Meeting
10–12 April 2019, Geneva, Switzerland
Background document for Session 4

Fourth meeting of the WHO Strategic Advisory Group on malaria eradication

Meeting report
28–29 November 2018, Geneva, Switzerland

Summary

On 28–29 November 2018, the WHO Strategic Advisory Group on malaria eradication (SAGme) convened for its fourth meeting in Geneva, Switzerland.[1] Major discussion points included the review of progress made by SAGme members, WHO staff, WHO collaborating centres and other partners on six work packages, and presentation and discussion of the preliminary conclusions drawn from these analyses. In addition, the SAGme discussed the format of the final product to be provided to the Director-General.[2]

This meeting involved 10 SAGme members, representatives from five WHO collaborating centres and other key malaria stakeholders, including observers from technical partners (PATH, CDC) and industry (Novartis), along with other UN agencies (UNICEF) and the Secretariat (WHO's Global Malaria Programme [GMP]).

Three new members joined the SAGme: Dr Scott Barrett (Columbia University, USA), Dr Neena Valecha (National Institute for Malaria Research, India)[3] and Dr Philip Welkhoff (Bill & Melinda Gates Foundation [BMGF], USA), who assumed the place formerly held by Dr Chris Elias (BMGF, USA).

The objectives for this meeting included the presentation of the preliminary findings and conclusions of six work packages. Members of each work package group met during the first day of the meeting to receive feedback, guidance and course corrections from the Advisory Group in order to determine the next steps, and presentations to the plenary were completed on the second day. In addition, the Group was updated on course activities undertaken in the year, such as informal meetings in September and October 2018, teleconferences and internal meetings in preparation for this fourth meeting.

Background

WHO's GMP convened the inaugural SAGme meeting in August 2016. Thirteen eminent experts representing a range of disciplines and geographies were selected as members and supported by representatives from WHO collaborating centres, WHO staff, and other key malaria stakeholders. The terms of reference for the SAGme outline its role in advising the Organization on the relevance, potential strategies and cost of malaria eradication over the next decades through a process of

[1] This report is considered preliminary while SAGme members complete their review of the document.

[2] *Update received at the end of December 2017:* On behalf of the Department for Governing Bodies, the SAGme will not have to report to the Executive Board and will only report to the Director-General of WHO. A progress report from WHO/GMP will be presented to the Seventy-second World Health Assembly, during which additional information can be provided.

[3] *Update from January 2019:* Dr Neena Valecha has been officially nominated as WHO Malaria Regional Adviser for the South-East Asia Regional Office in New Delhi, India and so will not be able to continue her appointment as SAGme member.

WHO/CDS/GMP/MPAC/2019.03

analysis and discussion, considering the agreement on the WHO *Global Technical Strategy for malaria 2016–2030* (GTS) adopted by the World Health Assembly in May 2015.

Updates from the Global Malaria Programme

Dr Pedro Alonso, GMP Director, presented the latest data from the World Malaria Report 2018, which was launched in Maputo, Mozambique in November 2018. The report documents the continuing high toll of malaria, with more than 200 million new cases in 2017. Despite significant progress in reducing cases and deaths between 2000 and 2014, the trend seems to have flatlined since 2015 with no further decreases reported. Dr Alonso noted that we are off track in meeting the targeted reductions in morbidity and mortality set out in WHO's GTS, i.e., a 40% reduction by 2020 (from 2015 levels); moreover, prospects for achieving these milestones are quite discouraging.

Despite the overall lack of progress on morbidity and mortality indicators, the data show signs of progress in some countries and regions of the world. To mention a few examples:

- The number of countries with fewer than 100 indigenous cases – a strong indicator that elimination by 2020 is within reach – increased from 15 countries in 2010 to 26 countries in 2017, while the number of countries moving towards elimination and reporting fewer than 10 000 malaria cases increased from 38 to 46 countries in the same time period.
- China and El Salvador reached zero indigenous cases of malaria for the first time in 2017, while WHO certified Paraguay as malaria-free in 2018. Paraguay is the first country in the Americas to be granted this status in 45 years.
- Focusing on the countries that represent the highest burden of global malaria, India registered an impressive 24% reduction in cases in 2017 compared to 2016, while countries such as Ethiopia, Pakistan and Rwanda noted considerable declines in cases in 2017 – by 8.9%, 20.5% and 6.6%, respectively.
- The African region, which has the highest burden of malaria, has significantly expanded access to diagnostic testing in the public sector, with a median of 74% of febrile children under 5 receiving a malaria diagnostic test prior to antimalarial treatment – an important increase from 35% in the period 2010–2012.

As a result of the stagnation in progress and to get the global malaria response back on track towards achieving the GTS goals, the GMP Director presented the new country-driven approach *"High burden to high impact: a targeted malaria response"*, which was launched on 19 November 2018. This aggressive approach has been catalysed by WHO and the RBM Partnership to End Malaria and will be led by the 11 countries that carry the highest burden of the disease. The approach aims to become the response to a critical inflection point for malaria.

Meeting opening

The Chair of the SAGme, Dr Marcel Tanner, opened the fourth meeting with a brief overview of the background and purpose of the SAGme, an introduction to the new members who had recently joined the group in 2018, and a summary of the work done over the past year by the different work groups and the GMP Secretariat.

Since the last meeting, work groups have held several internal meetings, regular calls and discussions with experts and members of their groups to incorporate all inputs and suggestions from the Advisory Group.

In brief:

- At the third SAGme meeting in December 2017, Rwanda was selected as a relevant context for field-testing the community engagement framework for quality, people-centred and resilient health services (CEQ)[4] and for validating a process to co-develop and co-learn with national malaria programmes how to improve community engagement. In January 2018, WHO received approval from the Ministry of Health in Rwanda to convene a three-day technical meeting in May to introduce the CEQ, further develop the preliminary assessment tools, and verify their relevance and utility for malaria control and elimination. The meeting was an opportunity to co-design with the national team an appropriate approach to field-testing.
- In September 2018, several of the work group leaders convened for an informal meeting at GMP to present an update of their work progress from Q1–Q2 2018 in order to ensure that the directions being taken were in agreement with SAGme guidance.
- In October 2018, GMP held a symposium on the *Lessons from the history of global policies against malaria and aspects of contemporary developments in global health governance* by Dr Julian Eckl from the University of Hamburg and University of St. Gallen. Dr Eckl contributed a historical perspective on past and present sociopolitical considerations for achieving a world free of malaria. This work package will be part of the historical and contextual background for the SAGme to consider when finalizing its recommendations.

