World Health Organization

Thursday, 11 September 2014

Time	Session	Purpose	Type
8.30 am	Session 5: Drug Resistance and Containment TEG: Update on April meeting/Presentation *(A Dondorp)*	For information	open
10.30 am	**coffee**		
11.00 am	Session 6 Drug Resistance and Containment TEG: Conclusions of the assessment on the feasibility of elimination in the Greater Mekong Subregion *(A Dondorp)*	**For decision**	open
1.00 pm	**lunch**		
2.00 pm	Session 7; Gaps in current WHO-GMP guidance for acceleration to elimination - planned revision of malaria elimination field manual and - proposed ERG on MDA, MSAT and FSAT in elimination/Presentation *(A Bosman /P Ringwald)*	For input	open
3.30 pm	**coffee**		
4.00 pm 4.45 pm 5.30 pm	Session 8; Gaps in current WHO-GMP guidance for acceleration to elimination (*continued*) Update on Round 5 product testing for RDTs/Summary results *(J Cunningham)* IPTi and mortality (*A Schapira*)	For input For information For conclusion	open
6.00 pm	**End of day**		

Friday, 12 September 2014

8.30 am – 3.30 pm	Finalization of wording of recommendations, and discussion on MPAC plans for 2015	**For decision**	**closed**

World Health Organization

Technical Expert Group on Drug Resistance and Containment

28-30 April 2014 – Starling hotel, Geneva, Switzerland

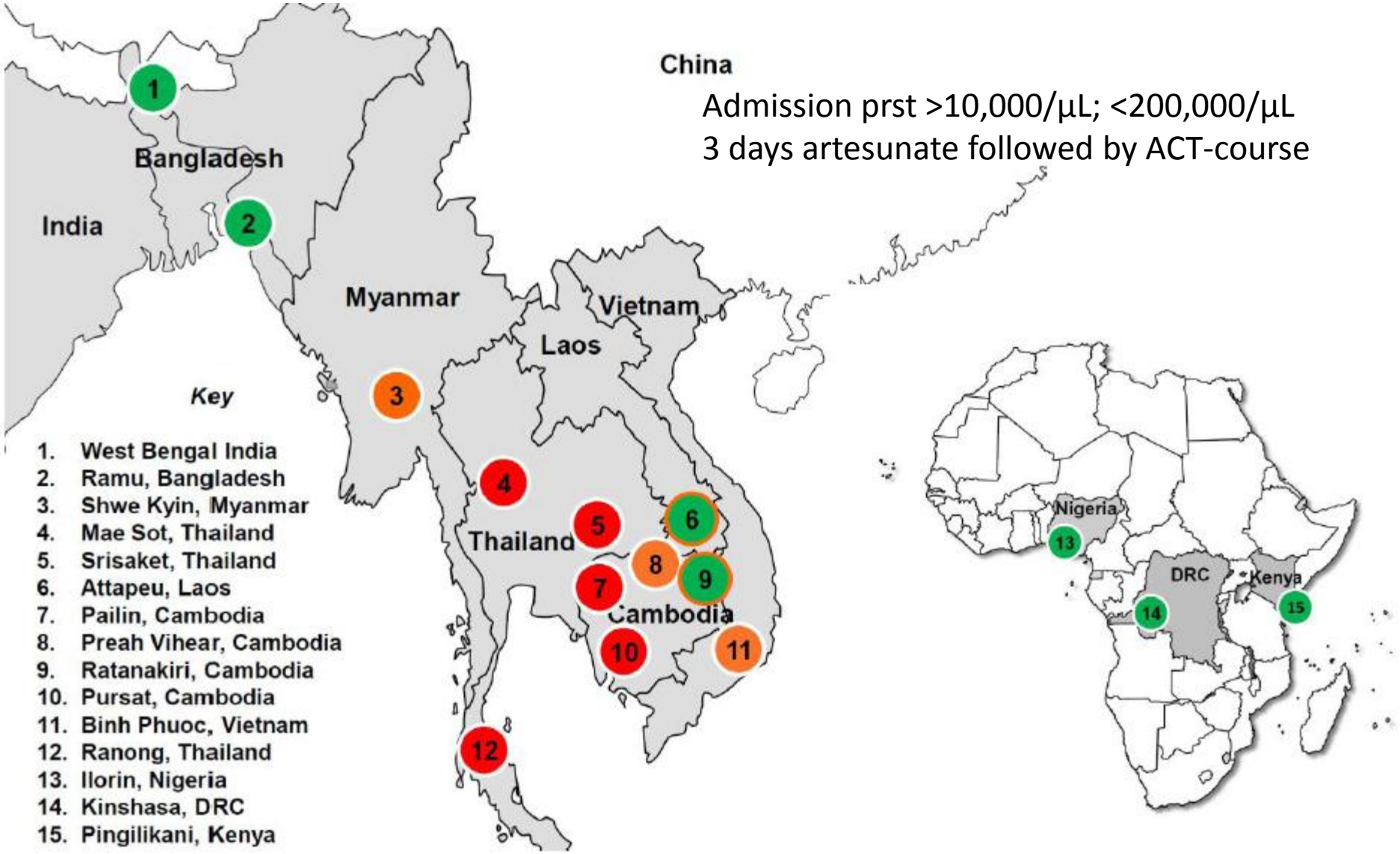
Summary and recommendations

Arjen Dondorp, on behalf of the
Technical Expert Group for Drug Resistance and Containment

Session 1: Update on drug resistance - surveillance

-Tracking Resistance to Artemisinin Collaboration studies
-Artemisinin resistance confirmatory study in Suriname
-Antimalarial treatment policy change in Cambodia
-Update on K13 molecular markers
-Update on artemisinin resistance definition and tier maps

TRAC: Heat-map Artemisinin resistance



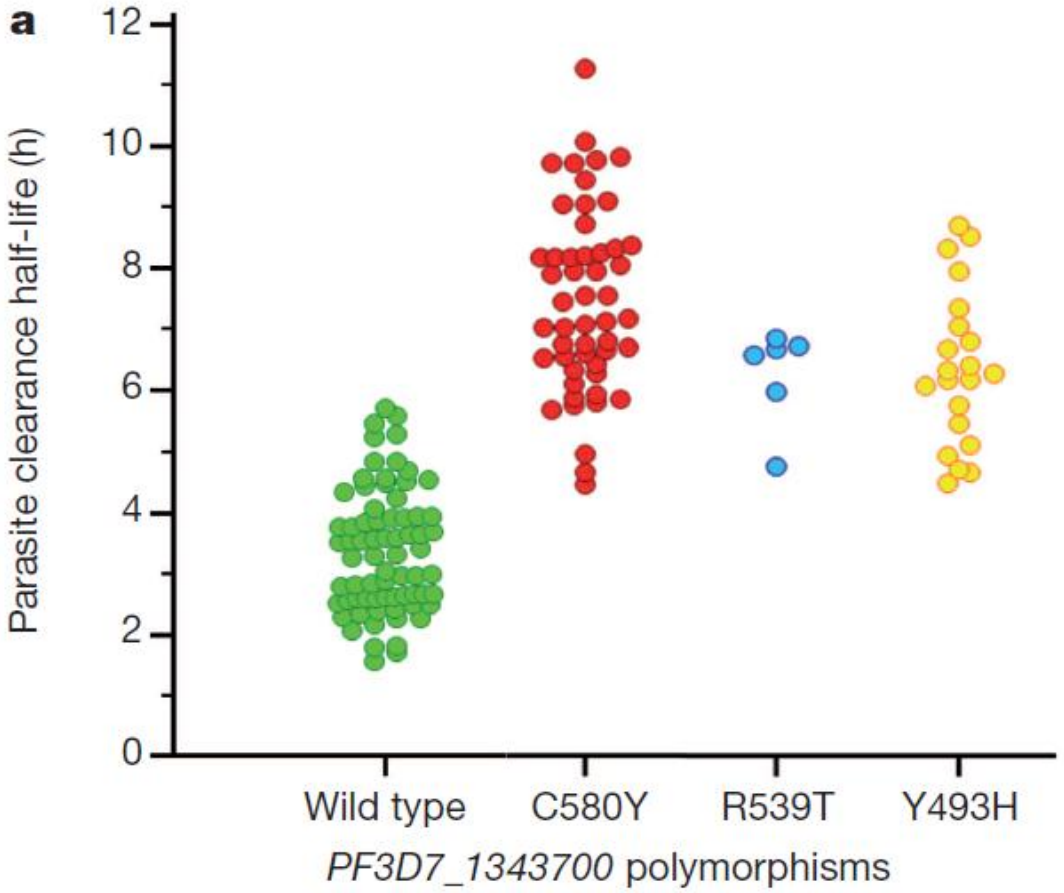
Admission prst >10,000/µL; <200,000/µL
3 days artesunate followed by ACT-course

Key

1. West Bengal India
2. Ramu, Bangladesh
3. Shwe Kyin, Myanmar
4. Mae Sot, Thailand
5. Srisaket, Thailand
6. Attapeu, Laos
7. Pailin, Cambodia
8. Preah Vihear, Cambodia
9. Ratanakiri, Cambodia
10. Pursat, Cambodia
11. Binh Phuoc, Vietnam
12. Ranong, Thailand
13. Ilorin, Nigeria
14. Kinshasa, DRC
15. Pingilikani, Kenya

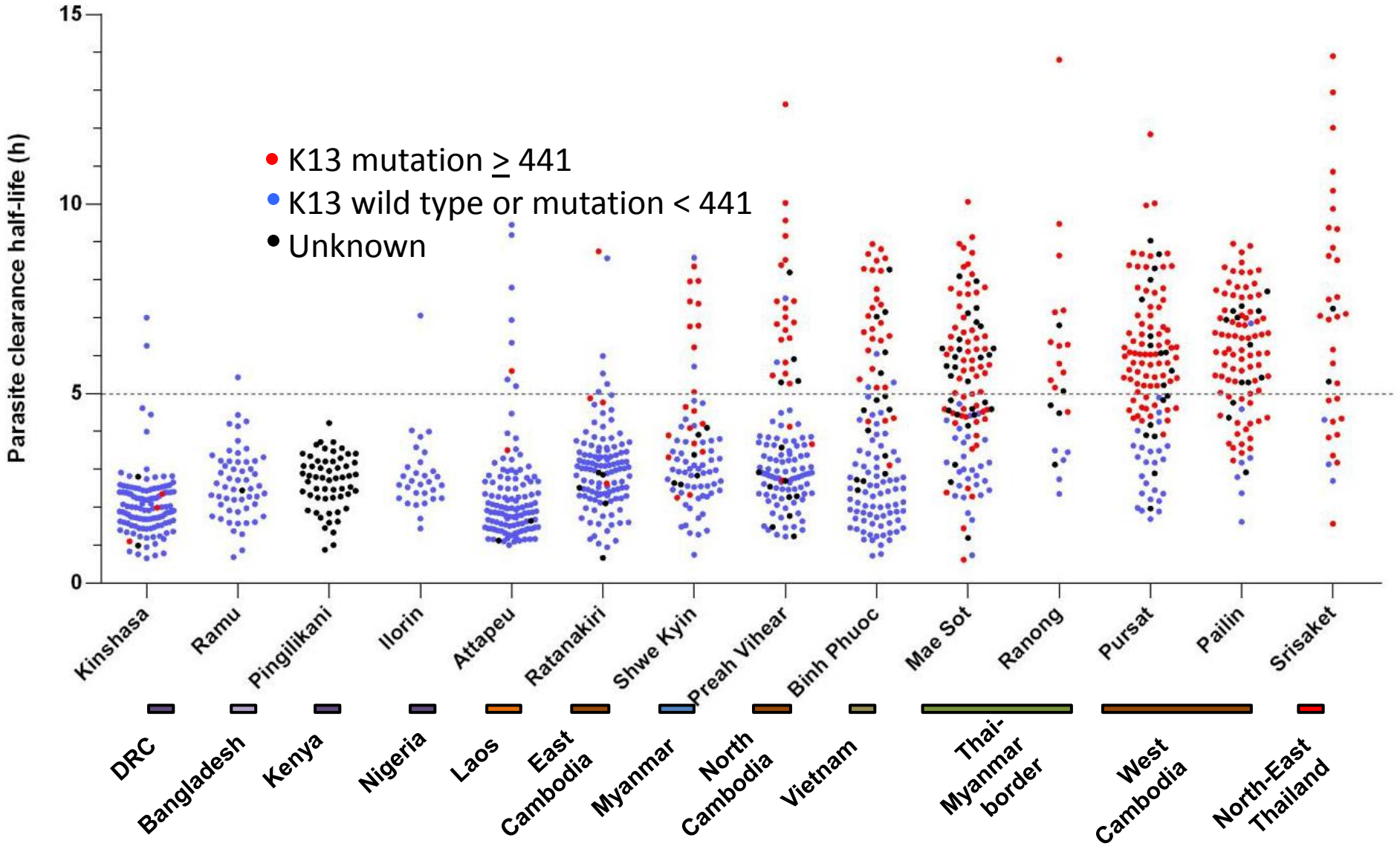
Ashley et al.
N Engl J Med 2014

K13 SNPs are associated with delayed parasite clearance



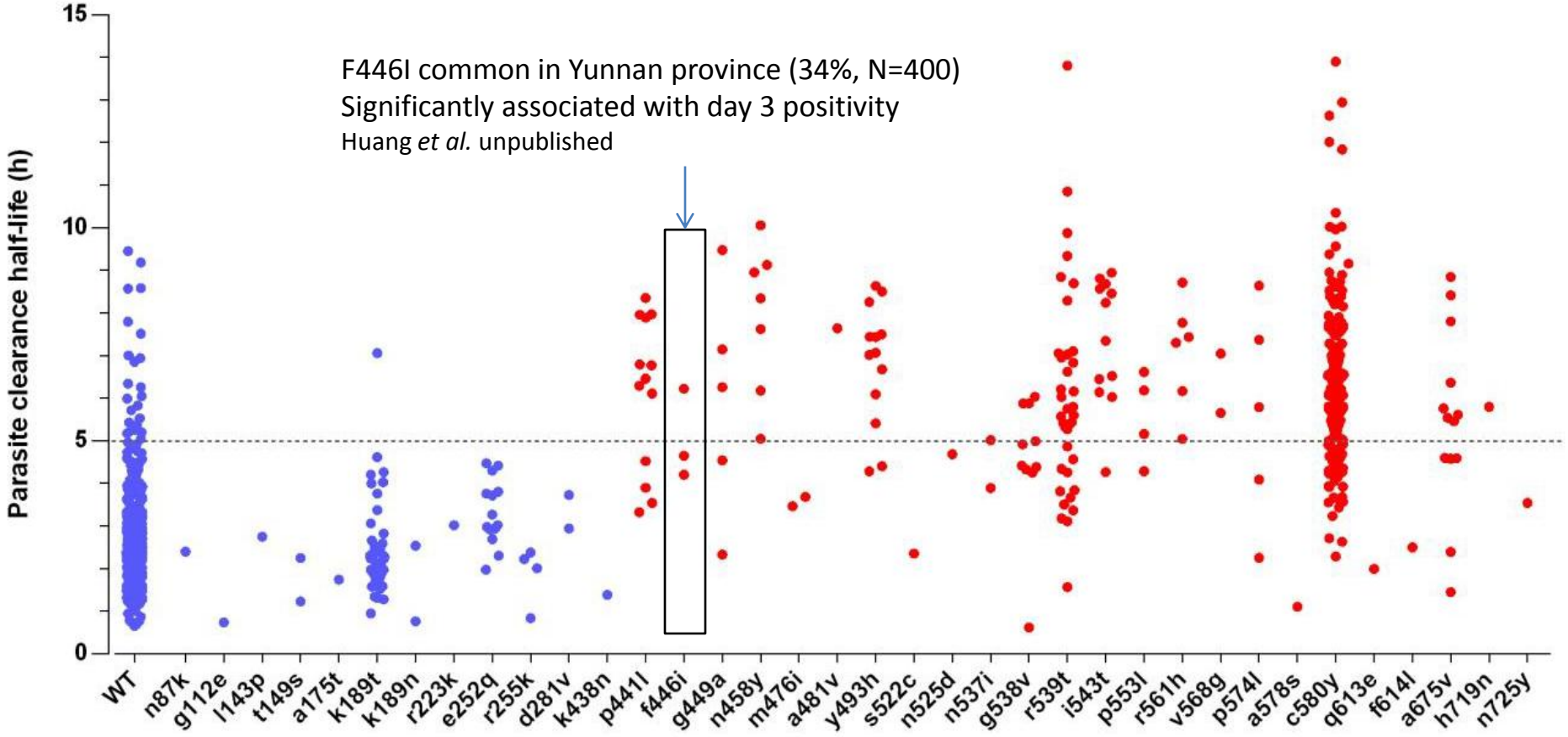
Ariey *et al. Nature* 2013

TRAC genotype-phenotype association



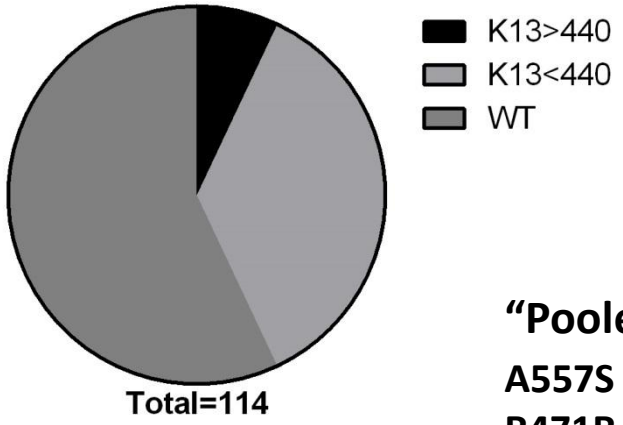
Ashley et al. N Engl J Med 2014

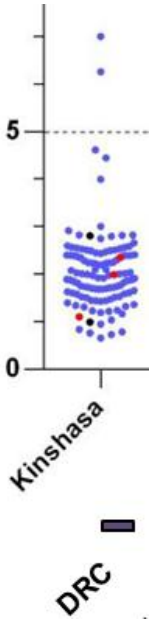
Genotype – phenotype associations (24 mutations in the propeller region of Kelch 13)



Kelch 13 in Africa

Q613E; A578S; A557S; S522C

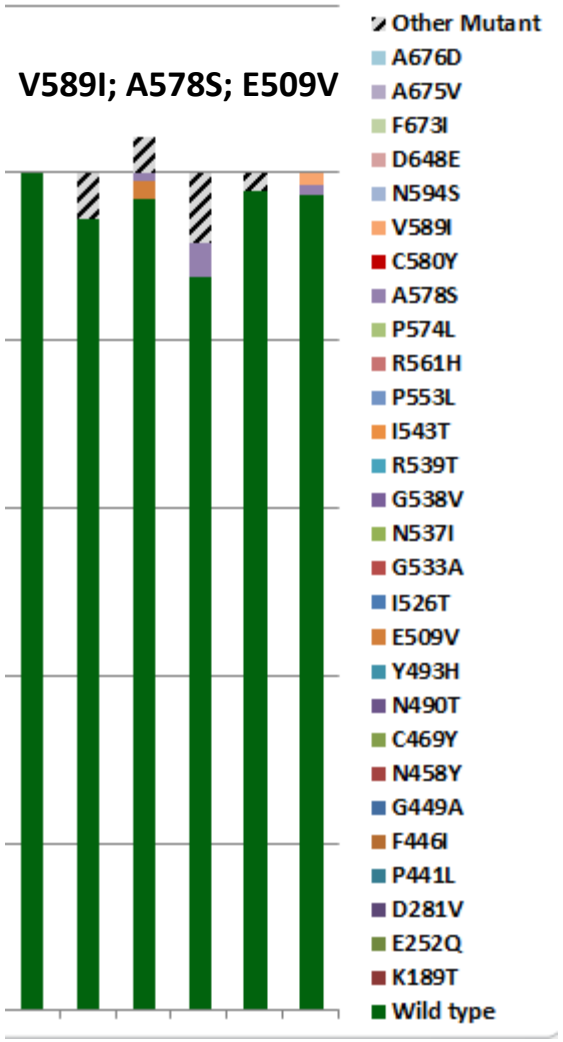




"Pooled" genotyping

A557S at 36.3% in DRC
R471R at 9.8% in DRC
V581V at 7.1% in Bas-Congo
V520A at 13 sites
(frequency1.3% - 3.3%)

V589I; A578S; E509V



Ashley et al. N Engl J Med 2014; Taylor et al. J Infect Dis 2014; Plowe et al. Takala Harison et al. J Infect Dis 2014

Artemisinin resistance in South America?

- *Fr. Guyana; Guyana; Suriname*

	Coartem 2005/06	Coartem 2011	Artesunate 2013/14 (33 pts.)
Day 2	18 %	75 %	60.6 % (20 pts.)
Day 3	2 %	31 %	9.1 % (3 pts.)

K13 genotyping: pending
Slope analysis: pending

Courtesy Dr Stephan Vreden

Conclusions (1)

- Artemisinin resistance is both spreading **and** emerging independently
  - Fire-wall strategy alone is not sufficient: **Pf elimination in affected areas;**

    Prevention of emergence: good quality drugs, no monotherapy etc.
  - However, prevention of spread of resistance from GMS, remains crucial, also because falciparum malaria is become increasingly resistant to the main new partner drugs (lumefantrine, mefloquine, piperaquine).
  - Adaptation of Tier map..
- K13 propeller region SNPs are closely associated with delayed parasite clearance in **Cambodia, Vietnam, Thailand, Myanmar and China (and Laos)**
- No convincing evidence that the slow clearance artemisinin resistant *P. falciparum* phenotype has reached Africa or South America
  - But: K13 propeller region mutations are present in low frequencies
  - Do other polymorphisms “permit”, modulate or compensate for K13 effects?
  - Certain SNPs associated with higher level resistance (as with DHFR, DHPS)?

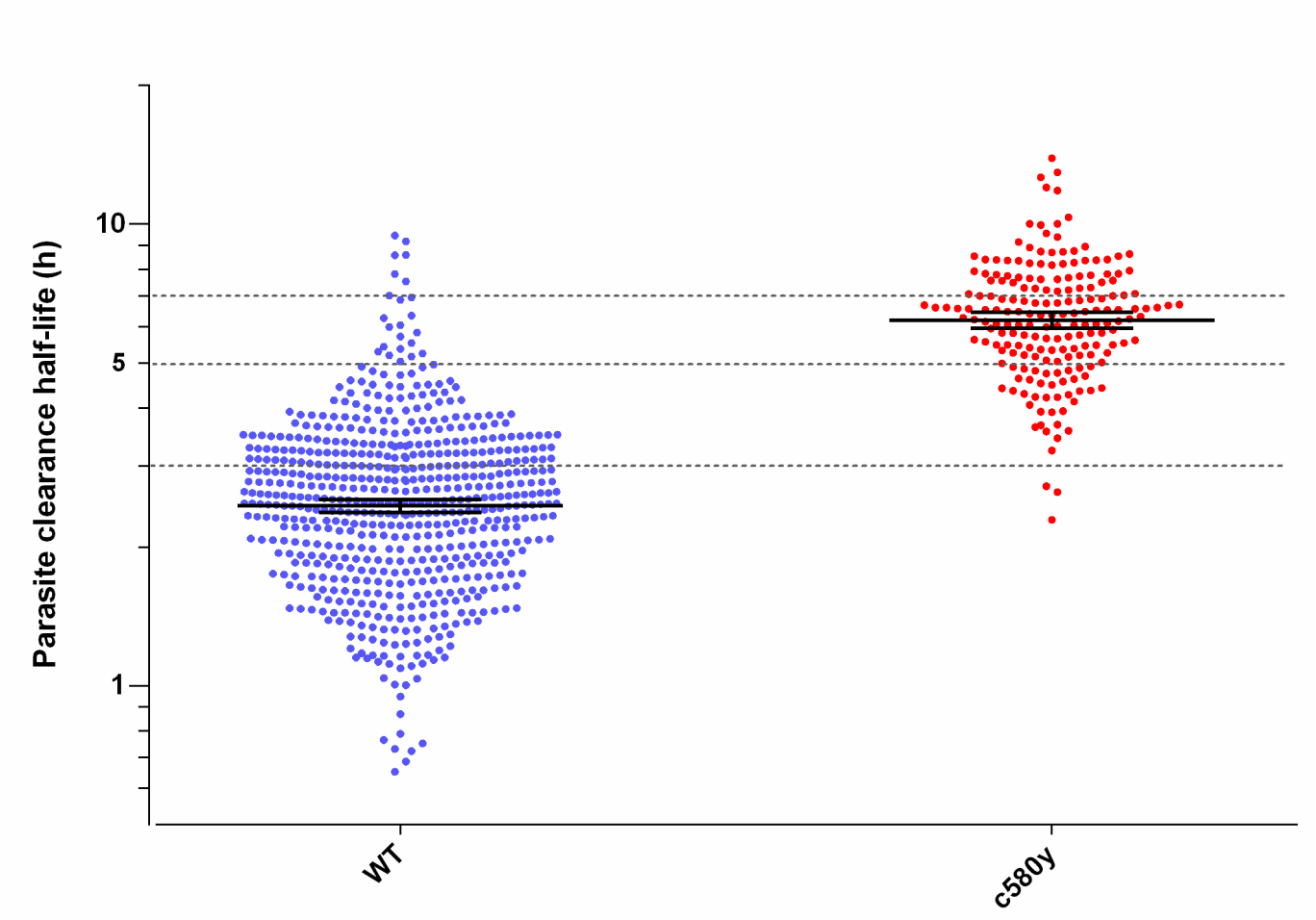
Definition of artemisinin resistance

- Current working definition (GPARC document):
  - an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
  - a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence after day 7 of parasites within 28/42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance)

Some guiding principles for a new definition

- it should be practical to use in the field
- should include both the clinical phenotype and genotype(since still remaining questions around K13)
- should be sensitive to detect new foci, but on the other hand not raise the alarm unnecessarily all the time
- a distinction is made between suspected and confirmed artemisinin resistance at a population level
- will acknowledge that refinement of the definition is likely with more data becoming available
- should clearly distinguish between artemisinin resistance and ACT failure/ resistance to both components

Parasite half life c580y vs wild type Kelch 13



Ashley et al. Submitted

New definition of artemisinin resistance

- **Suspected artemisinin resistance:**
  - ≥ 5% of infecting parasite strains carrying Kelch 13 resistance-associated mutations, or
  - a proportion ≥ 10% of patients still parasitaemic on day 3 by microscopy or
  - ≥ 10% of patients with a peripheral blood parasite half-life ≥ 5 hours following a treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy

New definition of artemisinin resistance

- **Confirmed artemisinin resistance:**
  - prevalence of ≥ 5% of infections with strains containing Kelch 13 resistance mutations if the patients carrying these mutants also have persistent parasitaemia by microscopy on day 3 or a peripheral blood parasite half-life ≥ 5 hours following adequate treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy

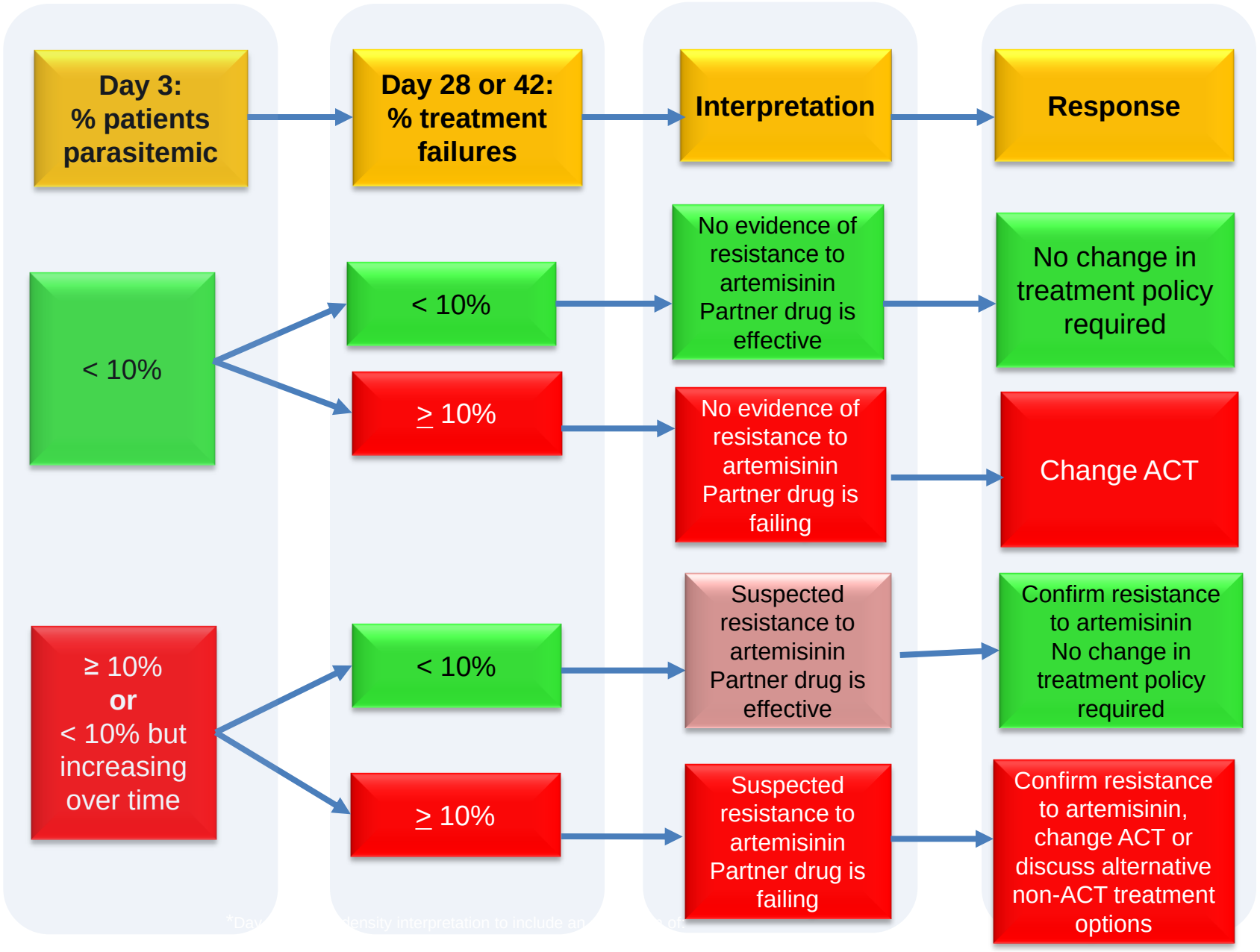
New definition of artemisinin resistance

- **Caveats**
  - Clearance is faster with ACTs than with AS monotherapy
  - There are many potential confounders:
    - Drug quality sub-therapeutic drug concentrations
    - immunity
    - splenic function/ splenectomy
    - others
  - K13/ genetic epidemiology evidence still rapidly evolving
  - Definition could thus change over time

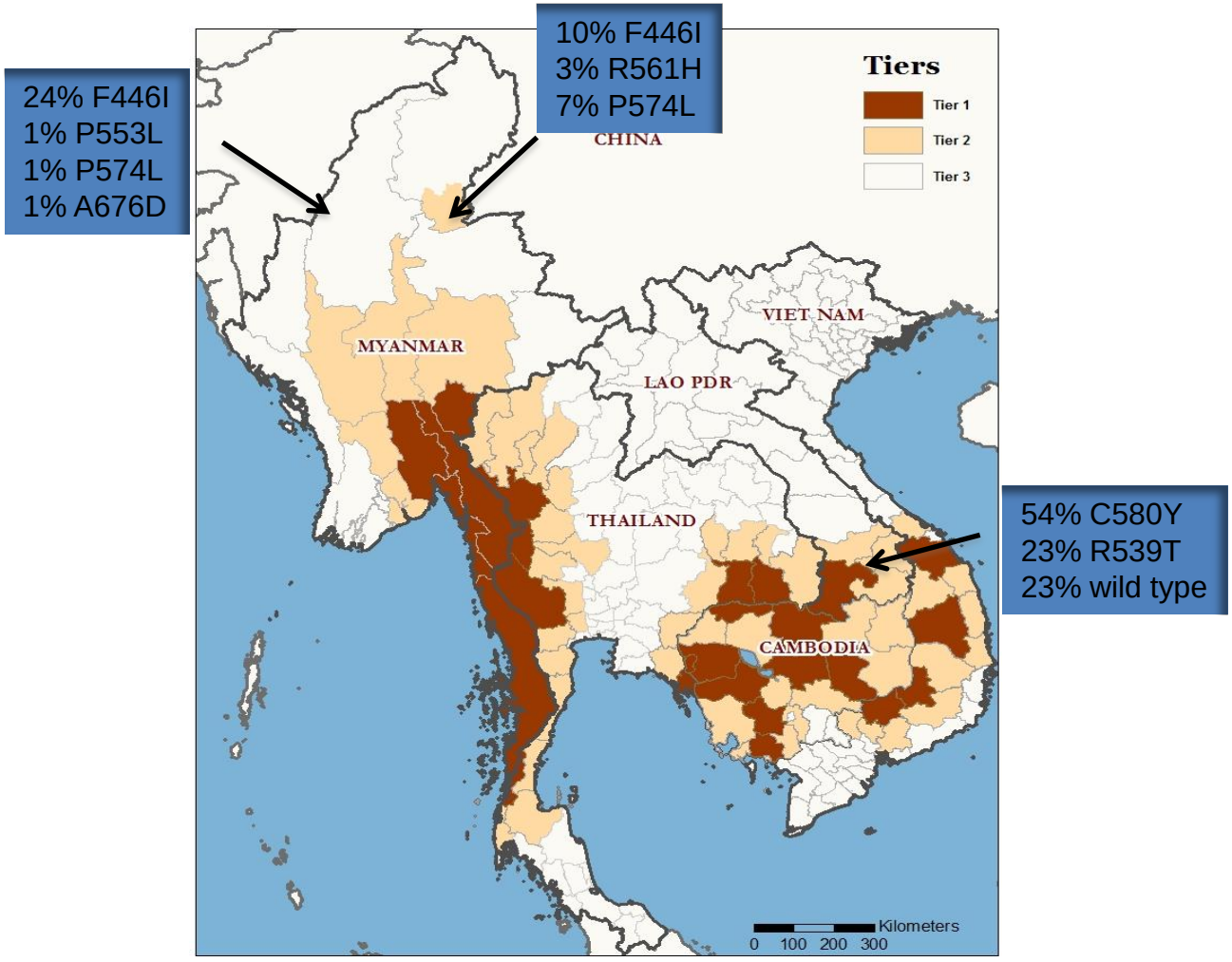
ACT resistance

- The term ACT resistance should be applied only when the therapeutic efficacy of ACTs start to fail in the context of resistance to both artemisinin and the partner drug(s). ACT failures > 10% should prompt a change in policy with another ACT.
- Beware of confounding factors affecting efficacy (such as drug quality).

Decision making for **TES studies**



New Tier map: whole Myanmar Tier 1 or 2 (to be adopted by countries)



Corresponding MPAC questions

Should the definition of artemisinin resistance be updated and, if so, in which way?

See above

Does the evidence support the inclusion of provinces in northwestern Myanmar in tier 1?

WHO is awaiting data from clinical studies and molecular analyses from three provinces of Myanmar before issuing formal recommendations. However, the probability of including northwestern provinces of Myanmar in tier 1 is high. For now the TEG recommends that whole Myanmar outside the Tier 1 areas should be denoted Tier 2, and that strategies and interventions for these areas should be the same as for tier 1 areas, the only difference being a lower priority under financial and operational constraints

Corresponding MPAC questions

How should K13 be used in the surveillance of artemisinin resistance; in particular is an evidence review group on K13 needed?

Given the significance of the discovery and the quickly evolving information, the TEG recommended the establishment of an ERG on the topic to 1) to collect and review data; 2) to indicate which polymorphisms on K13 (and 'backbone' mutations, or partner drug associated mutations) should have consequences, if detected in a given area, and describe these consequences; this includes a discussion on the development of integrated mapping of the relevant K13 mutations; 3) to propose organizational structures (such as a reference center) that can facilitate standardization of methods and information flow to national programs and WHO; 4) to identify remaining knowledge gaps for research.

Corresponding MPAC questions

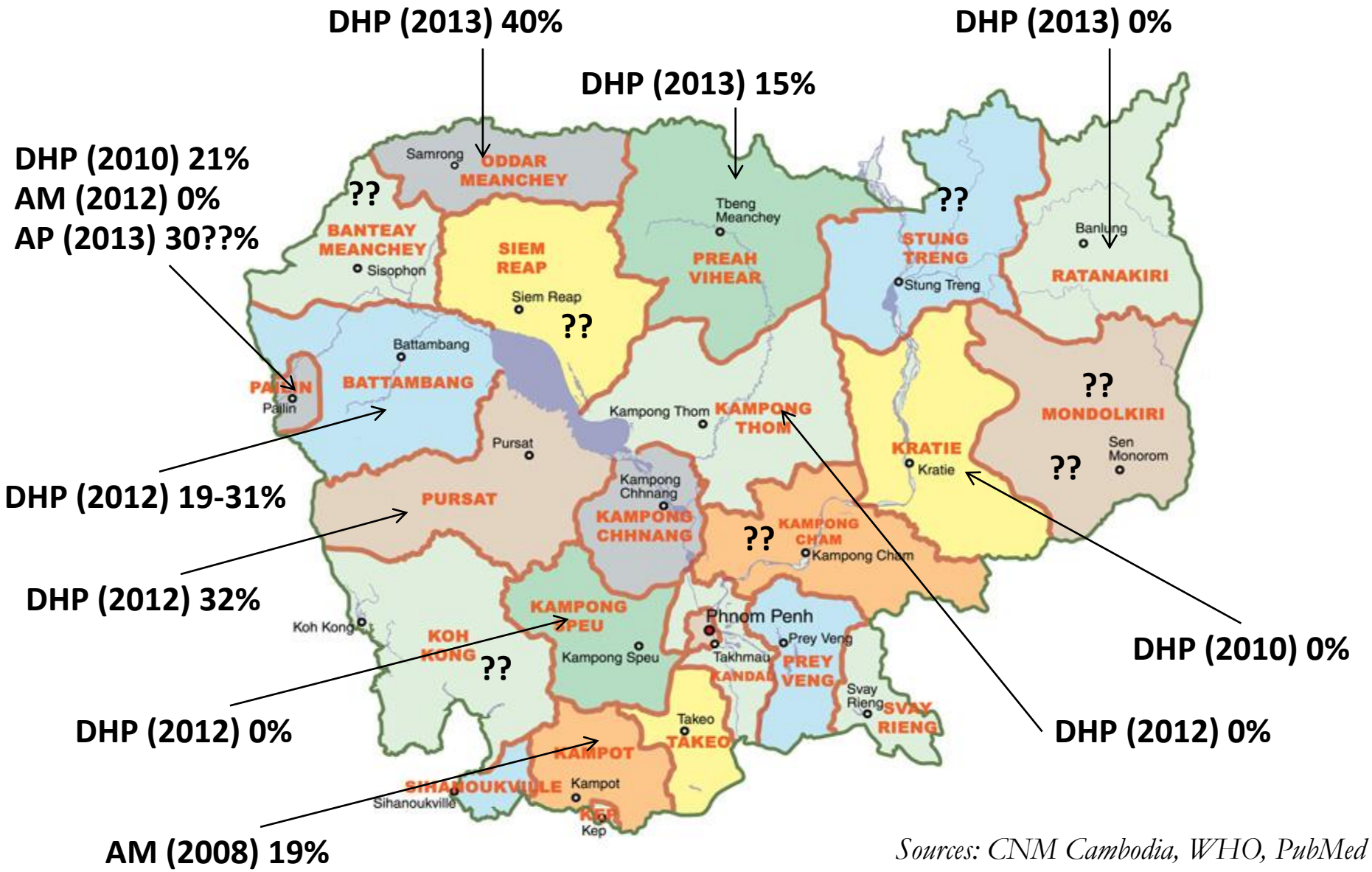
Which implications does the identification of the K13 mutation have on the response to artemisinin resistance?

There is 'spreading and popping'. The "firewall approach" remains necessary for tier 1 and 2 areas but additional measures are necessary, which includes an effort for elimination *of P. falciparum* malaria in all affected countries in the GMS where artemisinin resistance has been detected, in addition to intensified measures in sub-Saharan Africa that include improved case detection and treatment of malaria, uninterrupted supply of essential commodities, scaled up and sustained coverage with vector control measures, intensified efforts to eliminate monotherapy, counterfeit drugs and other substandard treatments, and enhanced therapeutic efficacy monitoring. Evidently, the K13 molecular marker will be an important additional tool for surveillance of artemisinin resistance.

Session 1: Update on drug resistance - continued

-Antimalarial treatment policy change in Cambodia

ACT (and other) 42-D failure rates



Sources: CNM Cambodia, WHO, PubMed

But high efficacy with 3 day AS followed by ACT

Location of study site	Treatment	Treatment duration (days)	N	N recurrences	Efficacy % (95% CI) without PCR correction	Efficacy % (95% CI) with PCR correction
Pailin	AS4 + DP	6	100	2	97.7 (90.9-99.4)	97.7 (90.9-99.4)
Binh Phuoc	AS2 + DP	6	60	0	100 (93.2-100)	100 (93.2-100)
Binh Phuoc	AS4 + DP	6	60	0	100 (93.0-100)	100 (93.0-100)
Attapeu	AS4 + AL	6	60	1	98.2 (88.0-99.8)	100 (93.5-100)
Attapeu	AS2 + AL	6	60	2	96.6 (86.9-99.1)	100 (93.6-100)
Shwe Kyin	AS4 + AL	6	40	0	100 (87.9-100)	100 (87.9-100)

Corresponding MPAC question

What are the TEG's recommendations on the national treatment policies in particular in Thailand and Cambodia?

- In Thailand, despite high failure rates the first line policy is still MAS3. The TEG strongly recommends an urgent policy change in Thailand. The TEG will inform MPAC if no policy change is achieved in Thailand by September 2014.
- For western Cambodia, the TEG supports the implementation of MAS3 (fixed combination) as a short-term alternative to now failing DHA-PPQ, but is concerned about the vulnerability of mefloquine (PfMDR1 amplification is acquired quickly). Quinine with doxycycline over 7 days is recommended as rescue therapy in case of failure with artesunate-mefloquine.