In terms of structure, this fourth meeting started with a day-long breakout session to review the evidence generated by the work groups and develop preliminary conclusions for each work package. The objective was for these final products and recommendations to be presented at a closing meeting of the SAGme in the second quarter of 2019. The second day of the meeting included brief presentations of the key findings from each work group and a discussion of the preliminary conclusions in Plenary. The findings and preliminary conclusions will be captured in a final report and presented to the WHO Director-General.

This meeting report gathers the key outcomes and points of discussion from the six work packages presented. All supporting documents and presentations (PDFs) can be downloaded from the Dropbox link. These materials complement the background sections and support key points addressed during the meeting. *If you have problems accessing or downloading the files, please contact the GMP Secretariat.*

Key findings and preliminary conclusions of the work packages

Lessons from the history of global policies against malaria and aspects of contemporary developments in global health governance

The sociopolitical dimension of malaria control that was discussed contributes to the work of SAGme by: (i) analysing historical experiences to better understand continuous challenges as well as present sociopolitical considerations for achieving a world free of malaria; (ii) analysing contemporary global health governance in order to put malaria into a broader context and to address the question of how malaria relates to (or could be linked to) the various other health and development challenges; and (iii) drawing on the previous two steps and on theoretical-conceptual literature in order to help SAGme better understand the character of the policy options that it might propose in light of its other findings.

This historical perspective demonstrates that the fight against malaria has had its challenges and successes. Moreover, successes in one place have often prematurely been seen as evidence of what

[4] WHO community engagement framework for quality, people-centred and resilient health services. Geneva World Health Organization; 2017 (WHO/HIS/SDS/2017.15; https://www.who.int/iris/handle/10665/259280).

can be achieved elsewhere and at a global level. These historical experiences resemble contemporary patterns, suggesting a continuity of malaria trends throughout history. For example, while there has been successful control and reduction of burden over the past decade, on the other hand, the plateauing of funding, emerging resistance and other rising challenges have stalled progress.

Building on the historical perspective, the challenge was discussed in terms of how different actors interpret the malaria problem in divergent ways. There are three interrelated questions that help to identify specific interpretations of the malaria problem: (i) what is the problem?; (ii) who should solve it?; and (iii) what is the solution? Various consequences follow from these divergent interpretations, one of which is that the overall complexity is easily overlooked by individual interpretations. Another consequence is that there is often a difference between global and local interpretations, while a third is that each interpretation necessitates the cooperation of specific actors and makes specific approaches to solving the malaria problem plausible.

Policy-making can be seen as a process during which several interpretations of the malaria problem are discussed, but at some point, one interpretation becomes the basis for the way forward. This process consists of three main stages or phases: perception of a problem and agenda setting (first phase); formulation of policy alternatives and decision-making – i.e., legislation (second phase); and implementation and evaluation (third phase). These phases can be thought of as the "dramatic structure" of the policy process, since the second phase is often viewed as the climax. The problem with this understanding, however, is that it implicitly takes for granted the required cooperation of various actors who are central during the implementation process in the third phase and whose roles vary with different interpretations of the malaria problem. By the same token, the specifics of global health governance (including WHO) as a political system are often overlooked. A related challenge is that, in global health, decisions are often taken in a decentralized manner (exit-based policy-making), which results in parallel processes and complicates implementation further.

In light of the historical record, it is pertinent to pay greater attention to phase three in general and to implementation in particular. In turn, a closer look at phase three shows that implementation has multiple facets. Most importantly, there is a notable difference between output, outcome and impact: output describes the immediate results of the activities of an organization; outcome comprises the behavioural change by target actors; and impact covers relevant changes in the policy area. Moreover, the specifics of the form, scope and domain of WHO's (contested) authority must be taken into consideration. It is also key to acknowledge the difference between "selling" and sustaining a decision. As a related point, the political commitment that eradication, in particular, implies and requires must not be downplayed. Furthermore, the challenge of opportunity costs has to be taken seriously.

Some tentative conclusions were drawn from the historical record, from contemporary developments and from the theoretical-conceptual literature. For example, it was stated that SAGme would make an important contribution if it clarified the characteristics of the available options, and it was recognized that it is important to specify the behavioural changes that are required to do so.

Another key conclusion discussed was that the perspectives, roles and contributions of affected countries and populations need to be integral elements in the decision-making process; it is not enough to mobilize affected countries as executors of global programmes, as seen in previous efforts, for example, with the Global Malaria Eradication Programme (GMEP).

The SAGme agreed that the vision of a malaria-free world is not in question, but there is a disagreement over the exact next steps to be taken to achieve this vision. This disagreement is due to another point of discussion about varying interpretations of malaria. The challenge of differing approaches to achieving the vision of a malaria-free world remains to be addressed, as does the fact that malaria eradication is not a priority for everyone. It was suggested that the SAGme link its recommendations to other contemporary developments – both for strategic reasons and for the sake of clarity.

To contextualize the way forward, a few steps WHO has taken to build on the GTS were summarized. To offer some examples: the "High burden to high impact" response and the most recent World Malaria Report are practical steps that have been agreed upon in a broader context to address the challenges facing the malaria world. With WHO undergoing a transitional period, the work towards the Sustainable Development Goals (SDG3.3 but also other SDGs as determinants of health) and the 13th General Programme of Work provide other examples of WHO increasing its representation in country offices, putting implementation onboard and taking practical steps towards greater integration among the country level, Member States and WHO, as well as with key stakeholders and funders.