  A study on artesunate-pyronaridine in Western Cambodia is ongoing and if still efficacious will be recommended. There was no consensus whether to recommend extension of dihydroartemisinin-piperaquine treatment from a 3 to 5 days course, because of potential safety issues (QTc prolongation). However, urgent safety, efficacy and effectiveness studies of the 5-day DHA-PPQ regimen was recommended by the TEG.

Session 2: Modeling

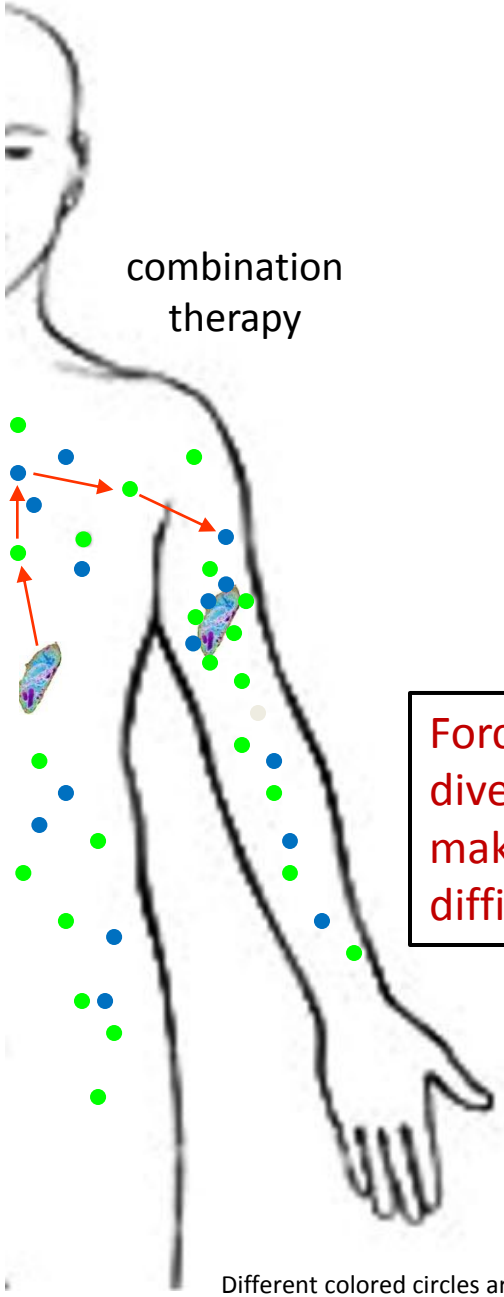
Impact of spread of artemisinin resistance in Africa *(shows the importance of concomitant partner drug resistance on increase in incidence, prevalence, mortality in the African context; slides on request)*

Multiple first-line treatments: outcome of recent modeling efforts

1. MFT

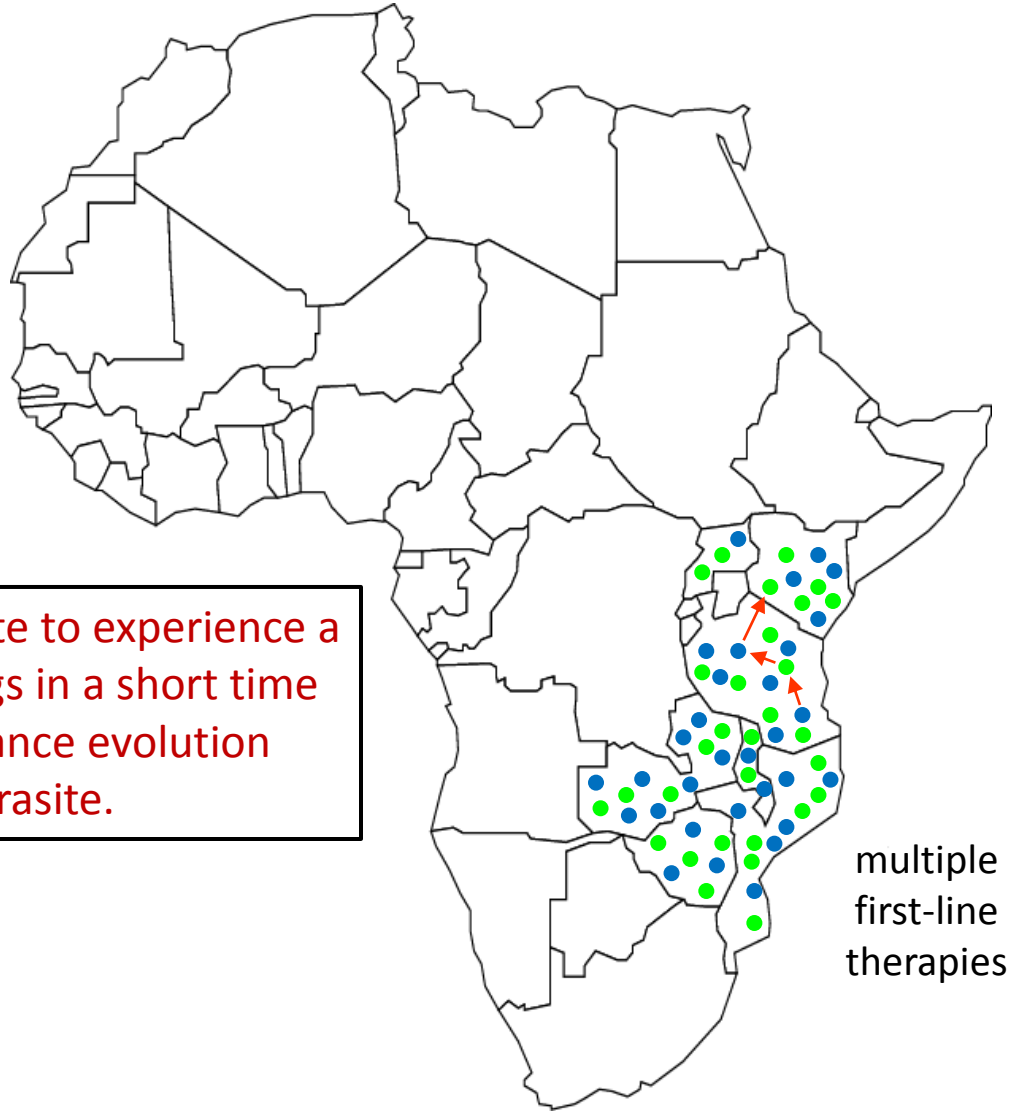
Boni et al 2008, PNAS 105:14216

combination therapy



Different colored circles are different drugs (different molecules).

Forcing the parasite to experience a diverse set of drugs in a short time makes drug resistance evolution difficult for the parasite.



multiple first-line therapies

Different colored circles are individuals treated with different drugs or therapies.

Comparison

Population Biology Methods

Track absolute population sizes, so we always know how many infected individuals there are.

Can explicitly track gene frequencies

(pop-bio papers on previous slide do track gene frequencies).

Do not assume a fixed multiplicity of infection.

Explicitly track the absolute number of treatment failures (**NTF**) in the population that result from drug resistance.

Population Genetic Methods

Do not track absolute population sizes, thus we do not know how many infected individual there are at any point in time.

Explicitly track gene frequencies.

Assume fixed multiplicity of infection, but these epidemiological features change during the course of a treatment strategy.

Cannot track the absolute number of treatment failures because changes in malaria prevalence are not tracked over time.

NTF = total number of people not receiving treatment +

total number of people receiving treatment but experiencing early/late treatment failure

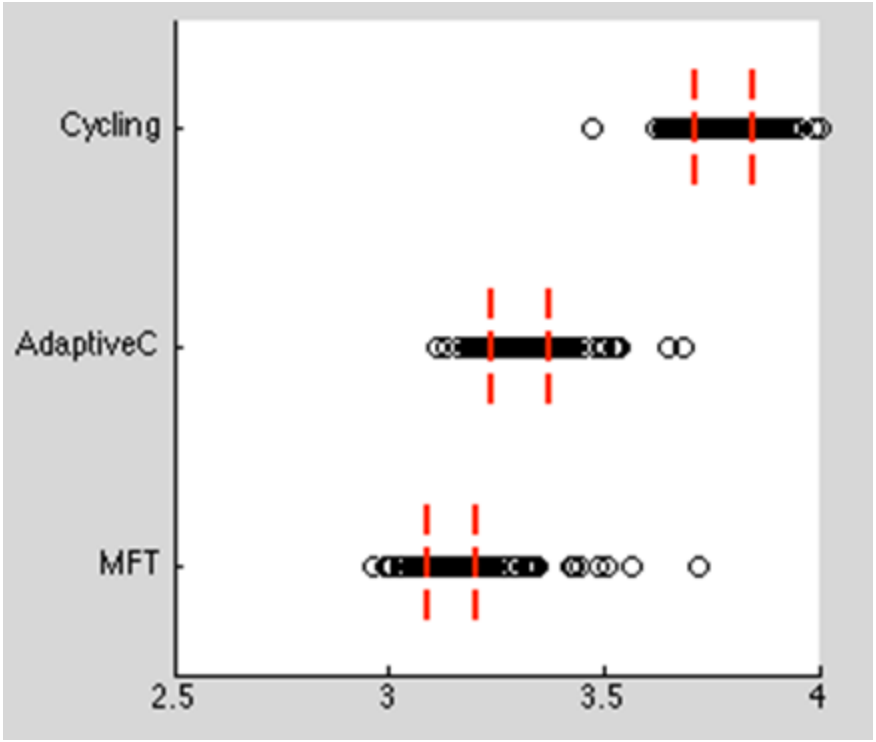
We want to choose a drug deployment policy that minimizes NTF.

Comparisons Using the Individual-Based Model

Cycling : a single drug is used for 5 years, after which it is replaced with a different drug, and so on. The cycling period is fixed at 5 years.

Adaptive Cycling : a single drug is used until the population experiences 10% treatment failure, at which point the drug is replaced, and so on.

Multiple First-line Therapies : three drugs are deployed simultaneously, with each individual having an equal probability of receiving a particular drug.



Each black circle represents the output of one stochastic individual-based simulation.

100 simulations were run for each strategy.

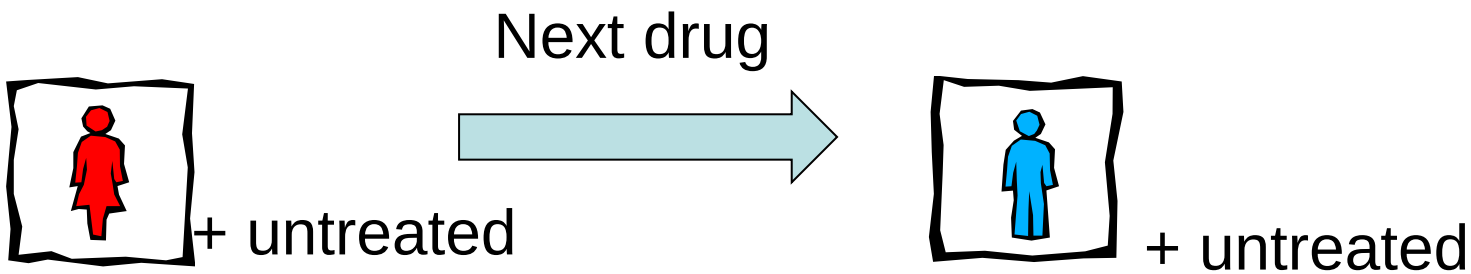
Red lines are inter-quartile ranges across the 100 simulation runs.

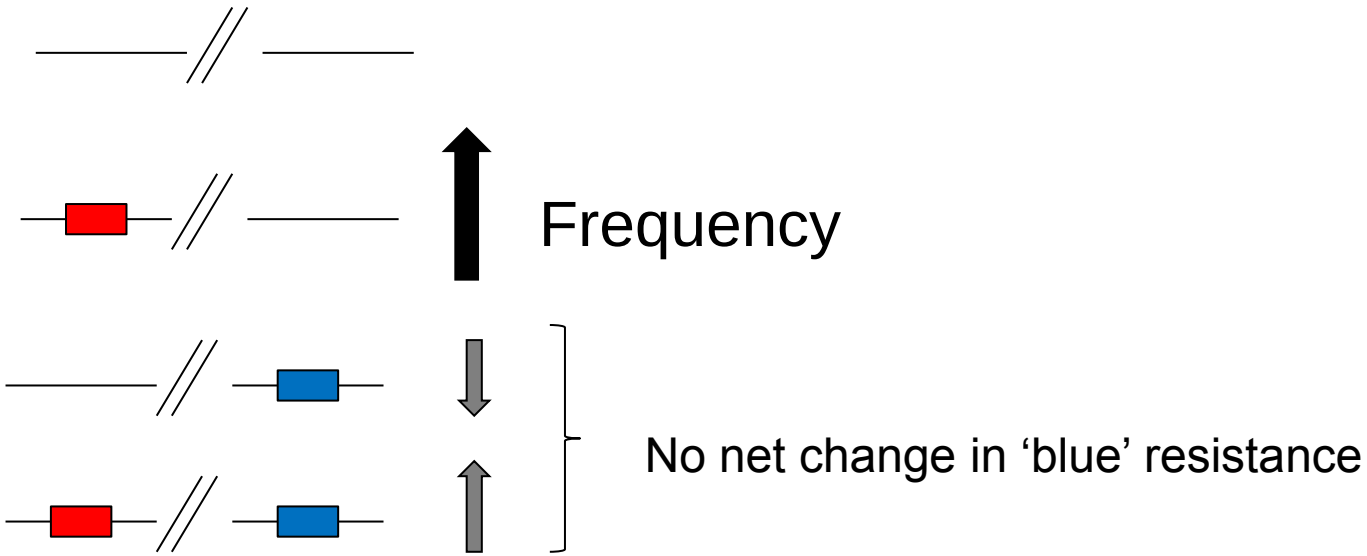
Population size is 1 million indivuduals in these simulations.

Number of treatment failures and non-treatments, per year per 100 population.

Boni et al 2008, PNAS 105:14216

The basics: Sequential drug deployment





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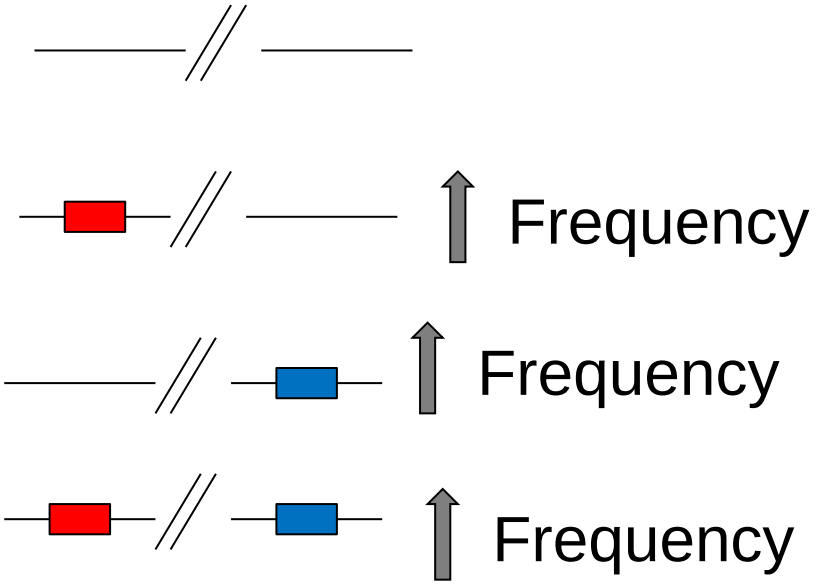
Antao, T. and I. M. Hastings (2012) Malar J 11:422

The basics: MFT drug deployment

+ untreated

No recombinational loss in treated individuals



Hitchhiking

Multidrug resistant

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How big is the effect??

“for 75.1% of the parameter combinations, MFT outperformed a cycling policy”

Number treatment failures:

- **64.4% policies within 5% of each other**
- **20.9%..... MFT 5-10% better**
- **9.5%..... MFT >10% better**
- **3.6%..... MFT 5-10% worse**
- **1.6%.....MFT >10% worse**

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Boni et al 2008, PNAS 105:14216

Summary MFT modeling (Ian Hasting)

Boni et al conclude MFT slightly better (~10%) overall. Hastings et al think it is slightly worse (~5%) at high drug coverage.

→*Given the size of these effects MFT unlikely to be a "game changer"*

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Corresponding MPAC question

Should multiple first-line treatments for malaria be promoted as part of the response to resistance?

The evidence examining multiple first-line therapies (MFLT) as a response to resistance is based on two modeling studies only, and those gave contradictory conclusions. Therefore, TEG cannot currently recommend adopting MFLT as a response to resistance but recognizes the need to be flexible and does not oppose such practice, in particular when it is already in place or when used to avoid drug stock outs. The TEG acknowledged that increasing the complexity of treatment policy risks practices that exacerbate rather than mitigate the problem. The potential benefit of doing so seemed insufficient justify recommending it. Measures to ensure drug quality and treatment compliance should be also emphasized.

Session 3:
Update on recent containment and elimination efforts

-ERAR
-RAI
-Multi-donor trust fund (secretariat: ADB)

Organogram – ERAR specific staff

Staff providing regional support

Regional hub, Cambodia

- Coordinator, Emergency response to art. resistance
- Technical officer, M&E
- Technical officer, Adv. & communication
- Assistant

WHO Thailand

- Technical officer, Migrant & Mobile populations
- Technical officer, TES

WHO China

- Technical officer, Pharmaceuticals

WPRO, Manila

- Medical officer, TES and research

WHO GMP, Geneva

- Technical officer, Reporting and surveillance

Staff providing country specific support

WHO China

- Medical officer, Communicable diseases
- National officer, Malaria

WHO Laos

- Malaria medical officer
- National officer, Malaria

WHO Viet Nam

- Malaria medical officer
- National Officer, Malaria
- National officer, Containment activities

WHO Cambodia

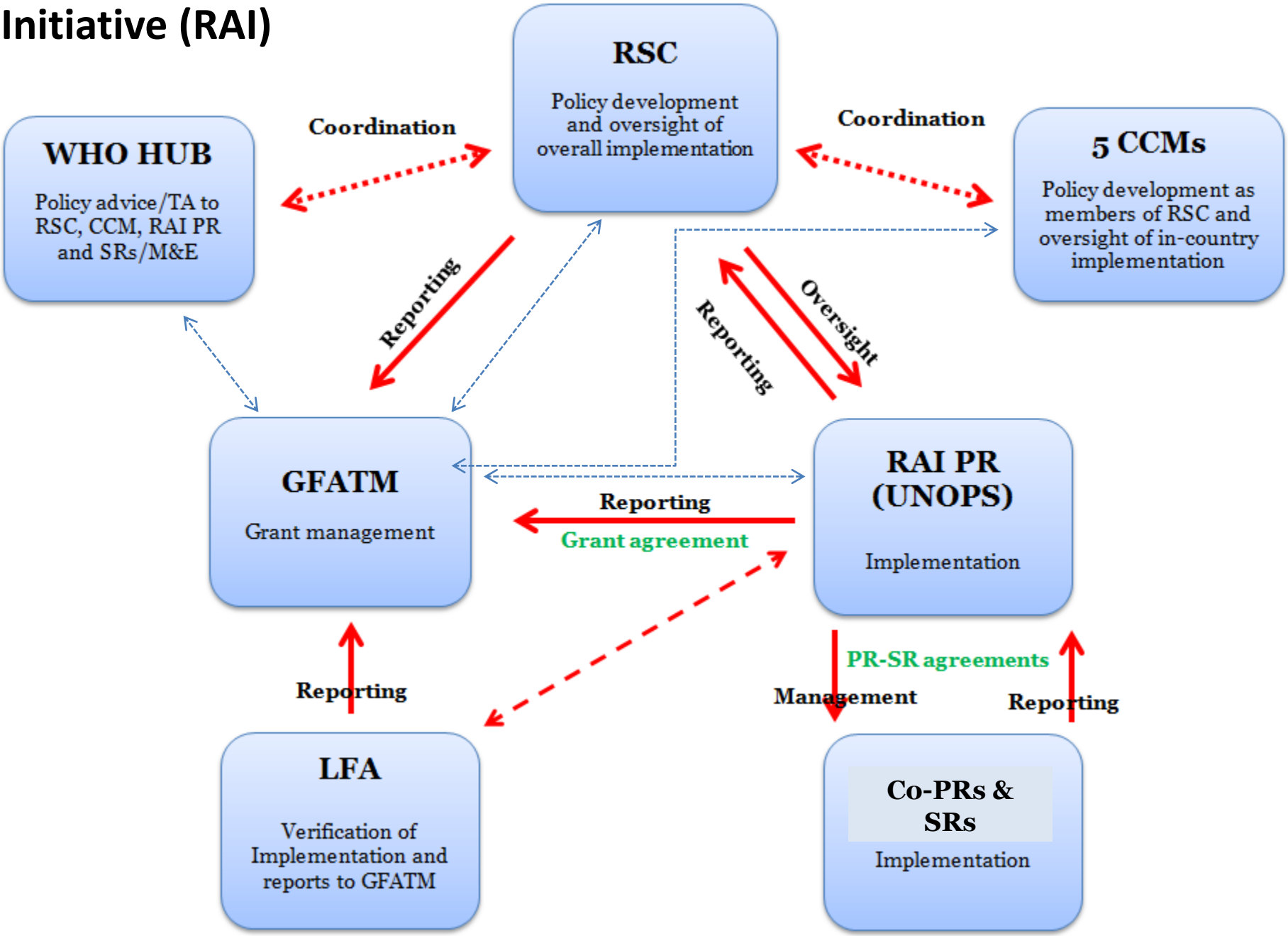
- Malaria Medical officer
- Medical officer, M&E
- National officer, Malaria

WHO Myanmar

- Malaria Medical officer
- Containment coordinator
- National Officer, M&E
- National Officer, MARC

Regional Artemisinin Initiative (RAI)

Implementation arrangement



TEG underlined the need for coordination between these initiatives and building synergy where possible.
It was noticed that key representatives of these initiatives are already in close communication.