The SAGme positively valued the presentation on the historical perspective, contemporary developments and theoretical-conceptual literature, recognizing the importance of the different levels and scenarios in which the malaria landscape operates. This complexity may at times hinder the broader vision and goals of the fight against the disease. The presentation also highlighted the importance of political will and elevating the issue to higher level discussion as part of the global health agenda. There was discussion on how to tackle political will in a broader context and link to the SDGs as determinants of health, as well as how the elimination of malaria can have a positive influence on these areas. Furthermore, there is a huge opportunity to look at this mutual relationship and to some extent highlight the importance of increasing mobilization and keeping up with momentum. The group agreed to the point around global thinking in terms of policy-making and raising the profile of the issue to secure a sustained investment and strong political commitment.

Considering the preliminary conclusions presented, the majority of the SAGme acknowledged a note of caution when calling for a World Health Assembly resolution, understanding that the global health context and political will differ greatly from previous times. However, the SAGme insisted that resource mobilization (locally and internationally) and political investment remain important, despite being highly dependent on the context of each country. Regarding the behavioural change this would require, SAGme acknowledged that it would take a global effort from all actors in the malaria space – from regional and local programmes to funding agencies – to align with the final outcome the SAGme would present to WHO.

The SAGme requested to see a final presentation at the meeting in June 2019.

Community engagement

In previous SAGme meetings, it was agreed that there has been growing appreciation of the importance of community engagement (CE) as fundamental to providing quality health care and services and core to achieving Universal Health Coverage (UHC). Paradoxically, despite this belief, there continues to be a lack of consensus on the definition of CE. The literature shows multiple definitions of CE that have been used in various settings. Most of these definitions have been underpinned by top-down, linear conceptualizations, with community members often considered to be passive recipients. Demonstrating the value of such approaches has been generally challenging and inconclusive, and across sectors, these approaches have not yielded the hoped-for gains in progress and/or development. A more helpful definition of CE would need to incorporate the notion of complexity in living human systems.

> *"The world and its systems are complex, dynamic, and unpredictable. Yet development approaches are largely fixed and tied firmly to preordained plans and change theories. As a result, development interventions often fail and are very rarely sustainable."*
>
> Burns D, Worsley S. Navigating complexity in international development: facilitating sustainable change at scale [e-book]. Rugby: Practical Action Publishing; 2015: Kindle Locations 130–1.

The work package presented how approaches based on complexity and systems thinking would require a change in mindset in a health system to acknowledge that everything and everyone is connected (systemic) and that the quality and performance of the system emerges in those

connections. From this perspective, CE is founded upon an understanding of the relationships between people, and the nature and quality of those relationships shape collaboration, co-creation, coordination and trust. Empowerment and partnership become co-constructed through the interactions between people. Engagement represents a relational and systemic process – a dialogue through which a shared vision arises.

The WHO Community Engagement Framework for Quality, People-Centred and Resilient Health Systems (CEQ) was created through a collaborative process to address the need to shift health systems, programmes and services from an almost vertically driven, transactional model of engagement to a relational model.

Three key conclusions/implications were agreed upon during and following the SAGme meeting in November 2017: (i) to adapt the WHO CEQ to the malaria context; (ii) to test and validate the adapted WHO CEQ for malaria control and elimination in collaboration with the National Malaria Control Programme in Rwanda; and (iii) in light of the adaptation and field-testing, to review the current status of WHO's policy, technical and strategic guidance and recommendations on CE for malaria. The findings would be critically reviewed considering the CE case studies being developed by the University of California, San Francisco (UCSF).

Rwanda was selected as the country to test the CEQ not only to provide valuable inputs on how the national programme can better engage and build relationships with its communities and stakeholders, but also to help the SAGme build these national experiences into global discussions and reinforce recommendations discussed during the meeting in November 2017.

The work package was presented at the CE technical meeting that took place in May 2018 in Kigali, Rwanda. Meeting participants included one SAGme member, technical leadership from the Rwanda National Malaria Control Programme, community health workers, implementing partners and stakeholders, and staff from the WHO Country Office and headquarters. The CEQ was introduced and discussed, and a team was established to develop a proposal to field-test a set of analytical tools.

The development and findings of this meeting were presented at the SAGme meeting, along with an overview and discussion of the data collection methods and pilot assessments carried out in the four selected districts in October 2018.

The SAGme recognized the progress of the CE work package and highlighted the request made from the work group regarding the opportunity to review the status of WHO recommendations on CE at policy, programme implementation and guideline levels with respect to achieving malaria elimination and eradication. SAGme noted that there would be an opportunity for the group to integrate the CE work at three different levels:

1. At the level of strategy and implementation, CE is included in technical guidance and strategy. However, through the SAGme work, there is an opportunity to emphasize how CE needs to be addressed at the start of the process and integrated throughout.
2. Reflecting on existing malaria-related guidance and interventions, it was also noted that there was a need to generate people-centred approaches that incorporate co-design of strategies and interventions.
3. At the operational level, the findings that emerge from the CEQ field-testing can help to make connections between different levels of the health system in a way that enhances and optimizes existing WHO guidelines, which need to be adapted and used, e.g., community health worker guidelines.

At the end of the review, the SAGme discussed and asked questions about the sustainability of the CEQ and the ability to scale up the findings. It was noted that the CEQ is broad enough in scope to include an understanding of how dynamic systems operate, while taking into account country and regional contexts and specificities. The process of introducing and field-testing the CEQ should include

developing the skills, knowledge and mindset to embed learning throughout the programme. Once the skills and conceptual knowledge have been developed, the people/community will be supported to engage in a different way. This could prove to be a much more cost-effective way to build engagement with communities in a way that is more enduring and more suited to individuals in a situation than it has been in the past.

The SAGme requested a presentation of the final data findings at the meeting in June 2019.

Health systems readiness for malaria control and eradication

The main objective of the analyses conducted by the Swiss TPH, a WHO Collaborating Centre, was to identify the characteristics of health systems that were most predictive of successful malaria control in the 2000–2016 period. The group presented all available information on health systems, combined in a new health systems database and linked to the most recent data on changes in malaria burden. Multivariable regression models were used along with a range of model selection algorithms in order to identify the factors most strongly associated with successful malaria programmes.

After reviewing the analyses, the group concluded the following:

- Overall, the health systems variables seem to be predictive of malaria progress in the period 2000–2016.
- Across subperiods, however, the best models identified do not seem to be very stable, and the best models based on the first period (2000–2008) do not seem to predict the subsequent period very strongly (2008–2016).
- One of the primary reasons as to why this seems to be the case is the substantial trend reversals in some high-burden countries with highly ranked health systems.