The TEG requested ERAR hub to prioritize the whole GMS mapping of which organizations are doing which activities in which areas targeting which population and in which time frame. This is a prerequisite for a further gap analysis regarding activities and funding.

To guide currently funded initiatives and those in the near future, TEG recommended urgent development of an action plan for elimination of *P. falciparum* in the GMS, which builds on the existing frameworks, but formulates and prioritizes concrete fundable activities.

Corresponding MPAC questions

Is regional Plasmodium falciparum malaria elimination a feasible, as opposed to desirable, goal?

See feasibility report (next session)

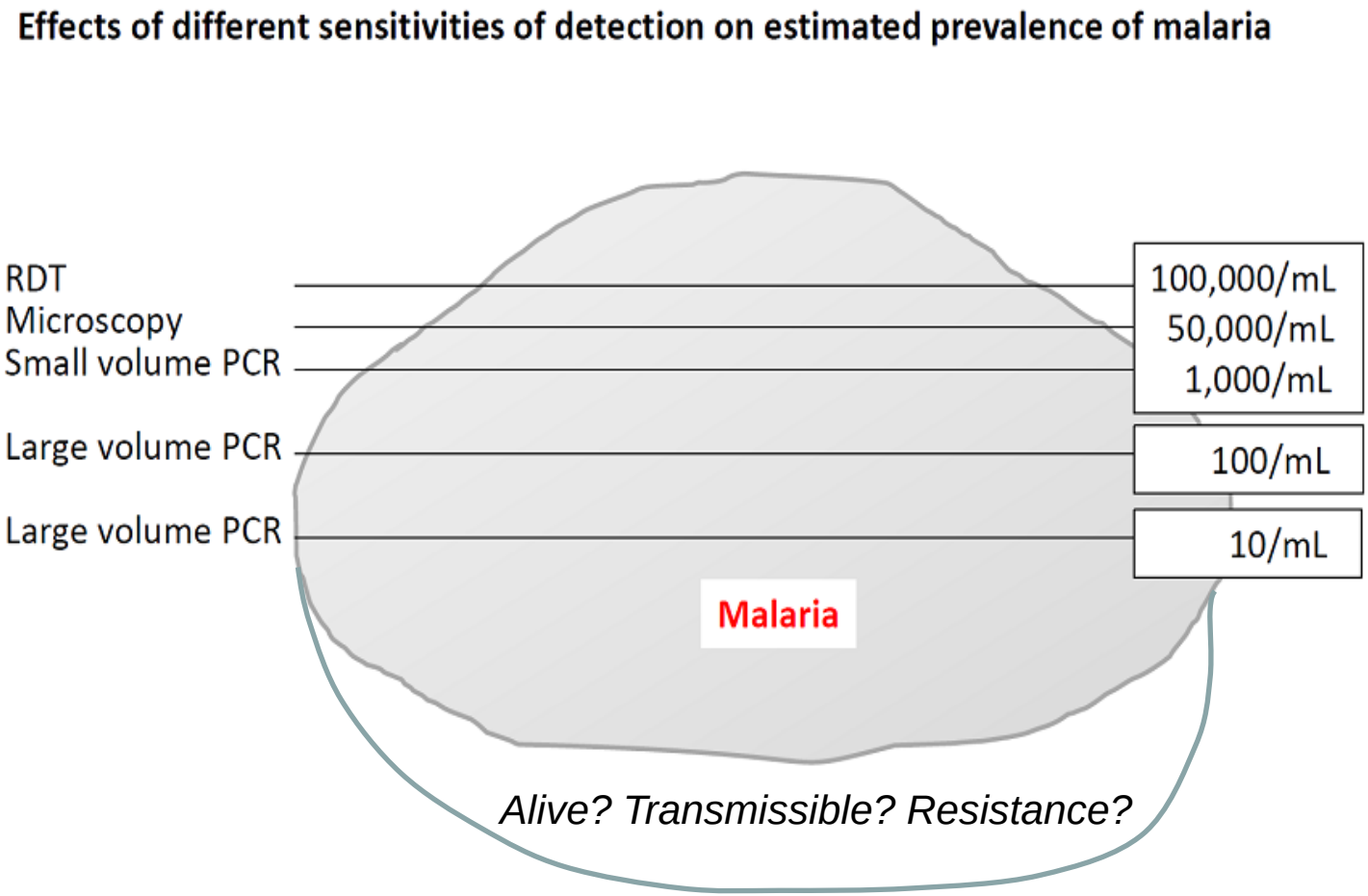
Should WHO work to have artemisinin resistance declared a "Public Health Emergency of International Concern" (PHEIC)?

WHO stated that the conditions for PHEIC outlined in the revised International Health Regulations (2005) are not met. Declaring an PHEIC has far reaching consequences, which we considered not appropriate for the response to artemisinin resistance.

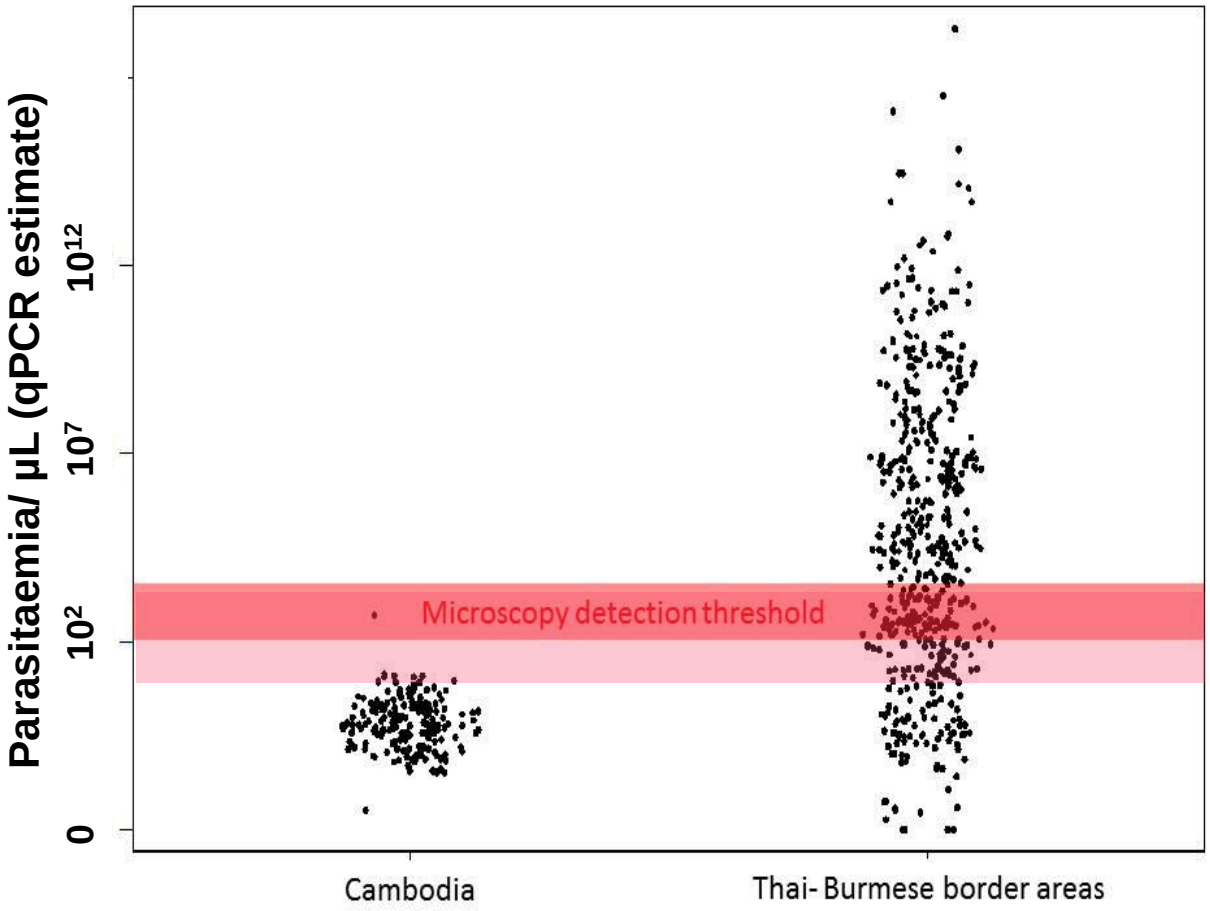
Session 4: Elimination of artemisinin resistance in the Greater Mekong subregion

-Mass drug administration pilot studies in the Greater Mekong subregion
-Malaria elimination strategies in the context of artemisinin resistance
-Vector control strategies in the context of artemisinin resistance
-Ivermectin
-Use of community health/malaria workers and volunteers for improved surveillance and response to support malaria elimination
-RTS,S/AS01 in low transmission settings for targeted elimination

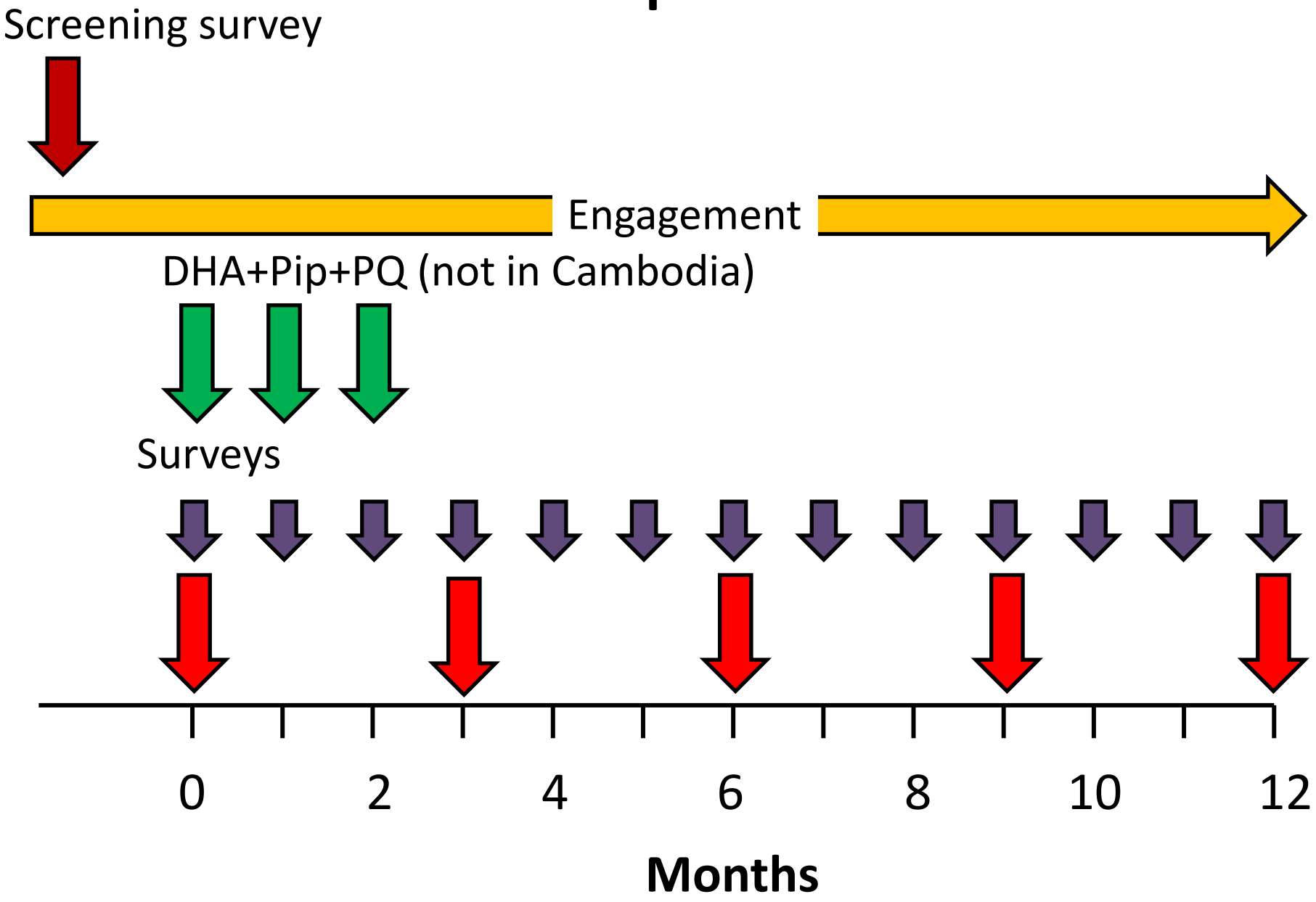
TME targeting the asymptomatic parasite reservoir



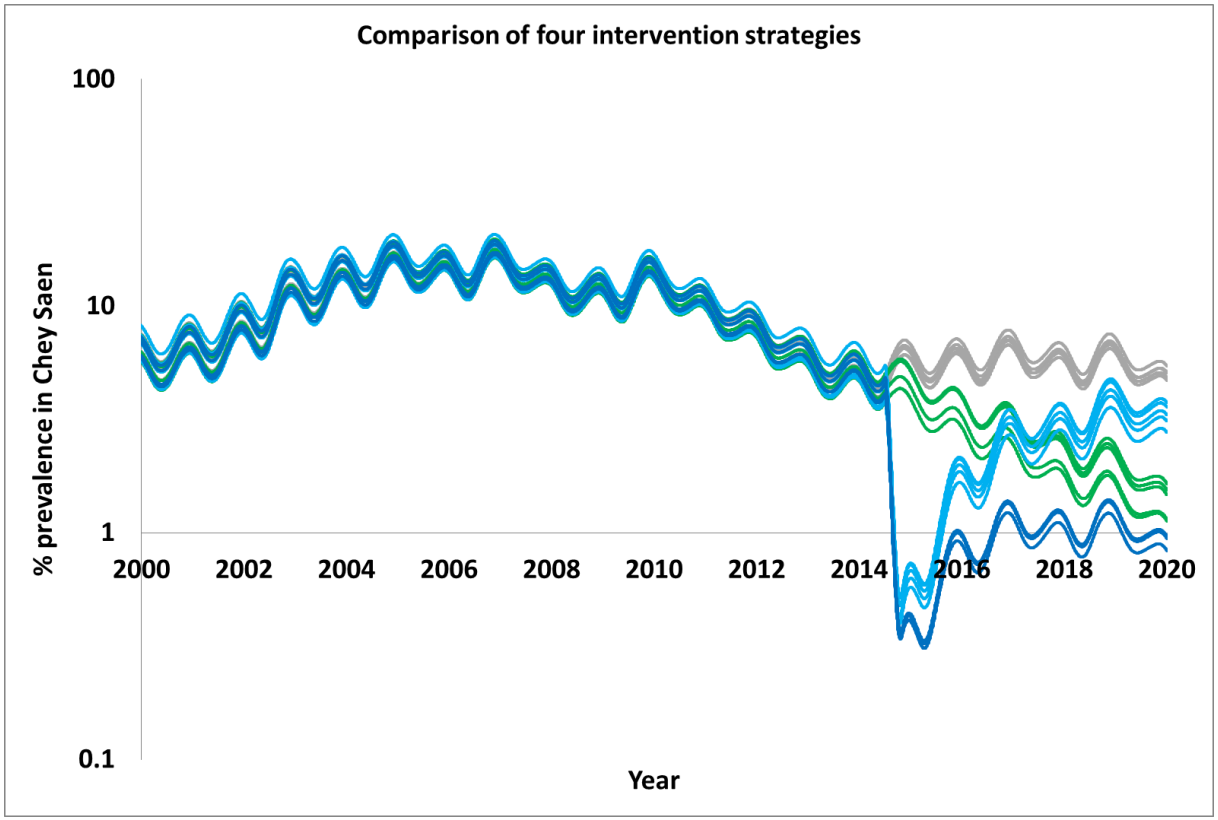
Parasitaemias Pailin compared to Thai-Myanmar border



TCE protocol



TME in the context of VMW/ ITN coverage



Do nothing [grey]
Scale up of VMW and ITN in all villages within10km of Chey Saen [green]
TME three rounds separated by 1 month in Q3 of 2014 no scale-up [Cyan]
TME three rounds separated by 1 month in Q3 of 2014 with scale up of VMW and ITN in all villages within 10 km of Chey Saen [blue]

Preliminary conclusions

-Asymptomatic reservoir considerable,
even in low transmission setting

Targeted malaria elimination with 3 rounds of
DHA-PQP and low dose PQ:

-Well tolerated
-Seems effective in eliminating the P.f. reservoir
But less effective for P.v.
-Maintenance of high coverage is a challenge
-Import of new cases from outside is a vulnerability

Data from Cambodia and Viet Nam to follow

The TEG considers that MDA can be useful as part of an elimination strategy if included in the context of a package of interventions.

Several questions must be addressed to optimize targeted MDA trials, which include strategies for scaling up (such as blood volumes and sample sizes for screening and large scale community engagement, and acceptance and support).

MDA remains a high-risk strategy, since it has the potential to increase drug pressure on the parasite population, driving increasing drug resistance (last man standing), so that efforts need to be maintained until elimination has been achieved.

In principle, the drug used for MDA should be different than the ones used for first line treatment. In some settings however, this is not possible due to resistance to partner drugs. When possible, rotating the drugs used in MDA is recommended.

The TEG recommends that more trials looking at various aspects of this strategy should be conducted as soon as possible and that national programmes and WHO should be involved in planning and evaluation with real-time sharing of information.

Corresponding MPAC questions

Does the resistance situation in the GMS mean that MDA is no longer rational?

Which drugs should be used in MDA?

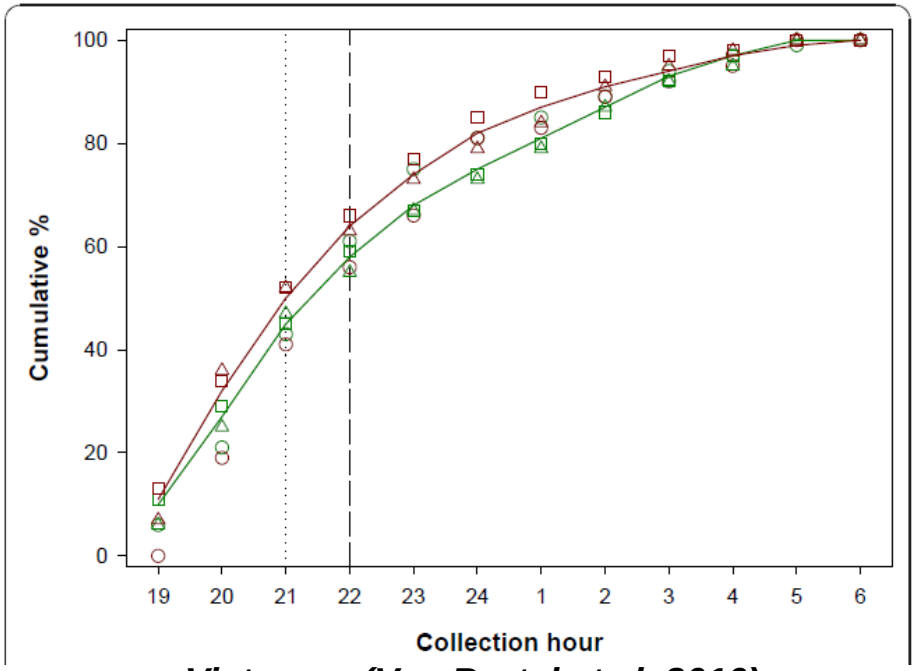
Are there other interventions with which MDA should be combined in a fixed way? If yes, which should be prioritized immediately in operations or in research?

How should MDA be planned and monitored?

Does the TEG recommend an evidence review group on MDA?

What further inputs are needed from geneticists and modelers on MDA?