The SAGme recognized the progress made in the work package, although a few members were concerned about the ability to arrive at specifics, such as being able to isolate specific features associated with more rapid progress in malaria control over the study period. Another point of discussion was around the private sector issue, which was raised in previous meetings and has not been entirely addressed. Some members mentioned that a large proportion of patients attend private facilities, and these are not reflected in the data collected.

Megatrends

For the fourth meeting of the SAGme, the megatrends work group presented an overview of the preliminary results characterizing expected global changes in a range of megatrends through 2050 and assessing the potential of these megatrends to compromise or accelerate malaria eradication. The megatrends taken into consideration were population growth, demographic shifts, urbanization, climate change, land use change, migration and economic development.[5] The SAGme had previously acknowledged the importance of prioritizing megatrends in factors having direct and significant impacts on malaria, given the potentially enormous number of megatrends that could be possibly considered.

Literature reviews were conducted for each of the megatrends to provide descriptions of how these factors are thought to affect malaria transmission in various places around the world, the direction the trends are likely to take and, therefore, the implications for malaria eradication in the future.

Population growth and demographic shifts

As the global population expands from the current 7.6 billion to 9.8 billion by 2050, 60% of that growth will occur in sub-Saharan Africa. In fact, 50% of the world's population growth in this period will occur

[5] All accessible pre-reads under the meeting folder on Dropbox - to access please click on the following link

in just eight malaria-endemic countries: India, Nigeria, Democratic Republic of the Congo, Pakistan, Ethiopia, United Republic of Tanzania, Uganda and Indonesia. At the same time, the population aged 10–24 years will increase substantially in Africa.

The implications for malaria eradication are evident, in that, increasing populations in Africa will require greater amounts of preventive, diagnostic and curative tools. Additionally, as the number of adolescents and young adults increases, and any remaining immunity is present in older adults, older adults may become an important reservoir for infection.

Urbanization

The majority of the world's population already lives in cities. By 2030, 60% of the world's population is expected to live in cities, with this figure rising to 66% by 2050. The United Nations estimates that more than 90% of future urban population growth will be in low- and middle-income countries (LMICs).

Cities are engines for economic growth, responsible for over 80% of global economic activity. Comparatively well resourced, cities have more health workers, financial resources and facilities, and better electricity supply, refrigeration and supply chain management than rural areas. High population density facilitates large-scale access to health care providers, and medical and other products. However, high population densities mean that people can be clustered around risks. Increased mobility and contact with people can result in increased risk of disease transmission.

The growth of cities has, however, been associated with reductions in the risks of malaria. Indeed, there is clear evidence that vectors are less plentiful and the prevalence of infection is lower in cities than in the surrounding rural areas. Nevertheless, given the vast numbers of people living in cities, even a low risk of urban malaria can translate into a considerable public health problem. Cities offer both opportunities and risks for malaria eradication, and links to urban planning will need to be made for malaria eradication in the future.

Climate change

Climate influences malaria both directly through vector and parasite development and indirectly through its influence on socioeconomic systems and processes relevant to malaria infection, control and elimination. Climate observations and forecasts may inform a wide range of decisions related to malaria elimination and eradication through an improved understanding of the mechanisms of infection transmission, better monitoring and evaluation of interventions, mapping of spatial variations in risk and management of temporal variations in risk (from subseasonal to decadal).

Although there is great uncertainty in estimating future climate patterns, we know that temperatures have risen significantly in almost all parts of the world and are expected to continue to rise. Rainfall changes in many regions are less clear. Although future projections are highly uncertain, there have been changes in extreme weather patterns and climatic events. Climate change will be felt not through trends, but through changes in the intensity, frequency and geographical extent of weather and climate shocks, seasonality and other components of climate variability. An important point to consider is that the climate change projections for the future are highly uncertain, particularly at the spatial and temporal scale relevant for decision-making. The conclusion is that eradication strategies will have to be flexible, building in monitoring and forecasting of climate impacts and evaluation of evidence of climate change affecting malaria.

Land use and land cover change

Land use and land cover change (LULCC) is primarily driven by agricultural expansion, deforestation and urbanization. These changes to the physical environment can affect mosquito breeding sites and, to a lesser degree, adult mosquito resting sites. LULCC may also push or pull human population movement, thereby affecting parasite movement as well. Remote sensing techniques can be used to monitor physical changes in the environment in order to predict near-future malaria risk. Overall, the

impacts of LULCC on malaria transmission are highly complex and context-specific, and dependent on the spatial and temporal units of data being analysed. Land use change is a dynamic process, with disease transmission finding a new equilibrium after each disruption.

Migration

The importance of migration to malaria elimination is that parasites move with people. Movement of (possibly asymptomatically) infected people into areas that have eliminated malaria but remain able to support transmission raises the spectre of reintroduction of the disease. Areas moving towards elimination may have their progress impeded by inward migration of parasites from outside. However, analysis of global migration patterns shows that internal migrants within a country outnumber international migrants three to one (740 million cumulative internal migrants in 2018 compared to 244 international migrants). It is expected that 35 million people will migrate from less developed countries (largely malaria-endemic) to more developed countries in Europe and North America through 2030. Nevertheless, this is not expected to pose a large challenge to the populations of the receiving countries, as they are generally less receptive to transmission than the sending countries. Review of these trends makes it clear that internal population movements within countries and subregions, and on a short time scale, will be more important to malaria eradication than population movements across continents.

Quantitative exploration of malaria trajectories in Africa to 2050

The Malaria Atlas Project at University of Oxford, a WHO Collaborating Centre in geospatial disease modelling, combined the effect of several megatrends to generate maps of malaria risk in Africa for 2030 and 2050. The Project explored the impact of keeping malaria interventions at current levels or increasing them to examine the effect of full-scale implementation. The first step was to characterize the relationship between environmental conditions, intervention coverage and malaria transmission. Data were combined in a Bayesian geostatistical model that allowed the empirical relationships to be characterized. Subsequently, plausible environmental conditions were projected spatially into 2030 and 2050 under particular scenarios of global change. Using the empirical relationships developed during the first step, the malaria scenarios in 2030 and 2050 were computed. Finally, enhanced coverage of current tools and innovation of new tools were added to the models to generate best case scenarios for the future.

The results indicate that malaria prevalence will decline substantially in 2030 and 2050 as a result of the combined effects of megatrends if current intervention impacts are maintained. However, malaria will not be eliminated in Africa. Scaling up existing interventions and adding new tools currently in the pipeline further reduces malaria but does not achieve elimination in Africa.

Eradicating in the hardest areas

Building on the megatrends work package, it was discussed and agreed that the Malaria Atlas Project at the University of Oxford, in support of the SAGme, would analyse the future malaria scenarios in 2030 and 2050 in order to (i) understand the factors that are most important in determining the hardest or last places to eliminate, and (ii) identify potential strategies to mitigate those factors and facilitate eradication. This analysis will be presented at the final SAGme meeting in June 2019.

Potential risks that could threaten or delay eradication

Simian malaria

During the last meeting of the SAGme, the group felt that there needed to be an acknowledgment that zoonotic malaria poses a risk to eradication, and the SAGme needed to be more proactive regarding the potential threat posed by zoonotic malaria. Systematic, longitudinal monitoring of populations at risk of simian malaria is required, and surveillance should be conducted in areas

identified as at high risk for zoonotic malaria. Moreover, it was recognized that there is a lack of information and tools to easily facilitate monitoring of simian malaria, and further investment in research and development is needed.[6]

In reviewing the reports, the SAGme concluded that (i) while zoonotic reservoirs of plasmodium parasites exist, there have yet to be documented cases of sustained human-to-human transmission of zoonotic malaria. Efforts to eradicate human malaria should not be derailed by focusing on simian malaria; (ii) existing prevention and treatment tools are currently effective at controlling zoonotic malaria; and (iii) the transmission potential of zoonotic malaria could change and thus continued surveillance and research are merited.

In addition, as part of the work package, the UCSF Global Health Group's Malaria Elimination Initiative (MEI) conducted and worked with GMP to present preliminary results on a series of short case studies developed to investigate malaria control and elimination efforts in the context of violent conflicts, natural disasters and other health emergencies, drawing out challenges, successes and lessons learned. In the previous meeting, the SAGme suggested an investigation of government health system breakdowns, complex emergencies and natural disasters. Preliminary findings were presented from case studies looking at violent conflict, focusing on Afghanistan; natural disasters, focusing on the 2010 earthquake in Haiti; and other health emergencies, focusing on the 2014–2015 Ebola outbreak in Sierra Leone.

The SAGme acknowledged that, although there is no one-size-fits-all approach that can span emergency types or locations, general lessons can be derived from countries that have dealt with a range of complex emergencies at various points along the malaria transmission continuum from high burden to eliminating and prevention of re-establishment.

After reviewing the case studies, the SAGme concluded that (i) complex emergencies are likely to cause disruptions in the progress towards elimination and eradication, but that should not deter us from pursuing this goal; and (ii) the impact of these inevitable events can be mitigated through various measures. For example:

- Robust health systems, complemented by specific emergency preparedness plans, play a key role in helping to mitigate the impact of disasters and hasten recovery.
- However, especially in terms of the endgame, this will need to be supplemented by a vertical approach with surge capacity at different levels.
- The potential for malaria resurgence needs to be included in the broader global and local discussions regarding disaster risk reduction and response.

Economics

The economics work package presented an overview of the work developed over the past year. Three studies were presented: (i) a retrospective cross-country regression study of the correlation between measures of malaria intensity and the level and growth of per capita income over the period 2000–2015; (ii) a cross-country modelling study of the impact of reaching malaria control targets on national and per capita income levels over the period 2016–2030 (towards a potential investment case on health benefits and economic returns); and (iii) a theoretical piece on the economics of malaria eradication that develops a conceptual framework for decisions about pursuing malaria eradication versus optimal control, focusing on human behaviour dynamics in order to study the feasibility and desirability of policy options.

[6] On drug resistance, a general agreement among the group was to consider it a risk and that it would be developed in-house by GMP given the significant attention it is already receiving.

From the first macro study (macro study 1), the group gave an update on the econometric analysis of the relationship between GDP and malaria, reviewing and replicating the highly cited paper by Gallup and Sachs (2001). The work estimates the association between case incidence and macroeconomic outcomes over the period 2000–2015, using recent data and updated econometric techniques. It concludes that if all malaria-endemic countries had eliminated over the same period, their GDP per capita would have been 5% higher on average and their GDP per capita would have grown 1% per annum faster on average.

From the second macroeconomic study (macro study 2), the group presented an estimate of the economic impact of return on investment from scaling up the coverage of malaria control interventions in accordance with GTS targets compared to a baseline of sustained coverage (at their 2015 level) over the period 2016–2030. Using the Economic Projections of Illness and Cost (EPIC) tool, this work analysed the impact of improved malaria control on the economic outputs of a set of 29 countries that accounted for 95% of global malaria burden in 2016.

For the conceptual piece, the discussions revolved around the challenges in developing a framework for malaria eradication. This third paper was presented on the malaria eradication game by Scott Barrett, economist and member of the SAGme, who is currently working on a study that looks at human behaviour dynamics in the context of a single country; further developments are required to think about the framework at regional and global levels. The research provides a conceptual framework for thinking about whether to pursue eradication versus optimal control (namely, country-specific optima). The study focuses on human behaviour feedbacks and steady-state analysis to study the feasibility and need for policy interventions, which can vary according to the intervention features. In general, the research shows that technical feasibility needs to be combined with policy actions (e.g., subsidy) in order to achieve elimination and potentially future eradication.

The SAGme valued the updates on the studies and concluded that the key contributions were, first, additional historical evidence on the relationship between malaria intensity and economic growth in terms of GDP and, second, evidence of increases in economic output attributable to improvements in malaria control.