Vector Control – Greater Mekong Subregion



Vietnam - (Van Bortel et al. 2010)

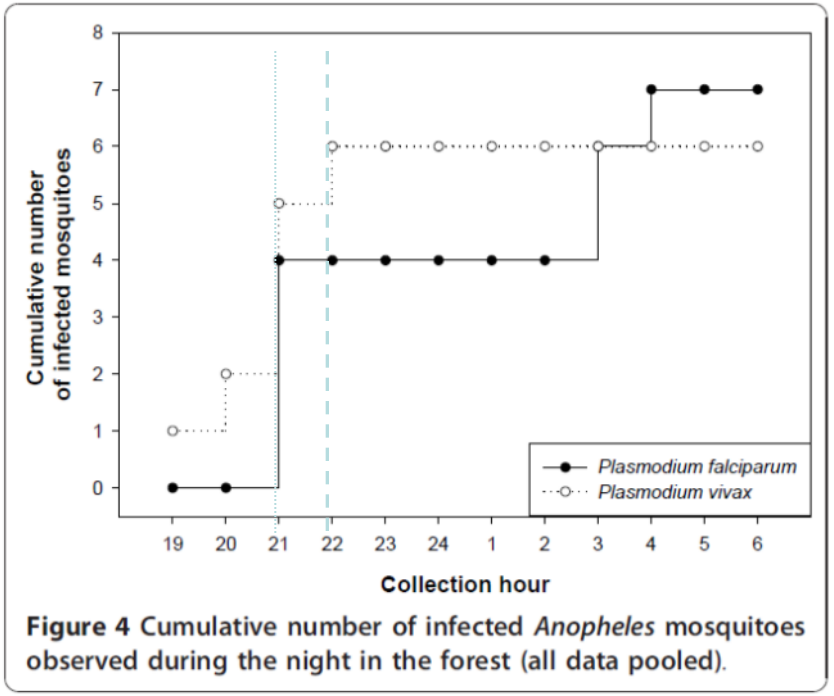
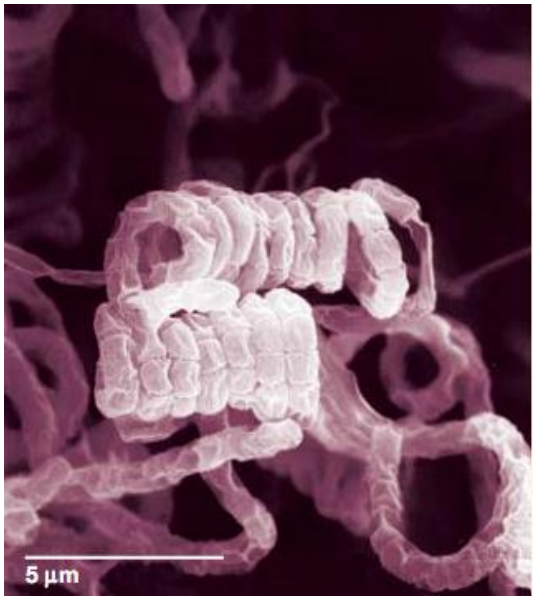


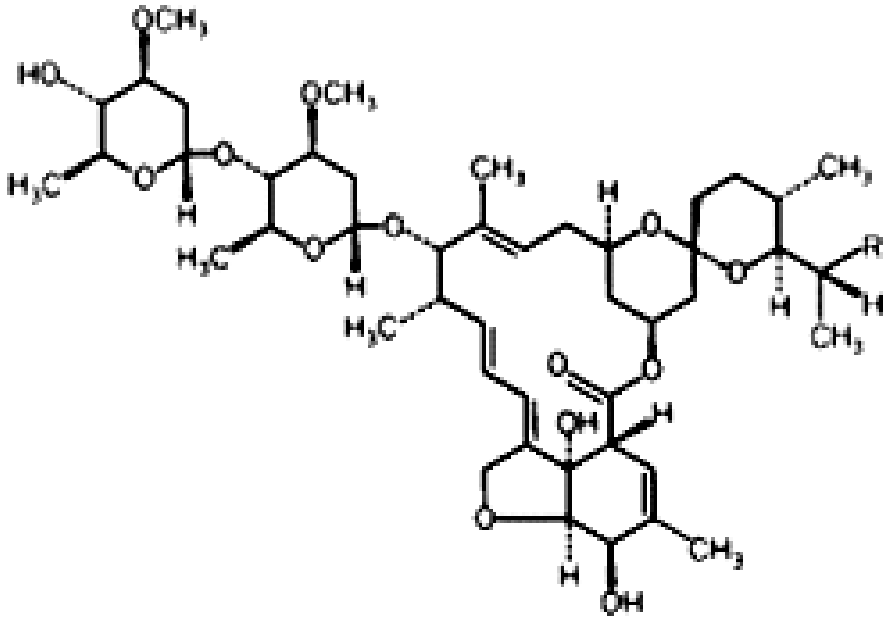
Figure 4 Cumulative number of infected *Anopheles* mosquitoes observed during the night in the forest (all data pooled).

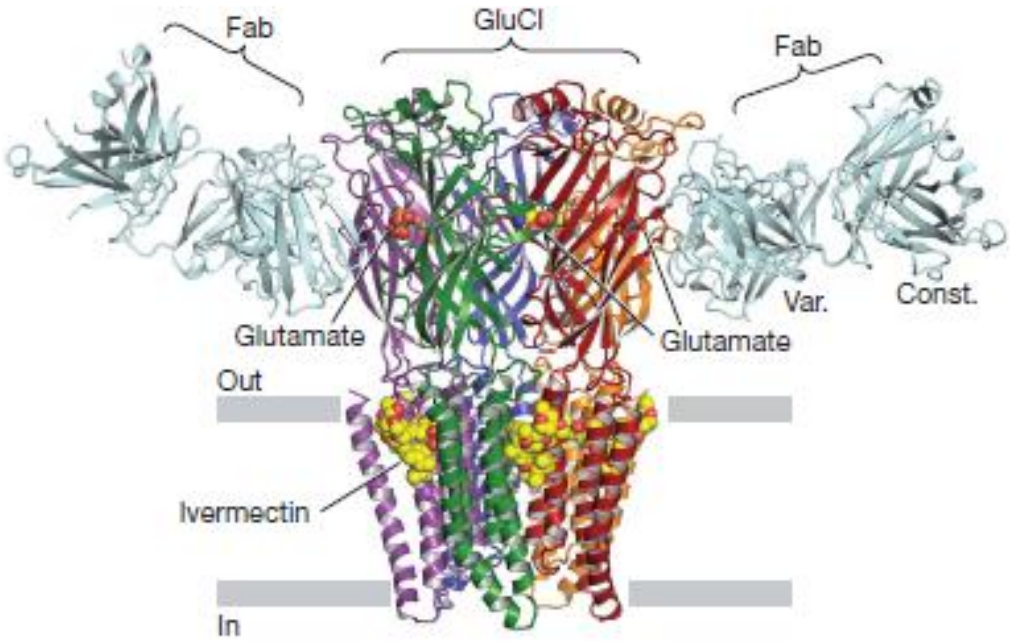
- **Most malaria vectors in the GMS are outdoor-feeding (exophagic), outdoor-resting (exophilic) or feed before bedtime (crepuscular), and much of the malaria transmission occurs in forested areas during work, not in the village home**
- **Therefore we need vector control measures that account for human and vector behavior!**
- **Treatment of human populations with a systemic insecticide would guarantee delivery of insecticides to human feeding malaria vectors regardless of feeding location or time**

Ivermectin

- Macrocyclic lactone isolated from the bacteria *Streptomyces avermitilis*
- Mode of action – binds at subunit interfaces next to the glutamate-gated chloride (GluCl) ion channels, which distorts the channel from closed to open, hyperpolarizing the cell (Hibbs and Gouaux 2011) which leads to the paralysis of the nematode or ectoparasite musculature (Cully et al. 1994, 1996, Cane et al. 2000)
- Different class of insecticides than those used for ITNs or IRS







Modified Vectorial Capacity Equation

(Garrett-Jones 1964, Black and Moore 2005)

$$V = \frac{m a^2 p^n b}{-\ln p}$$

V – average number of potentially infective bites that will by delivered by all vectors feeding on a single host in one day

***p* – daily probability of adult mosquito survivorship**

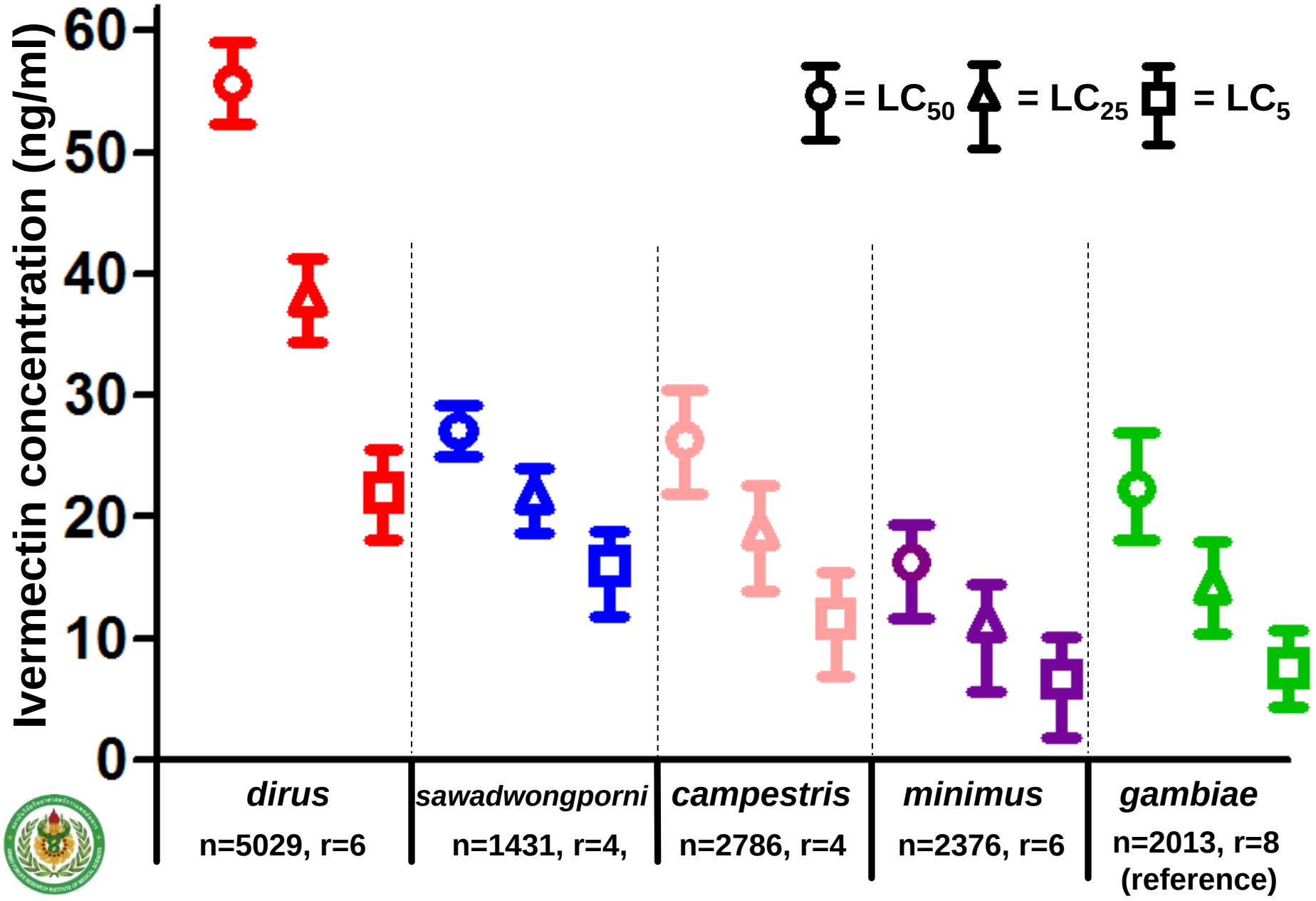
***a* – daily probability an *Anopheles* feeds on a human (human bloodmeal index x feeding frequency)**

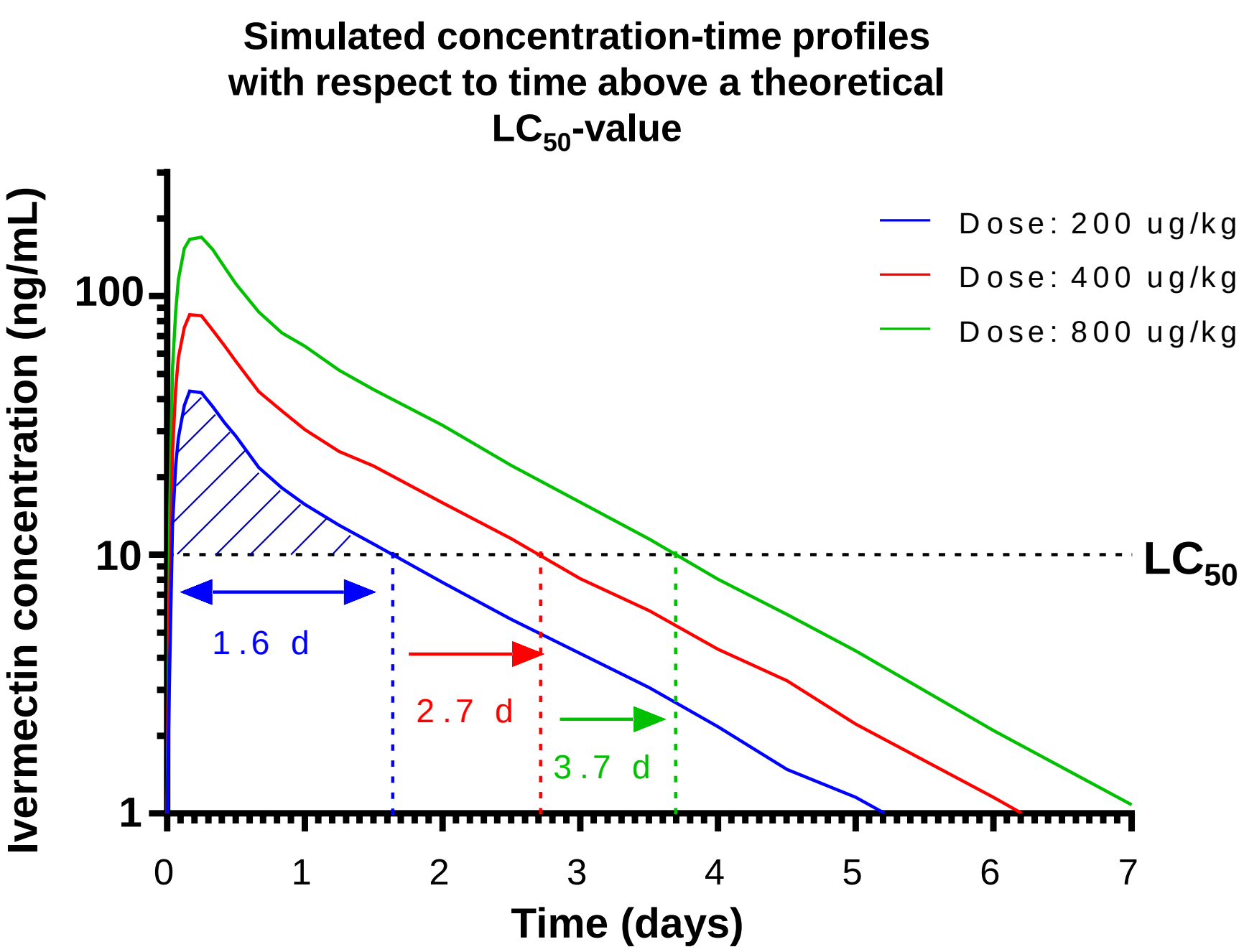
***n* – duration of the extrinsic incubation period**

***b* – vector competence (ie. proportion of *Anopheles* that ingest *Plasmodium* and successfully become infectious)**

***m* – vector density in relation to the host**

Lethal concentration ivermectin for *Anopheles*:




Simulated concentration-time profiles with respect to time above a theoretical LC50-value
Dose: 200 ug/kg
Dose: 400 ug/kg
Dose: 800 ug/kg
Ivermectin concentration (ng/mL)
100
10
1
LC50
1.6 d
2.7 d
3.7 d
0
1
2
3
4
5
6
7
Time (days)

Imperial College London

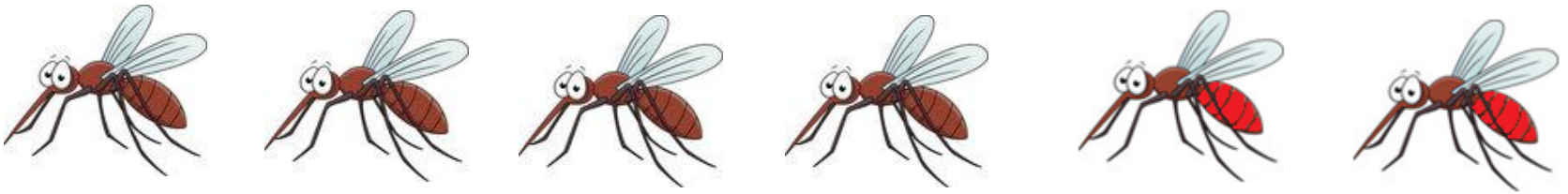
MRC Centre for Outbreak Analysis and Modelling

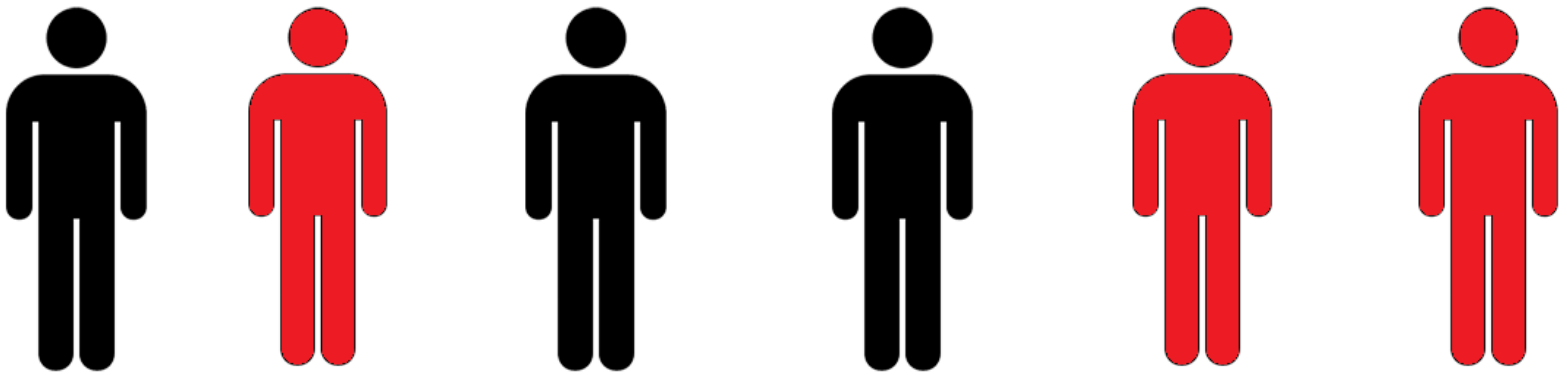
Impact on transmission

Normal vector lifespan

Approx. 10 days after biting, vector becomes infectious

Day 0 | Day 3 | Day 6 | Day 9 | Day 12 | Day 15





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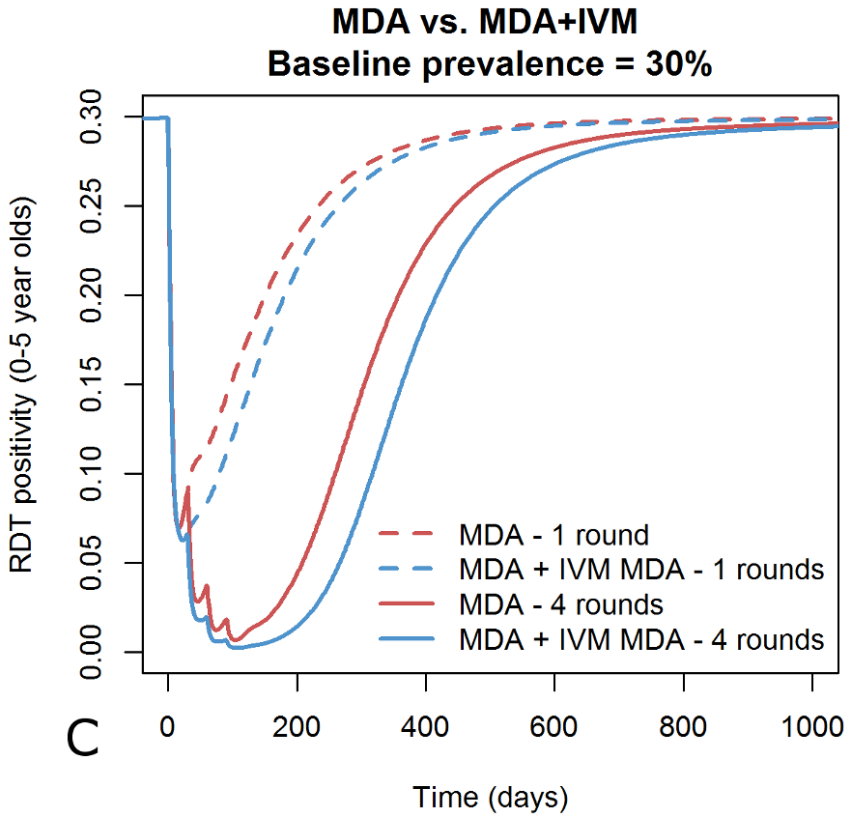
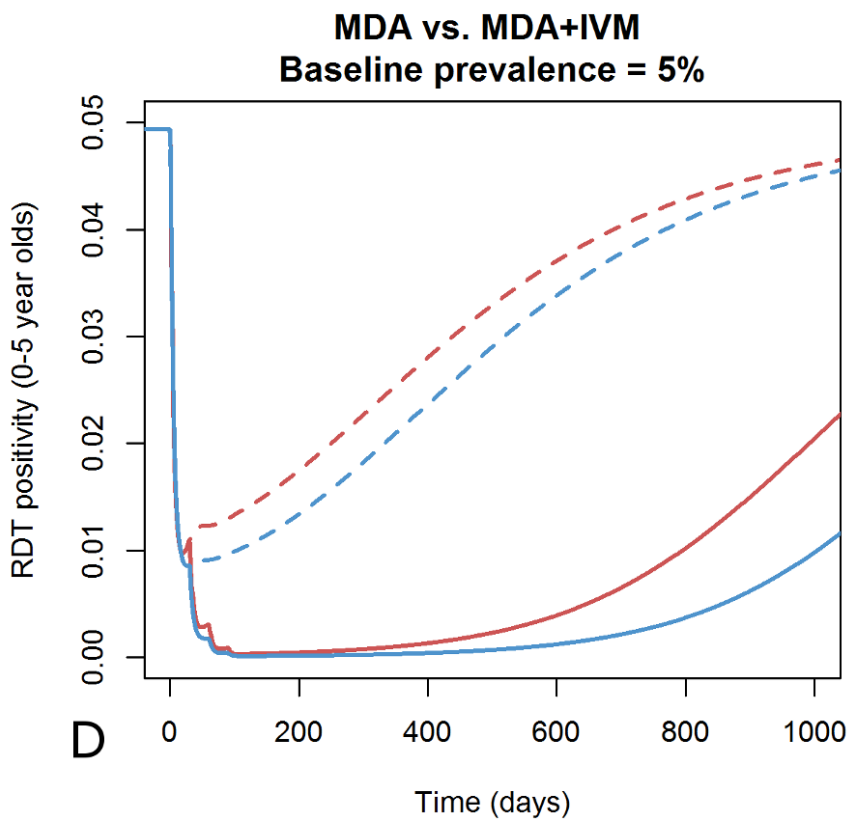
MDA alone vs. MDA + IVM

ACT given to everyone, IVM given to everyone >5yrs old, coverage=90%

Same affect as with MSAT, but **more sustained reduction in transmission**, especially in a low prevalence setting





The added value of ivermectin when combined with targeted MDA should be investigated.