The plateauing of progress in reducing the malaria burden calls for a rapid, immediate and sustained increase in funding, pointing to the question of the feasibility and sustainability of such increasing funding needs over the long term. Continued progress towards a malaria-free world would need to be demonstrated in order to sustain willingness of donors to pay for malaria eradication. One challenge is that “malaria is not a priority for everyone,” which suggests that there should be a stronger representation of malaria in global, regional and national health financing dialogues. A final point of discussion regarding these studies was on funding sources. It was emphasized that the development assistance for health would likely be limited and not sustainable in a UHC context, and that governments of endemic countries play a critical role in terms of political commitment and increased resource allocation for health and malaria.

Final conclusions and next steps

The SAGme received all reports from the working groups and appreciated the thought and experience that had gone into preparing the evidence base, as well as the careful consideration of the implications of the findings in light of the SAGme’s terms of reference. A spirited discussion followed to draw preliminary conclusions from the meeting that would contribute to a final document back to the Director-General. The SAGme determined that one additional meeting would be required in 2019 to allow sufficient time to digest the findings and foster thoughtful reflection on the final conclusions and recommendations of the SAGme.

At the final session, the SAGme's preliminary conclusions were as follows:

1. Global megatrends are likely to contribute to reductions in malaria, but they will not be enough to eradicate by 2050, even with a full scale-up of current interventions.
2. New tools will be needed to achieve eradication.
3. Good, people-centred health systems will be fundamental to achieving eradication.
4. Willingness of Member States to embark on eradication is likely to be affected by the consequences of and reflections on the polio transition.
5. It will not be possible to estimate costs until the strategy is clearer.
6. Targets for the GTS are achievable, but while this will contribute significantly to eradication, it will not get the world to eradication.
7. In sum, in preparation for the launch of a successful malaria eradication campaign, the GTS 2030 targets must be met along with several key conditions.

The GMP Director concluded that the meeting had crystallized a lot of the work developed since the November 2017 meeting. The GMP Director explained that the new WHO administration was undergoing a transitional period over Q1 2019 to transform the Organization, and therefore the SAGme should reconvene for a last meeting in June 2019 in order to finalize the recommendations it will present to the Director-General.

It was agreed that the most effective way to capture the contributions of all work packages would be in a final report coordinated by the GMP Secretariat. An interim outline and draft executive summary will be presented at the next meeting.

List of participants

Members

Dr Scott Barrett
Lenfest-Earth Institute Professor of Natural Resource Economics
Columbia University, School of International and Public Affairs & Earth Institute
USA

Professor Sir Richard Feachem
Director
The Global Health Group
University of California San Francisco
USA

Professor Nyovani J. Madise
Director
Research and Development Policy
Head of Malawi Office
MALAWI

Dr Lindiwe Makubalo
Health Expert
Permanent Mission of South Africa to the United Nations Office and other International Organizations
SWITZERLAND

Dr Cheikh Mbacké
Senior Independent Advisor, Global Development and Population
SENEGAL

Dr Mirta Roses
Senior Independent Advisor, Global Public Health
Special Envoy for the Global Network for Neglected Tropic Diseases
ARGENTINA

Professor Marcel Tanner (Chair)
Director Emeritus
Swiss Tropical and Public Health Institute
SWITZERLAND

Dr Philip Welkhoff
Director, Malaria
Bill & Melinda Gates Foundation
USA

Professor Xiao-Nong Zhou
Director
National Institute of Parasitic Diseases
Chinese Center for Disease Control and Prevention
CHINA

Dr Neena Valecha (*unable to attend*)
Director
National Institute for Malaria Research
Indian Council of Medical Research
INDIA

Dr Alex Coutinho (*unable to attend*)
Global Health Consultant
UGANDA

Dr Kevin Marsh (*unable to attend*)
Senior Adviser
African Academy of Sciences
KENYA

Invited Speakers

Dr Julian Eckl
Post-doctoral Research Fellow
University of St. Gallen
SWITZERLAND

Dr Justin Cohen
Senior Director, Global Malaria
Clinton Health Access Initiative
USA

Dr John Parrish-Sprowl
Director, Global Health Communication Center
Indiana University Purdue University Indianapolis
USA

Professor Chris Drakeley
Professor of Infection and Immunity
London School of Hygiene & Tropical Medicine
UNITED KINGDOM

WHO Collaborating Centres – Observers

Dr Regina Rabinovich
Director
Malaria Elimination Initiative
Barcelona Institute for Global Health
SPAIN

Professor Peter Gething
Professor of Epidemiology
Big Data Institute
Nuffield Department of Medicine
University of Oxford
UNITED KINGDOM

Amelia Bertozzi-Villa
Postgraduate Research Scientist, Institute for Disease Modeling, Seattle
Dphil Student, Malaria Atlas Project
University of Oxford
UNITED KINGDOM

Dr Peter D. McElroy
Chief, Program Implementation Unit
Malaria Branch
Centers for Disease Control and Prevention
USA

Dr Hannah Nissan
Associate Research Scientist
International Research Institute for Climate and Society – Earth Institute
Columbia University
USA

Dr Guenther Fink
Head of Unit, Household Economics and Health Systems Research
Swiss Tropical Public Health Institute
SWITZERLAND

Maitreyi Sahu
Scientific Assistant, Health Systems and Policy
Swiss Tropical Public Health Institute
SWITZERLAND

Partners – Observers

Dr Larry Slutsker
Director
Center for Malaria Control and Elimination
PATH
USA

Dr Bruno Moonen
Deputy Director for Malaria
Bill & Melinda Gates Foundation
USA

Dr Scott Filler
Senior Disease Coordinator, Malaria
The Global Fund to Fight AIDS, Tuberculosis and Malaria
SWITZERLAND

Dr Beverly Fenton Hall
Chief, Parasitology & International Programs
National Institutes of Health
USA

Dr Valentina Buj de Lauwerier
Global Malaria Advisor
Health Section, Programme Division
UNICEF
SWITZERLAND

Dr Ingrid Chen
Assistant Professor, Department of Epidemiology and Biostatistics
Associate Director, Eradication Research
Malaria Elimination Initiative, Global Health Group
University of California, San Francisco
USA

Dr Wiweka Kaszubska
Head of R&D Drug Development Team
Medicines for Malaria Venture
SWITZERLAND

Dr Lutz Hegemann
Global Development Head
Established Medicines & Anti-Infectives
Novartis Pharma AG
Global Drug Development
SWITZERLAND

Dr Richard Steketee
Deputy U.S. Global Malaria Coordinator
U.S. President's Malaria Initiative
USA

Janet Kristen Ginnard
Strategy Director
Unitaid
SWITZERLAND

Alexandra Cameron
Technical Manager, Strategy Team
Unitaid
SWITZERLAND

Prof Jean-Louis Arcand
Head, International Economics Department
Head, PhD in Development Economics Programme
Graduate Institute of International and Development Studies
SWITZERLAND

Seoni Han, PhD candidate
Graduate Institute of International and Development Studies
SWITZERLAND

Nayantara Sarma, PhD candidate
Graduate Institute of International and Development Studies
SWITZERLAND

Dr Joshua Lenvens
ARMPC Manager
RBM Partnership to End Malaria
SWITZERLAND

WHO Secretariat

Dr Soumya Swaminathan
Deputy Director General for Programmes

Dr Pedro Alonso
Director, Global Malaria Programme

Dr Kim Lindblade
Team Leader and SAGme Coordinator
Malaria Elimination Unit
Global Malaria Programme

Dr David Schellenberg
Scientific Adviser
Global Malaria Programme

Dr Abdisalan Mohamed Noor
Surveillance, Monitoring and Evaluation Unit
Global Malaria Programme

Dr Richard Cibulskis
Strategy, Evidence & Economics Unit
Health Metrics and Measurement Cluster
Global Malaria Programme

Dr Edith Patouillard
Health Economist
Strategy, Evidence & Economics Unit
Global Malaria Programme

Dr Jeremy Lauer
Health Economist
Health Systems Governance and Financing

Charlotte Rasmussen
Technical Expert
Drug Efficacy & Response Unit
Global Malaria Programme

Dr Li Xiao Hong
Technical Officer
Certification, Border Malaria and Training
Malaria Elimination Unit

Asiya Odugleh-Kolev
Technical Officer, Community and Social Interventions
Quality Systems and Resilience Unit
Universal Health Coverage and Health Systems

Dr Salim Sadruddin
Team Leader
Rapid Access Expansion (Race) Programme
Global Malaria Programme

Dr John Aponte
Epidemiologist
Surveillance, Monitoring and Evaluation Unit
Global Malaria Programme

Erin L. Shutes
Programme Manager
Programme Support and Management Unit
Global Malaria Programme

Saira Stewart
Communications Specialist
Programme Support and Management Unit
Global Malaria Programme

Selome Tadesse
Administrative Assistant
Programme Support and Management Unit
Global Malaria Programme

Carlota Gui
Project Officer – Consultant
Malaria Elimination Unit
Global Malaria Programme

Agenda

Wednesday 28 November 2018		
8.00 – 8.30	Registration	
Session 1, Chair: Marcel Tanner		**Open**
8.30 – 8.45 8.45 – 9.10 9.10 – 9.30	Welcome and opening of the meeting Update from GMP Director and round of introductions Conclusions of the meeting in November 2017 in New Delhi, India Structure and expected outcomes of this meeting: • First day, breakout into groups to review progress and work on key conclusions • Second day, outcomes of each group's work • Discussion on key set of conclusions/implications for SAGme to consider	Pedro Alonso Marcel Tanner
9.30 – 10.15	Lessons from the history of global policies against malaria and aspects of contemporary developments in global health governance Discussion	Julian Eckl
10.15 – 10.30	Introduction to breakout sessions; group divisions and structure	Marcel Tanner
Breakout session		**Open**
11.00 – 13.00	Plenary breaks into working groups: • Summary of work developed over the past year; background and timeline progression of work package, methods, results • 3–5 key implications/conclusions for SAGme • Final steps	Work packages
14.00 – 15.30	Continue with breakout session	Work packages
16.00 – 17.30	Continue with breakout session – please send final presentations and outcomes by the end of the day	Work packages
Session 2, Chair: Marcel Tanner		**Open**
17.30 – 18.00	Summary, outlook for second day and close	Marcel Tanner
Thursday 29 November 2018		
8.00 – 9.00	Working breakfast for SAGme members at the Mandarin Oriental, Geneva	**Closed**
Session 3, Chair: Lindiwe Makubalo		**Open**
9.00 – 9.30	Presentation 1 – Community engagement	Presenter: TBD
9.30 – 10.00	Presentation 2 – Health systems readiness	Presenter: TBD
10.30 – 11.00	Presentation 3 – Megatrends	Presenter: TBD
11.00 – 11.30	Presentation 4 – High transmission areas to eliminate	Presenter: TBD
11.30 – 12.00	Presentation 5 – Threats towards eradication	Presenter: TBD
13.00 – 13.30	Presentation 6 – Economics	Presenter: TBD

Session 4, Chair: Marcel Tanner		**Open**
13.30 – 13.45	Introduction to final session	Marcel Tanner
13.45 – 15.30	Preliminary conclusions	SAGme
Session 5, Chair: Marcel Tanner		**Open**
17.00 – 18.00	Strategic Directions: Report back on 2020 GTS milestones and process to update the GTS to incorporate SAGme conclusions	Soumya Swaminathan (DDP), Pedro Alonso and SAGme
18.00 – 18.30	Update of SAGme timeline Summary of meeting and close	Marcel Tanner
**Please note the agenda is subject to change. You will be notified of any changes*		

Strategic Advisory Group on Malaria Eradication

MPAC

10 April 2019

Global **Malaria** Programme

World Health Organization

SAGme Terms of Reference

- Advise WHO on the **feasibility**, **potential strategies** and **cost** of **eradicating malaria** over the next decades.
  - To prepare an *analysis of future trends* of malaria
  - Based on these analyses of the determinants described above, provide advice to WHO on the feasibility, expected cost and potential strategies of malaria eradication over the next decades, including through provision of a final report
- SAGme has met 4 times in 2016, 2017 and 2018
- Likely final meeting in June 2019

Approach

- Developed a report to the Executive Board in 2017 affirming malaria eradication as the ultimate goal
- Identified critical work streams to analyze determinants of malaria in the future and understand feasibility and cost
- Collaborated with WHO and collaborating centers, and commissioned analyses and position papers to complete the work packages
- Met several times to review progress and redirect
- Last meeting, developed general conclusions
- Currently editing papers into body of a report and developing the executive summary