The TEG was encouraged by the widespread and apparently safe and effective use of this drug in MDA campaigns against onchocerciasis in western Africa.

Entomological data from areas where ivermectin was deployed and safety data (in terms of highest tolerated doses) should be reviewed prior to MDA trials.

Dosing and interaction with antimalarial drugs used in MDA will also need careful consideration.

The TEG also recommends other field studies with ivermectin given as MDA, but not necessarily in combination with antimalarial drugs.

The TEG concluded that personal repellents couldn't be recommended as a programmatic intervention in the GMS.

Use of repellents can still be an important tool for individual protection in particular circumstances and there is still a scope for research on this tool and other anti-vector measures to address residual transmission.

Corresponding MPAC question

Which role should vector control interventions including ivermectin play in elimination/containment/control strategies in the GMS, considering effect, cost-effectiveness and alternative uses of the resources?

Mosquito nets should be part of the containment activities and are already an integral part of national malaria control programme with high population coverage in many regions. Personal repellents as programmatic interventions have shown very limited impact, but can be important for individual protection.

Role of village malaria workers and community health workers

Village malaria workers (VMWs) and community health workers (CHWs) have important roles in several key areas of the response to artemisinin resistance, particularly in providing early diagnosis and quality treatment and behavioral change communication, surveillance and providing data for information systems, and in reaching migrant or mobile populations or hard to reach populations.

Having VMW and CHW perform directly observed treatment (DOT) may be considered, in the context of the later stages of malaria elimination, when there are only a few cases left, and in non-mobile populations. In other settings, the TEG does not recommend a general emphasis on DOT, since at the population level the effectiveness of DOT for malaria treatment in the region has not been shown to be superior to nonsupervised treatment.

Research to identify other methods to improve adherence is important.

Role of malaria vaccines in elimination

There is currently insufficient data to suggest a role for the RTS,S vaccine in containment/elimination strategies. In the context of malaria elimination, all age groups should be vaccinated.

The final formulation of the RTS,S vaccine has not been tested in South-East Asia. In addition, it has to be confirmed that RTS,S does not increase the asymptomatic *P. falciparum* parasite reservoir of transmissible parasites by inducing partial immunity.

The TEG considered it important to invest in the development of a vaccine that interrupts malaria transmission, since this could prove an important additional tool in malaria elimination.

Additional MPAC questions (1)

What should be the ideal profile of the next generation of antimalarial treatment?

The TEG considered triple combinations of drugs with different modes of actions to be a target product profile for the next generation of antimalarial drugs either using current drugs or by adding a new compound to some of the existing ACTs. The selection of drugs will require appropriate matching of pharmacokinetic profiles (linked to drug potencies) and investigation of potential drug interactions. The absence of new drugs is a major impediment in fighting antimalarial resistance, and TEG expresses desperate needs to accelerate the development of new chemical entities.

Additional MPAC questions (2)

What is the role of classical elimination tools such as focus-based interventions and active case detection in the context of artemisinin resistance in GMS?

These tools are relevant, but need to be assessed and adapted to the epidemiological and operational realities of each country. However, the assessments that have been done offer little encouragement. The diagnostics technology that would enable such an approach is simply not available; the simple and quick methods are far too insensitive, and the complex and slow methods are more sensitive but, in any event, too expensive for consideration by NMCPs.

Additional MPAC questions (3)

Is there any role for financial incentives to seek proper treatment in any areas?

The TEG believes financial incentives for seeking proper treatments is ethically dubious and socially not sustainable.

Additional MPAC questions (4)

What actions, if any, should be recommended for groups such travelers and military entering or leaving areas with artemisinin resistance?
This topic was addressed only partially but will be included on the agenda of the next TEG. It was agreed that military should be treated for preventing importation or exportation of resistant parasites in the GMS. Specific actions will be needed for UN. The TEG will review a set of recommendations for the UN through email. Recommendations to travelers should be issued by the TEG on Chemotherapy in concert with the WHO division of International Travelers and Health. A regional meeting addressing the issues of malaria control in the military in the context of artemisinin resistance, organized by donors, WHO ERAR hub and the RSC RAI, will take place in Viet Nam 19-20 June.

Does the TEG recommend the use of standby treatment for mobile populations?
Under exceptional circumstances, when there are no malaria workers or health services, the TEG considers standby treatment for mobile populations acceptable provided the treatment is a quality assured ACT. Drug should be provided as part of a kit containing nets and diagnostic tool(s). However, mobile malaria workers are a better solution and experience with them is accumulating.

Additional MPAC questions (5)
Next steps

Since the development of the Global Plan for Artemisinin Resistance Containment (GPARC), research has provided additional information on artemisinin resistance, and resistance has been identified outside the area on the Cambodia-Thailand border. Is it now possible to identify a strategy for containment of artemisinin resistance i.e. to prevent or significantly and verifiably delay its spread beyond GMS biogeographic region or eliminate artemisinin resistant parasites?

See feasibility assessment….

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In press: 18 December 2013

ARTICLE

nature

doi:10.1038/nature12876

A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

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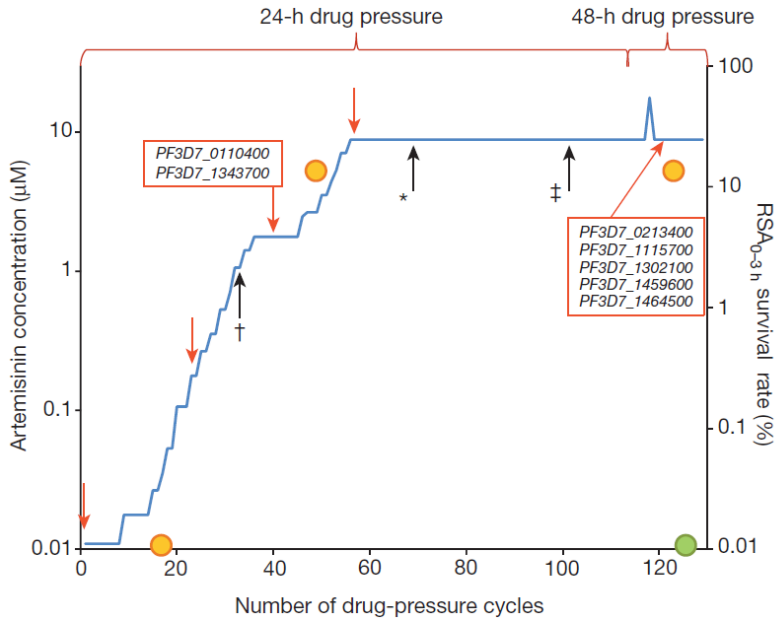
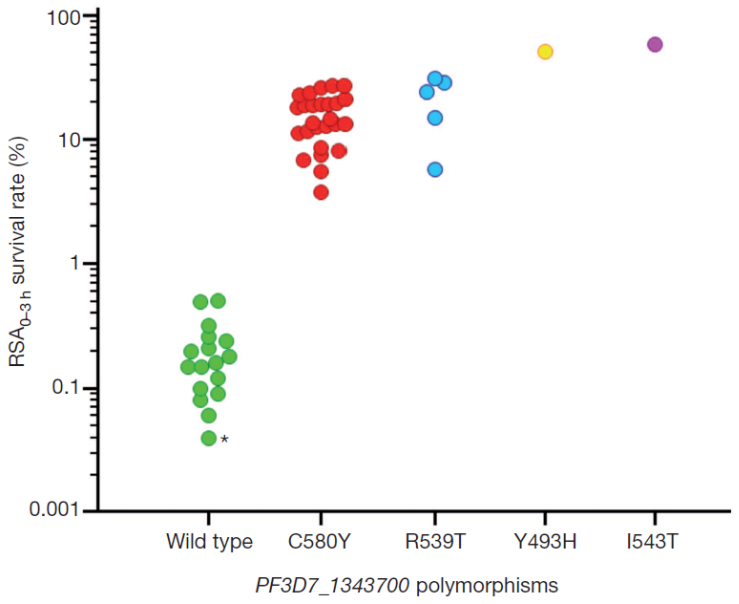
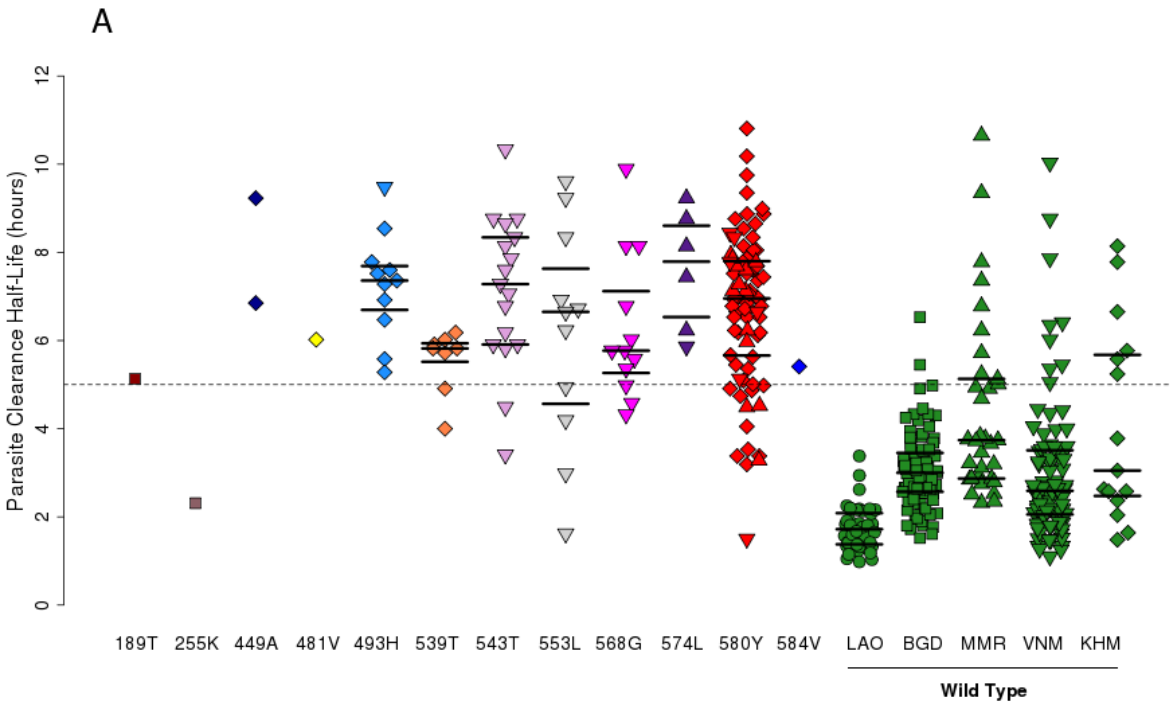
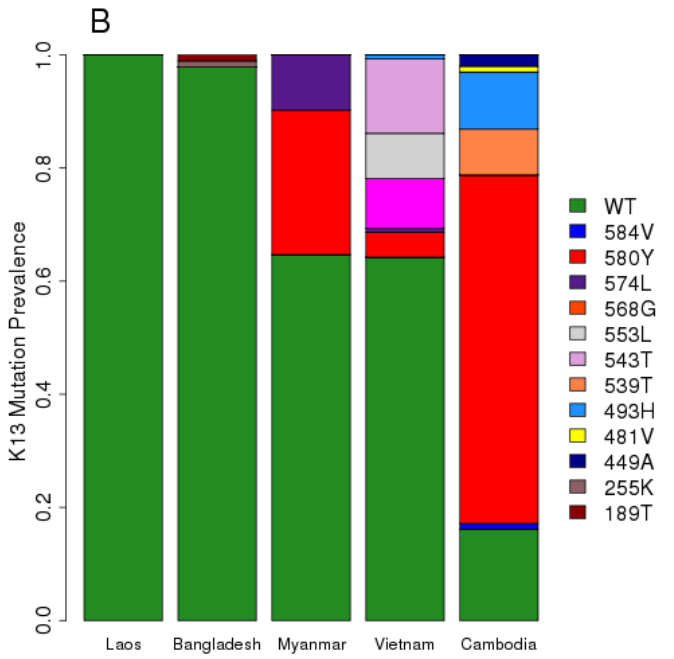




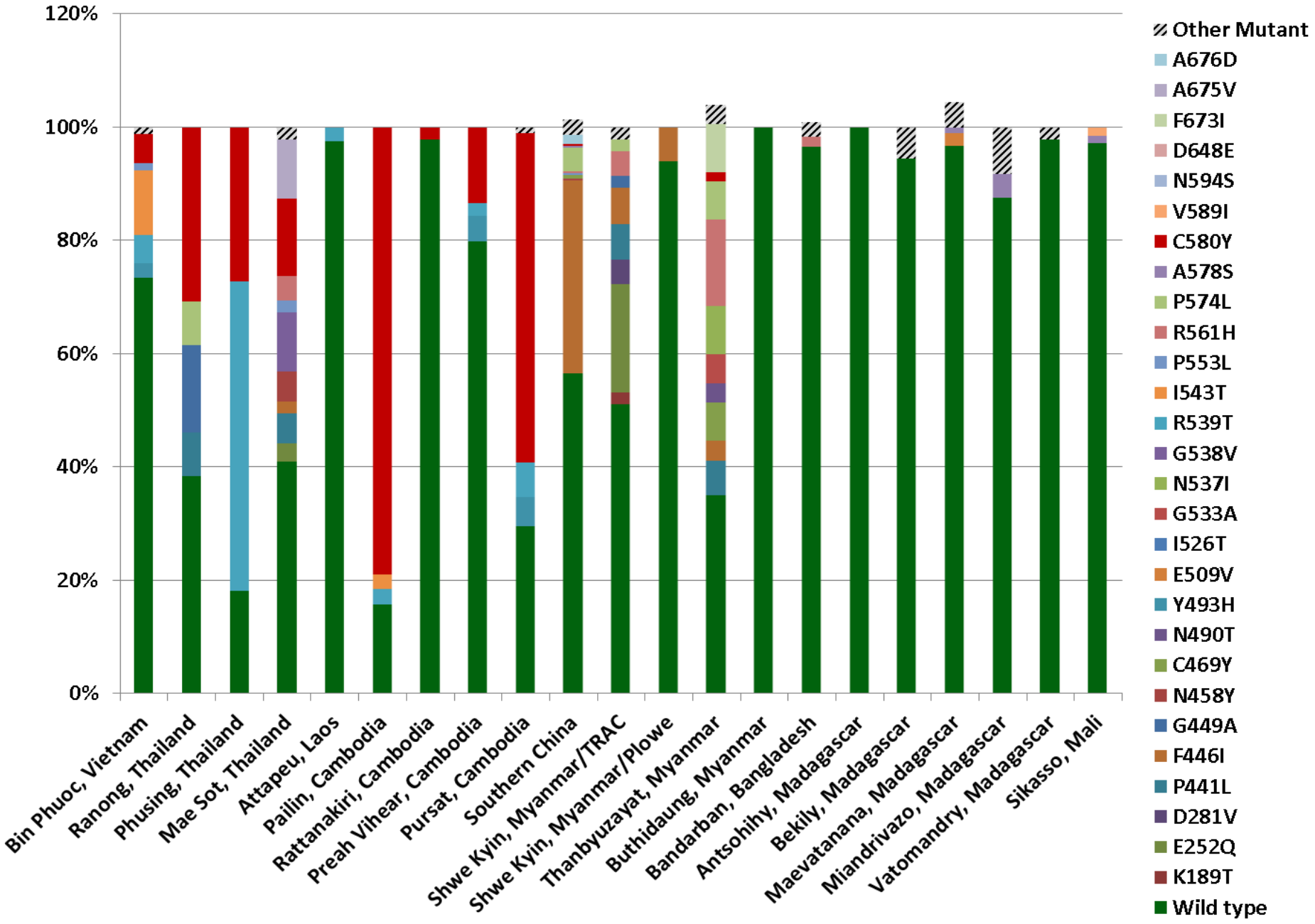
K13 SNPS are associated with clinical artemisinin resistance in Myanmar and Vietnam as well as Cambodia

Takala-Harrison, Jacob *et al.* submitted



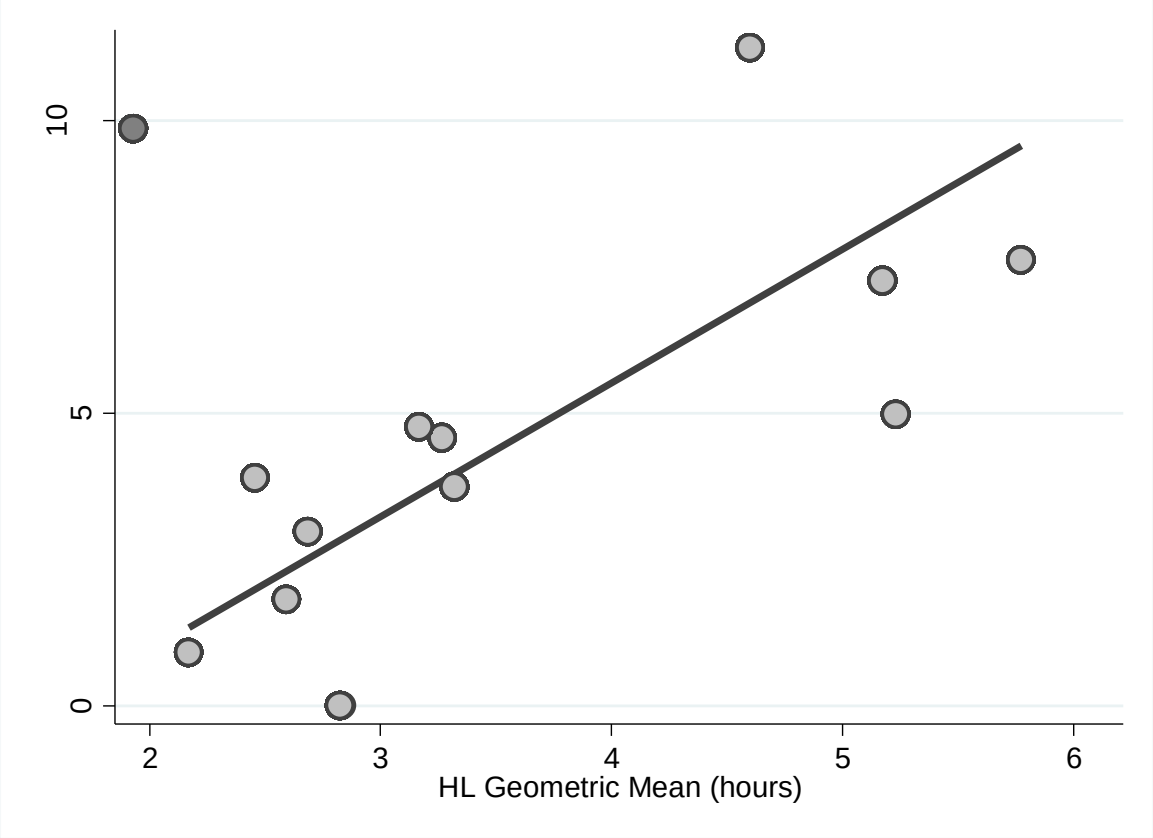


Prevalence of K13 SNPs in Asia, Madagascar and Mali

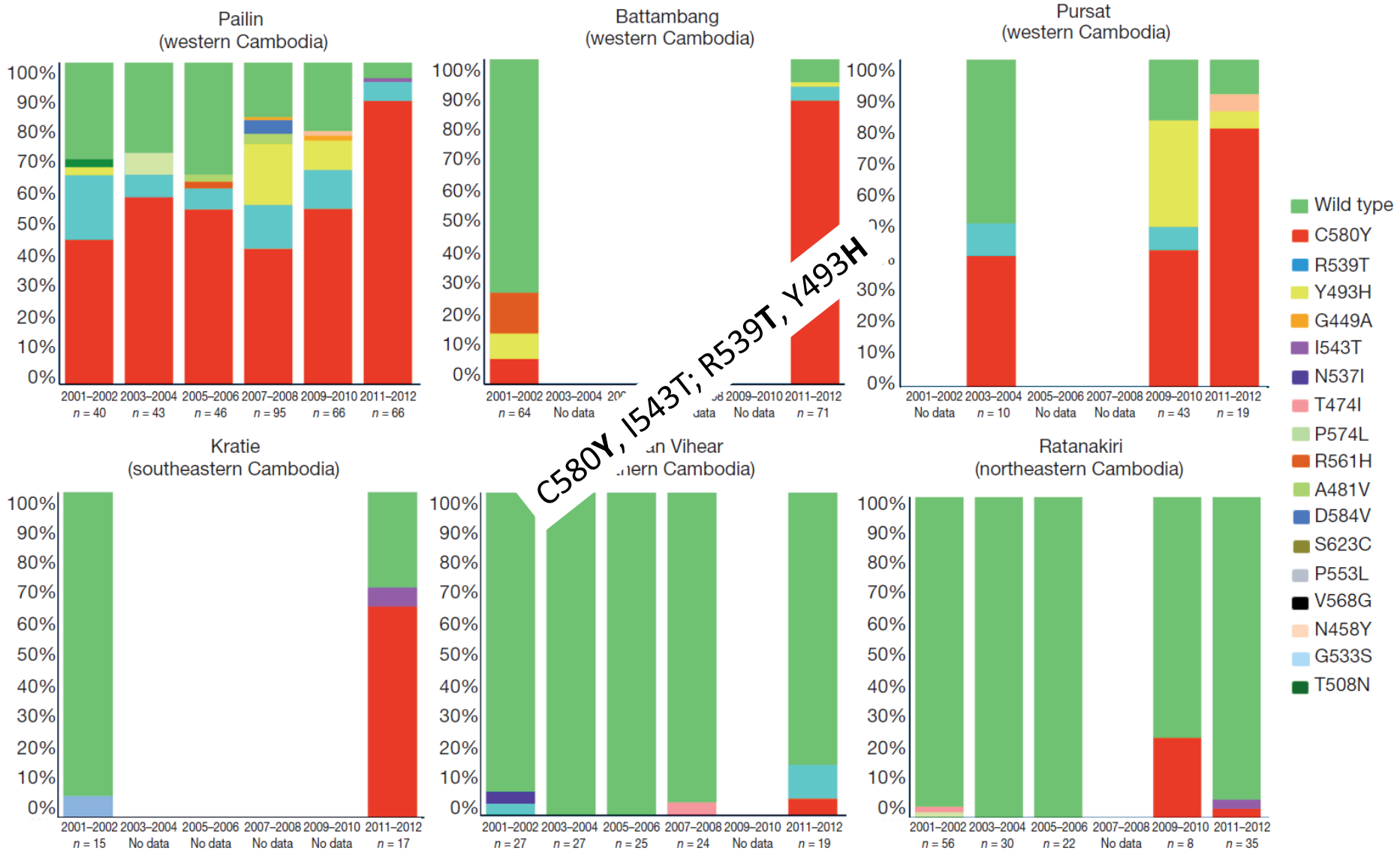


De-novo gametocyte vs parasite clearance half-life

(24 hours to 7 days after the onset of treatment)

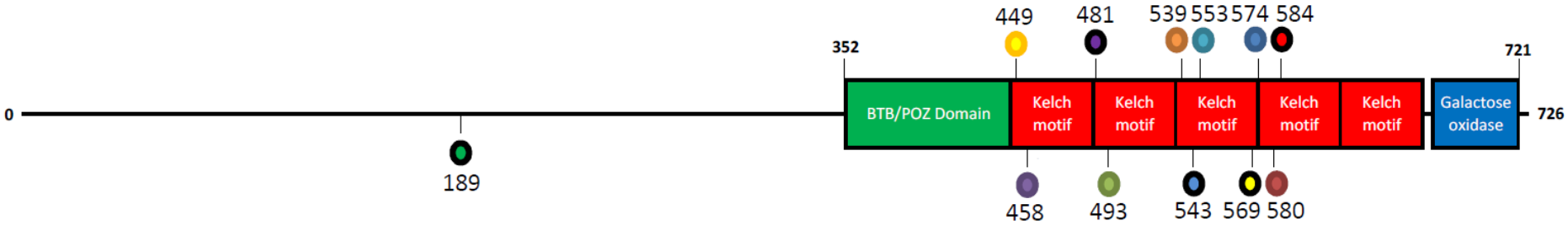


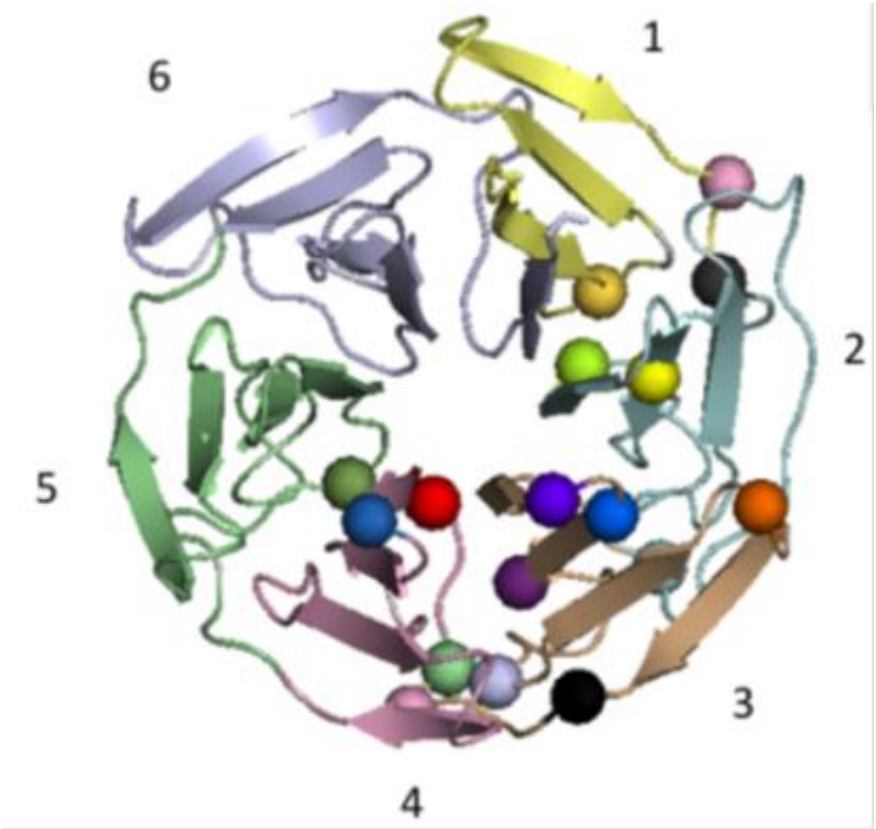
Frequency of K13 SNPs in 886 parasite isolates in six Cambodian provinces in 2001–2012



Ariey *et al. Nature* 2013

Most K13 SNPs reside in the “propeller” domains





What is antimalarial drug resistance?

- 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" (WHO, 1973)
- Therapeutic efficacy is used as an 'alert' to drug resistance but not all treatment failures are due to resistance. Treatment failure can be due to:
  - pharmacokinetic (low absorption, increased metabolism, etc…)
  - immunity (HIV, pregnancy, etc…)
  - confirmed resistance
- Therefore other tools are needed to confirm resistance
  - pharmocokinetics
  - in vitro efficacy
  - molecular markers

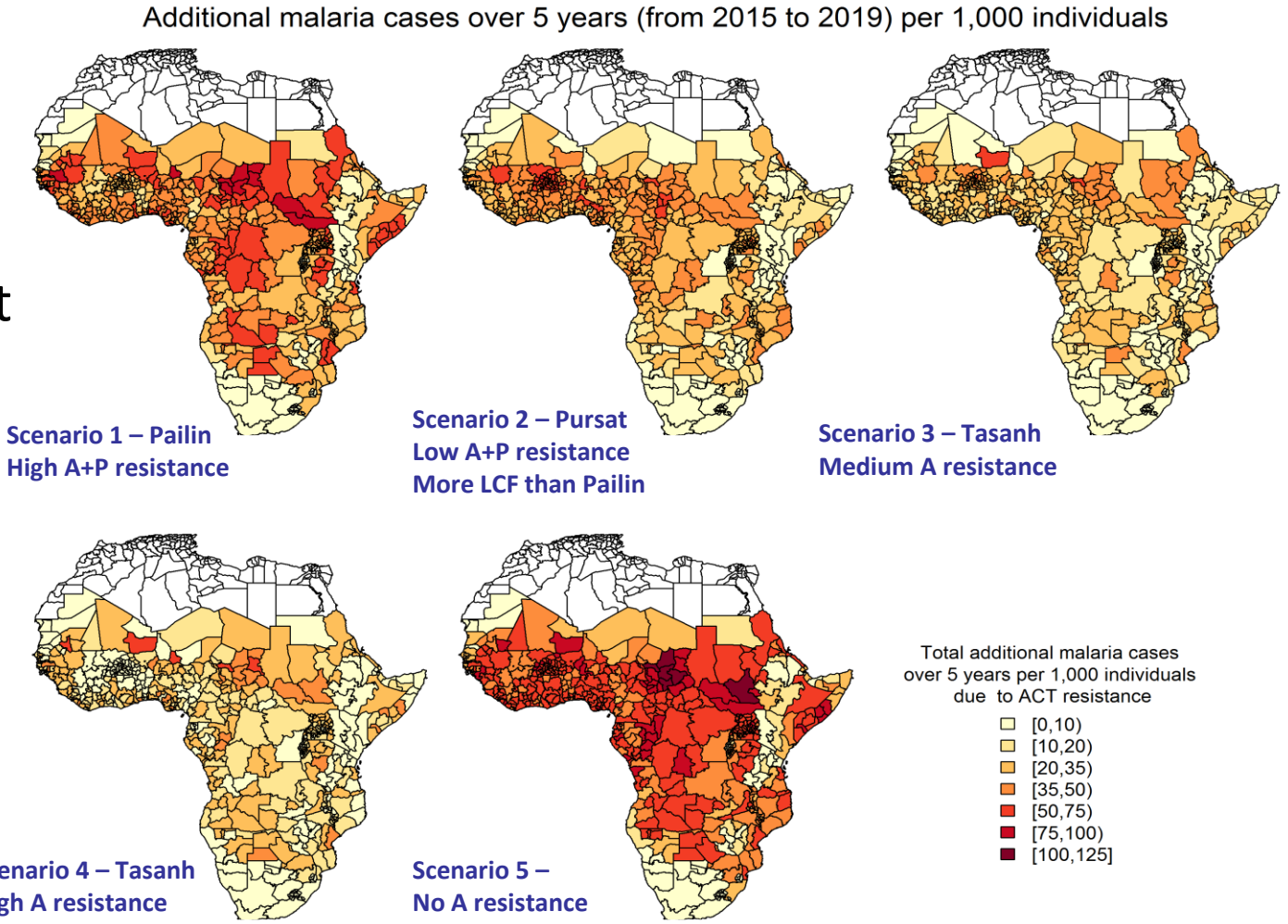
Imperial College London

MRC Centre for Outbreak Analysis and Modelling

Main result 1

CLINICAL INCIDENCE IS HIGHEST IN A SCENARIO WITH HIGHEST PARTNER DRUG RESISTANCE

Additional malaria cases over 5 years if resistance is at the level defined by each scenario



H. Slater Imperial College

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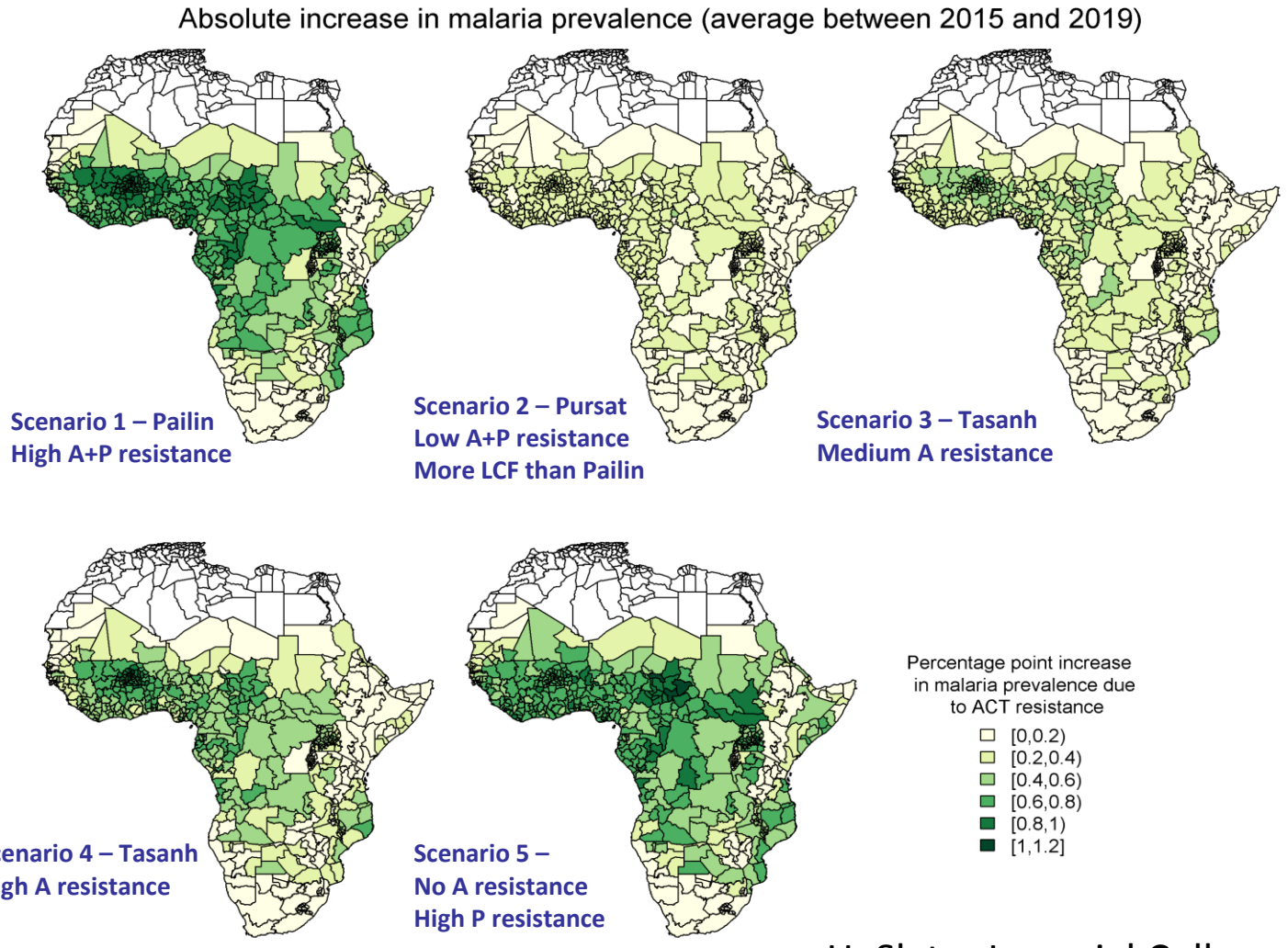
Main result 2

PREVALENCE IS HIGHEST IN A SCENARIO WITH BOTH ARTEMISININ AND PARTNER DRUG RESISTANCE

Absolute increase in prevalence if resistance is at the level defined by each scenario

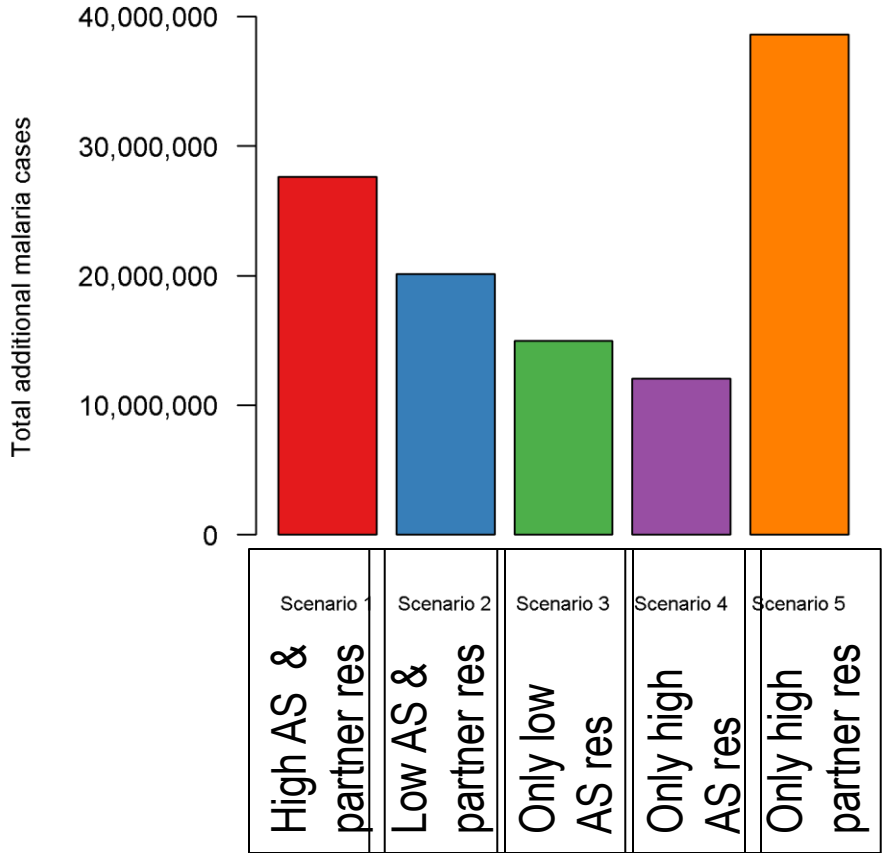


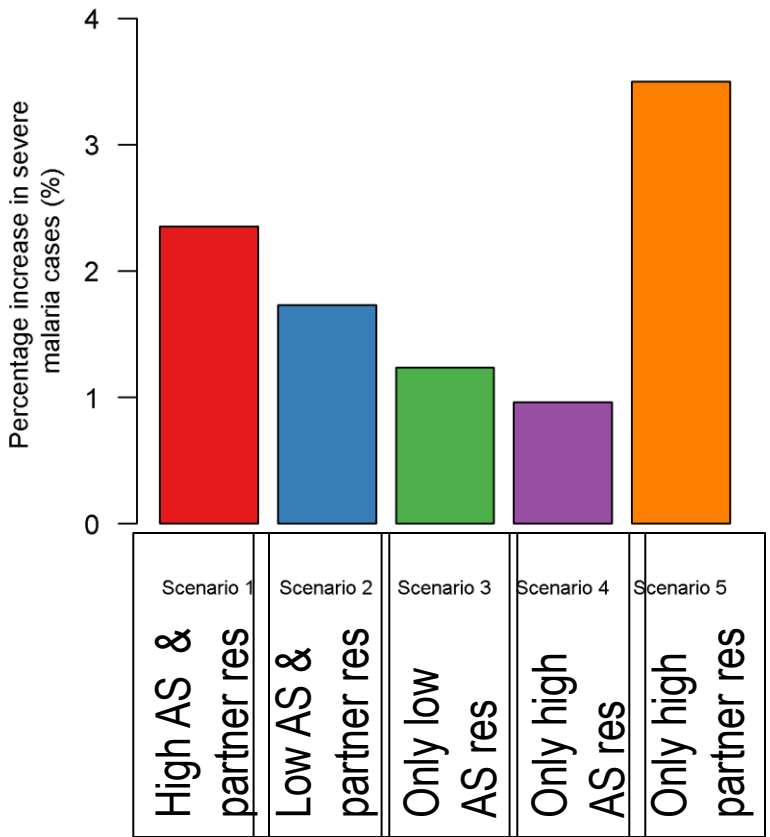
H. Slater Imperial College

Main result 3

THE SCENARIO WITH HIGH PARTNER DRUG RESISTANCE HAS THE GREATEST IMPACT ON MORBIDITY

Total additional clinical cases and percentage increase in severe malaria cases in Africa betwen 2015 to 2019





Key focus areas for resistance response – many roles for Village Malaria Workers

- Surveillance and information systems +++
- Reaching mobile and migrant populations +++
  - Diagnosis, treatment, referral, BCC
- Other hard to reach populations +++
- Suppression of using monotherapies ?
- Mosquito protection indoors and outdoors ?
- Dealing with asymptomatic/low density parasite carriers ?

Sylvia Meek

Minutes of the Drug Resistance and Containment Technical Expert Group

28-30 April 2014

Starling Hotel, Geneva, Switzerland

This document was distributed as a pre-read for the September 2014 meeting of the Malaria Policy Advisory Committee (MPAC) and is not an official document of the World Health Organization.