Work Streams

1. Developing people-centred health systems through community engagement
2. Health systems determinants for elimination
3. Global megatrends and impact on future scenarios for malaria eradication
4. Mitigating potential threats to malaria eradication
5. Targeting the last areas first: interventions for the areas likely to be the most difficult for eradication
6. Global economic benefits on the path to malaria eradication
7. Lessons learned from other disease elimination and eradication efforts
8. Lessons from the history of global policies against malaria and aspects of contemporary developments in global health governance

Key Findings (1)

- Health Systems
  - Stronger health systems associated with greater reduction of malaria incidence at national level
  - Investments in malaria specific activities will achieve significant impact even in countries with weak health systems but strong health systems needed for last mile
- Megatrends
  - Population growth and urbanization most significant in Africa
  - Urbanization and development positively effect malaria elimination
  - Migration most important within large regions or countries
  - Land-use change impact will depend on type and region
  - Climate change impact will be on elimination through decadal variations

Key Findings (2)

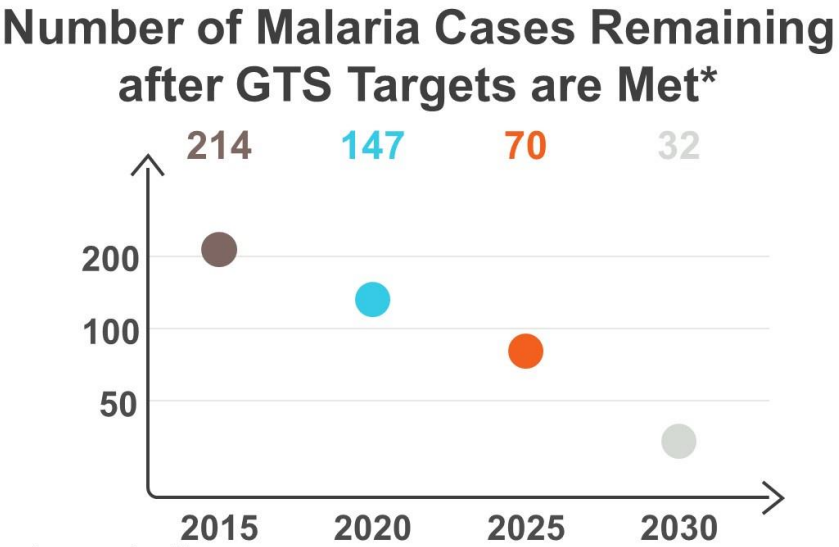
- Megatrends (cont.)
  - Socioeconomic development the most important factor in future scenarios
  - By 2050, the aggregate effects of these megatrends in Africa may result in substantial declines in transmission, but not widespread elimination
- Threats to elimination
  - Complex emergencies are likely to cause disruptions but should not deter
  - Mitigation through community engagement, stronger health systems with strong surveillance capacity, specific emergency preparedness plans, and surge capacity when needed
  - Transmission potential of simian malaria could change, and continued surveillance and research are merited, but efforts to eradicate human malaria should not be derailed by focusing on simian malaria

Key Findings (3)

- Economic benefits
  - Reducing malaria incidence by 20 percent is associated with an increase of 1% of GDP per capita .
  - Malaria eradication, corresponding to a 100% decrease in malaria incidence, would therefore be associated with a 5% increase in GDP capita on average.
  - This is equivalent to an estimated gain of 0.15% of world GDP in 2015.
  - Incentives for investment at country level will depend on other national priorities
  - Cost estimates of eradication *per se* are not possible given uncertainty over the last-mile strategy in high-burden countries.

Key Findings (4)

- Lessons learned from other eradication efforts
  - Smallpox started with 100,000 cases in 1959
  - Polio started with 350,000 cases in 1988
  - Guinea worm started with 423,000 in 1991
  - In 2017, 219 million estimated malaria cases
  - If GTS targets achieved in 2030, 32 million cases remaining



Key Findings (5)

- History of global policies and contemporary developments in global health governance
  - Must distinguish between conceptual feasibility and practical feasibility (or actionability).
  - If a plan for malaria eradication is promised too early in order to use it as a resource mobilization strategy, there is a danger.
    - Massive underestimation of the costs of malaria eradication was a reason for the failure of the 1955 GMEP.
  - The time and energy of the malaria community could be better invested by harnessing opportunities and focusing on avoiding setbacks
    - Disagreement on long-term projections or eradication feasibility should not distract from what can be done now

Key Findings (6)

- History of global policies and contemporary developments in global health governance
  - Central task is probably not to project at what point in time the journey towards eradication will be successfully completed. Rather, the question is where the journey is currently heading and what crossroads are coming up in the near future.

Preliminary Conclusions

Conclusions

- Global megatrends will contribute but won't be enough to eradicate by 2050, even with full scale-up of current interventions
- New tools will be needed, particularly for vector control
- Good, people-centred health systems will be fundamental to achievement of eradication
- Strong surveillance and response will help adapt to and mitigate threats
- Estimation of costs will not be possible to calculate until the strategy is clearer
- Willingness of Member States to embark on eradication is likely to be affected by the consequences of, and reflections on, the polio transition
- Targets for the Global Technical Strategy for Malaria 2016-2030 are achievable and contribute significantly towards eradication

Setting the Prerequisites for Malaria Eradication

GTS 2030

Subnational strategies to get back on track to meet 2030 milestones

OTHER DISEASES

Achieve and reflect on eradication of polio

NEW TOOLS

Develop new tools to attack malaria in the most difficult places

REGIONS

Establish and achieve national and regional elimination goals

RESEARCH

Resolve bottlenecks through operational and implementation research

CAPACITY

Develop a national and global malaria workforce

Continue financial commitment to malaria eradication

FINANCING

Make key investments in strengthening people-centred health systems

HEALTH SYSTEMS

Build investment cases for contribution to other national priorities

OTHER PRIORITIES

Countries take ownership of malaria elimination and eradication

LEADERSHIP

Global **Malaria** Programme

World Health Organization

Thank you