Contents

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Abbreviations

ACT	artemisinin-based combination therapy
APLMA	Asia Pacific Leaders Malaria Alliance
CHW	community health worker
DOT	directly observed treatment
ERAR	Emergency Response to Artemisinin Resistance
G6PD	glucose-6-phosphate dehydrogenase
GMP	Global Malaria Programme
GMS	Greater Mekong subregion
GTS	Global Technical Strategy
GWAS	genome-wide association study
IRS	indoor residual spraying
K13	gene on *P. falciparum* chromosome 13 encoding a Kelch protein
LC	lethal concentration
LLIN	long-lasting insecticide-treated net
MDA	mass drug administration
MFLT	multiple first-line treatments
MPAC	malaria policy advisory committee
MMW	mobile malaria worker
PCR	polymerase chain reaction
Pfmdr1	gene encoding *P. falciparum* multidrug resistance 1 protein
RAI	Regional Artemisinin Initiative
RSC	regional steering committee
SAGE	strategic advisory group of experts
SNP	single nucleotide polymorphism
TEG	technical expert group
TRAC	Tracking Resistance to Artemisinin Collaboration
VMW	village malaria worker
WHO	World Health Organization

Summary and recommendations

Answers to malaria policy advisory committee questions

The format of the summary and recommendations has changed compared to the previous TEG meetings. The TEG's recommendations made specifically in response to questions posed by the malaria policy advisory committee (MPAC) including the major strategic issue of redefining containment in the light of recent epidemiological findings are placed separately in Annex 1. The summary and recommendations below partly overlap with these, but also cover additional issues discussed during the meeting.

"K13" molecular marker for artemisinin resistance

The recent discovery of a marker for artemisinin resistance in the gene located on chromosome 13 of *P. falciparum* encoding a Kelch protein (K13) has greatly impacted the field, including definitions of resistance and surveillance methods. The science around this new marker is quickly evolving and not yet fully understood. More than 30 different mutations in the K13 gene have been reported so far, not all of them being located in the resistance domains (presently thought to include amino acid positions ≥ 440), and different mutations may confer different resistance phenotypes. Given the significance of the discovery, its technical complexity and the rapidly growing information, the TEG expressed agreement for that an evidence review group (ERG) on the topic should be established to 1) to collect and review data; 2) to indicate which polymorphisms on K13 (and beyond) should have consequences, if detected in a given area, and describe these consequences; this includes a discussion on the development of integrated mapping of the relevant K13 mutations; 3) to propose organizational structures (such as a reference center) that can facilitate standardization of methods and information flow to national programs and WHO; 4) to identify remaining knowledge gaps for research. TEG recommended that future clinical studies, and all therapeutic efficacy studies, should include collection of (dry blood spot) samples for K13 assessment.

Definition of artemisinin resistance and consequences for the resistance tier-map

With the discovery of the K13 molecular marker, the definition of artemisinin resistance was adapted to incorporate K13 mutations:

Suspected endemic artemisinin resistance is defined as:

- a prevalence ≥ 5% of infecting parasite strains carrying Kelch 13 resistance-associated mutations; **or**
- a proportion ≥ 10% of patients still parasitemic on day 3 by microscopy; **or**
- ≥ 10% of patients with a peripheral blood parasite half-life ≥ 5 hours following a treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy.

Confirmed endemic artemisinin resistance is defined as:

- a prevalence of ≥ 5% of infections with strains containing Kelch resistance mutations if the patients carrying these mutants also have persistent parasitaemia by microscopy on day 3 or a peripheral blood parasite half-life ≥ 5 hours following adequate treatment with ACT or artesunate monotherapy.

The term ACT resistance should be applied only when the therapeutic efficacy of ACTs start to fail in the context of resistance to both artemisinin and the partner drug(s). ACT failures > 10% should prompt a change in policy with another ACT.

The new definition will impact current tier classifications. Pending new data from studies conducted in Myanmar, it is likely that in addition to the eastern provinces, the northwestern provinces of Myanmar will be classified as tier 1.

Furthermore, the temporal and spatial trends of findings on artemisinin resistance indicate that all falciparum endemic areas in GMS countries, which are not already affected by artemisinin resistance, are at high risk. The TEG recommends that all such areas should now be classified as tier 2. The strategies and interventions for these areas should be the same as for tier 1 areas, the only difference being a lower priority under financial and operational constraints.

Multiple genetic lineages of artemisinin resistance in the Greater Mekong subregion

Analysis of the recently identified molecular marker for artemisinin resistance showed that the C580Y mutation was the most prevalent in parts of the Greater Mekong subregion (GMS), but many other mutations in and near the K13 propeller region were also identified that are associated with resistance. Genetic analysis identified multiple genetic lineages of artemisinin resistance, suggesting that it is not only spreading but also emerging de novo, thus raising concerns about the effectiveness of a "firewall approach" (delaying or preventing spread from a focus) and giving further support to the advisability of eliminating falciparum malaria transmission in all areas of confirmed artemisinin resistance. The answers to the questions by MPAC (Annex 1) identify the implications of this strategic shift for the GMS. Prevention of spread of resistance from GMS, however, remains crucial because falciparum malaria is become increasingly resistant to the main new partner drugs (lumefantrine, mefloquine, piperaquine).

Is there artemisinin resistance in South America?

In Suriname, the study conducted to determine the presence of artemisinin resistance is still on going. Calculation of parasite half-life and molecular marker studies are needed before any further conclusions can be made.

Treatment policy in Cambodia in the context of high failure rates of dihydroartemisinin-piperaquine

In Cambodia, atovaquone-proguanil resistance conferring mutations were observed less than a year after the implementation of the drug as the first-line treatment in Pailin (2012) and tier 1 areas (2013), which emphasized the urgent need for policy change. For this reason, artesunate-mefloquine was re-introduced as first-line treatment in five provinces (tier 1), since the proportion of falciparum strains with multiple *Pfmdr1* copy numbers (which confer mefloquine resistance) is currently minimal in the area. Quinine and doxycycline over 7 days has been adopted as rescue therapy. Dihydroartemisinin-piperaquine remains the first-line treatment in the rest of the country. Since resistance to mefloquine following its re-introduction is likely to reappear quickly, the TEG considers reintroduction of artesunate-mefloquine in western Cambodia a short-term solution. Artesunate-pyronaridine is currently being re-evaluated in Western Cambodia and may provide an alternative first line treatment for uncomplicated falciparum malaria in these provinces. Clinical studies (phase I and II) to assess the safety, efficacy, and effectiveness of a 5-day dihydroartemisinin-piperaquine treatment course were recommended. Future drug development should consider triple combinations of drugs with different modes of action, either with current drugs or by adding a new compound to some of the existing ACTs.

Impact of artemisinin resistance in Africa

Using current artemisinin and partner drug resistance data from Asia and Africa, five potential resistance scenarios were modeled to estimate the impact of artemisinin resistance on clinical incidence, severe incidence, and parasite prevalence in Africa. Scenarios with high levels of recrudescent infections resulted in far greater increases in clinical incidence compared to scenarios with high levels of slow parasite clearance. The model confirms the importance of protecting the partner drug, especially in Africa, which also emphasized the need to consider triple combination therapies. However, important issues, such as the choice of matching drugs, drug interactions and regulatory hurdles need to be addressed to take this further.

Update on current initiatives

Since the last TEG meeting in June 2013, the WHO hub for the Emergency response to Artemisinin Resistance (ERAR) has become functional, and the Global Fund US$ 100 M Regional Artemisinin Initiative (RAI) has started. A new multi-trust fund initiative, coordinated by the Asian Development Bank, is under way. TEG underlined the need for coordination between these initiatives and building synergy where possible. It was noticed that key representatives of these initiatives are already in close communication.

The TEG requested ERAR hub to prioritize the whole GMS mapping of which organizations are doing which activities in which areas targeting which population and in which time frame. This is a prerequisite for a further gap analysis regarding activities and funding.

To guide currently funded initiatives and those in the near future, TEG recommended urgent development of an action plan for elimination of *P. falciparum* in the GMS, which builds on the existing frameworks, but formulates and prioritizes concrete fundable activities.

Multiple first line treatments

The current evidence examining multiple first line treatments (MFLT) as a response to resistance is based on two modelling studies only and those gave contradictory conclusions. In the study which was found to support MFLT, the potential benefit the potential benefit was estimated to relatively minor; likewise the model that did not support MFLT also showed a small effect. Therefore, TEG cannot currently recommend adopting MFLT as a response to resistance but recognizes the need to be flexible and does not oppose such practice, in particular when it is already in place or when used to avoid drug stock outs. The TEG acknowledged that increasing the complexity of treatment policy risks practices that exacerbate rather than mitigate the problem. The potential benefit of doing so seemed insufficient justify recommending it. Measures to ensure drug quality and treatment adherence should be also emphasized.

Targeted mass drug administration as part of the malaria elimination strategy

Initial analysis of a pilot study using targeted mass drug administration (MDA) (3 rounds of a monthly full course of dihydroartemisinin-piperaquine) in villages with high malaria prevalence, show the expected results in reducing prevalent *P. falciparum*, but (as expected due to the untreated hypnozoite reservoir in the community) less so for *P. vivax*. Although not measured in that pilot work, success with MDA almost certainly depends on the coverage achieved, i.e. the proportion of people receiving therapy. The people most likely to be missed in MDA may also be the most likely to later reintroduce parasites into

their communities, i.e. mobile and migrant populations, or those frequenting the forest. This potential pitfall implies that a sufficiently large area has to be covered when implemented. The TEG considers that MDA can be useful as part of an elimination strategy if included in the context of a package of interventions. Several questions must be addressed to optimize targeted MDA trials, which include strategies for scaling up (such as blood volumes and sample sizes for screening and large scale community engagement, and acceptance and support). MDA remains a high-risk strategy, since it has the potential to increase drug pressure on the parasite population, driving increasing drug resistance (last man standing), so that efforts need to be maintained until elimination has been achieved. In principle, the drug used for MDA should be different than the ones used for first line treatment. In some settings however, this is not possible due to resistance to partner drugs. When possible, rotating the drugs used in MDA is recommended. The TEG recommends that more trials looking at various aspects of this strategy should be conducted as soon as possible and that national programmes and WHO should be involved in planning and evaluation with real-time sharing of information.

Ivermectin as an adjuvant in elimination strategies

The added value of ivermectin when combined with targeted MDA should be investigated. The TEG was encouraged by the widespread and apparently safe and effective use of this drug in MDA campaigns against onchocerciasis in western Africa. Entomological data from areas where ivermectin was deployed and safety data (in terms of highest tolerated doses) should be reviewed prior to MDA trials. Dosing and interaction with antimalarial drugs used in MDA will also need careful consideration. The TEG also recommends other field studies with ivermectin given as MDA, but not necessarily in combination with antimalarial drugs.

Effectiveness of repellents

Malaria elimination in the GMS is challenged not only by drug resistance but also highly exophilic vectors. Results of a recent large study on the effects of personal repellents, in addition to long-lasting insecticide-treated nets (LLINs) on malaria transmission in Ratanakiri (eastern Cambodia), do not show an impact on overall prevalence (by real-time PCR) of either *P. falciparum* or *P. vivax*, likely because of poor adherence to the intervention. The TEG concluded that personal repellents couldn't be recommended as a programmatic intervention in the GMS. Use of repellents can still be an important tool for individual protection in particular circumstances and there is still a scope for research on this tool and other anti-vector measures to address residual transmission.

Role of village malaria workers and community health workers

Village malaria workers (VMWs) and community health workers (CHWs) have important roles in several key areas of the response to artemisinin resistance, particularly in providing early diagnosis and quality treatment and behavioral change communication, surveillance and providing data for information systems, and in reaching migrant or mobile populations or hard to reach populations. Having VMW and CHW perform directly observed treatment (DOT) may be considered, in the context of the later stages of malaria elimination, when there are only a few cases left, and in non-mobile populations. In other settings, the TEG does not recommend a general emphasis on DOT, since at the population level the effectiveness of DOT for malaria treatment in the region has not been shown to be superior to non-supervised treatment. Research to identify other methods to improve adherence is important.

Role of malaria vaccines in elimination

There is currently insufficient data to suggest a role for the RTS,S vaccine in containment/elimination strategies. In the context of malaria elimination, all age groups should be vaccinated. The final formulation of the RTS,S vaccine has not been tested in South-East Asia. In addition, it has to be confirmed that RTS,S does not increase the asymptomatic *P. falciparum* parasite reservoir of transmissible parasites by inducing partial immunity. The TEG considered it important to invest in the development of a vaccine that interrupts malaria transmission, since this could prove an important additional tool in malaria elimination.

Meeting Minutes

1. Welcome and introduction of guest speakers

All members attended the meeting, except K. Barnes and C. Karema. The Australian Department of Foreign Affairs and Trade, the Bill & Melinda Gates Foundation, the Global Funds to fight AIDS, Tuberculosis and Malaria (GFATM), the UK Department for International Development, the Medicines for Malaria Venture, and the US Agency for International Development were invited as observers. The full list of participants is provided in Annex 2.

2. Declaration of interest, agenda and minutes of TEG 2013

All members of TEG participating in the meeting submitted their declaration of interest, which was assessed by the Drug Resistance and Containment Unit at GMP and by Legal at WHO. All the reported relevant interests were read to participants. The agenda is provided in Annex 3. The TEG members endorsed the TEG 2013 meeting minutes.

3. Global Technical Strategy

The MPAC tasked GMP with the development of a Global Technical Strategy (GTS) for malaria 2016-2025. GMP and the Roll Back Malaria Partnership are working together to align the development of GTS and Global Malaria Action Plan 2. GTS will be launched jointly with Global Malaria Action Plan 2 further to its endorsement by the World Health Assembly 2015. A Steering Committee will provide guidance to GMP on the development of GTS to ensure that the process is rigorous and collaborative, involving consultations at all levels. WHO held the first series of consultations in October 2013 and seven regional consultations led by WHO Regional Offices are ongoing through June 2014. A GTS consultation website is available for contributing additional comments. The TEG members are encouraged to participate in the online consultation.

Discussion

TEG members welcome this initiative but stress the importance of ensuring harmonization between the GTS recommendations and those of TEG and other committees.

4. Session 1: Update on drug resistance

4.1 Tracking Resistance to Artemisinin Collaboration studies

Presentation

Tracking Resistance to Artemisinin Collaboration (TRAC) study monitors in detail the parasite clearance parameters (including parasite clearance half-life and day 3-positivity) after a 3-day treatment regimen of artesunate (either 2 or 4 mg/kg/day), followed by a full-course ACT. The main goal was to detect and map the spread of the delayed clearance phenotype defined as a parasite clearance half-life equal or greater than 5 hours. Since the last TEG meeting, analysis of mutations in and near the K13 propeller domains was also performed on samples collected from the sites participating in the study. Data on parasite half-life and K13 mutations from different study sites confirm the existence of artemisinin resistance in northern Cambodia and in Myanmar. Prevalence of K13 resistance mutations correlates strongly, but not always, with slow clearance. Data on delayed clearance phenotype from TRAC are consistent with those of WHO therapeutic efficacy studies. Molecular marker analyses showed that C580Y mutation was the most prevalent in parts of the GMS, but many other mutations in and near the

K13 propeller region were also identified that are associated with resistance. Molecular marker analyses of TRAC studies have also shown that low-level prevalence K13 mutations in Africa are not associated with slow parasite clearance. Overall, 3-day artesunate followed by an ACT is highly efficacious as measured by adequate clinical and parasitological cure rates between 95-100%, including dihydroartemisinin-piperaquine in areas where piperaquine resistance is found. The delayed parasite clearance phenotype was also associated with increased gametocyte carriage, but for the moment without evidence of resurgence of transmission.

Discussion

Higher cure rates observed in the artesunate plus ACT regimen could be due to the effect of 6-days artemisinin derivative, while the increased gametocytemia could result from not only artemisinin resistance, but also be due to failure of the partner drug.

Molecular and clinical studies must be seen as complementary. A number of samples have already been collected for K13 analysis. The spread of phenotypic resistance being associated with several independently occurring genetic polymorphisms and evidence that common mutations such as K13 C580Y are found in distinct genetic lineages in different geographic locations (see 4.4) means that artemisinin resistance is not only spreading, despite the vigorous efforts at containment, but also emerging de novo, thus raising concerns about the effectiveness of a "firewall approach" to containment of resistance (delaying or preventing spread from a focus) and giving further support to the advisability of eliminating falciparum malaria transmission in all areas of confirmed artemisinin resistance). Prevention of spread of resistance from GMS, however, remains crucial because falciparum malaria is become increasingly resistant to the main new partner drugs (lumefantrine, mefloquine, piperaquine).

Recommendations

A new strategy (further elaborated below) should be based on a principle of *P. falciparum* elimination in all areas of artemisinin resistance in GMS. One immediate measure should be change of the tier classification in GMS (see 4.5). All WHO-funded therapeutic efficacy studies should now include collection of samples for monitoring K13 mutations (this new requirement is communicated to national malaria control programmes through regional networks).

4.2 Artemisinin resistance confirmatory study in Suriname

Presentation

Further to TEG 2013 recommendations, a study to confirm artemisinin resistance was initiated in Suriname and bordering countries. The study employs a 3-day course of 4 mg/kg artesunate followed by one dose of mefloquine and one dose of primaquine, with 8-hourly monitoring of parasitaemia and follow-up until day 28. The study was initiated in July 2013 and 35 patients have been enrolled as of March 2014, with the majority coming from French Guyana. Of the 33 patients, who were followed-up to 72 hours, only 3 had positive parasitaemia on day 3. Only 7 patients have completed the study to day 28, all of whom had adequate clinical and parasitological response.

Discussion

The TEG noted that very low baseline parasitaemia could affect the sensitivity of the day 3 measurements. There is not enough information on study populations to implicate factors such as

immunity, which might explain the change in the day-3 positivity rate compared to 2011. The microscopy threshold of parasite detection is lower than in the WHO standard (100 fields read to consider a slide negative), as up to 500 fields are read before considering a slide negative.

Recommendations

Based on these data, it is still too early to determine whether artemisinin resistance is present in South America: calculation of parasite half-life and molecular marker studies are needed before drawing further conclusions.

4.3 Antimalarial treatment policy change in Cambodia

Presentation

Malaria cases and deaths have decreased steadily since 2000, but drug efficacy is rapidly lost to resistance. Atovaquone-proguanil was adopted as first-line treatment for falciparum malaria in Pailin Province in 2012 and in all tier 1 areas in 2013. Within 7 months of the introduction of this regimen, 5% of parasites sampled in Pailin harbored 268-*cyt b* mutation. In 2014, efforts to re-introduce artesunate-mefloquine as first-line treatment are in progress for 5 provinces, while dihydroartemisinin-piperaquine continues to be used in the rest of the country. The full implementation of the new policy is hindered by delayed registration and procurement of artesunate-mefloquine. The treatment failure rate with dihydroartemisinin-piperaquine is increasing despite adequate piperaquine plasma concentrations, suggesting high level resistance to this drug in Cambodia. New alternatives are needed to replace rapidly failing drugs. Therapeutic efficacy studies on artesunate-pyronaridine will start soon.

Despite the WHO recommendation for single low dose primaquine as gametocytocidal treatment in uncomplicated falciparum malaria in areas of artemisinin resistance, the implementation of a single low dose of primaquine as a transmission-blocking treatment in Cambodia has been delayed because of the perceived risks of hemolysis. Treatment policy must also take into account that treatment adherence is usually poor in the general population, especially among mobile and migrant populations. For this reason, DOT is considered a priority by the national malaria programme, provided that it is feasible, and that financial resources are available. The small number of malaria cases makes it difficult to conduct TES, and thus hinders timely surveillance to inform treatment policy.

Discussion

TEG is concerned about the complexity and the length of time it takes to change drug policy, and suggested it could facilitate the process by formulating specific recommendations.

For western Cambodia, the TEG supports the implementation of artesunate-mefloquine as a short-term alternative to the now failing dihydroartemisinin-piperaquine, but is concerned about the vulnerability of mefloquine. The re-introduction of artesunate-mefloquine makes sense at this time because the prevalence of *pfmdr1* copy number has decreased; however, resistance is expected to re-emerge rapidly. For the time being, in case of failure of artesunate-mefloquine, quinine and doxycycline over 7 days is used as rescue therapy and the TEG endorsed this policy. The results of a study evaluating the efficacy of artesunate-pyronaridine in Western Cambodia may provide a new alternative for treatment.

The absence of new drugs is a major impediment in fighting antimalarial resistance. The TEG discussed alternative options. There was no consensus in the committee whether to recommend extension of dihydroartemisinin-piperaquine treatment from 3 to 5 days, because of potential safety issues regarding

the increased piperaquine dose (QTc prolongation). In clinical trials, piperaquine causes QTc prolongation in a dose-dependent manner, but within the recommended doses these effects are negligible; torsade de pointes has never been reported. Two independent modeling efforts yielded different predictions on piperaquine blood concentrations after a 5-day therapy; in one model the peak levels would not exceed 12% of the 3-day therapy and would remain below the threshold level for QTc prolongation, while in the second model, a more significant accumulation of piperaquine is predicted.

The TEG considered triple combinations of drugs with different modes of actions to be a target product profile for the next generation of antimalarial drugs, either using current drugs or by adding a new compound to some of the existing ACTs. The selection of drugs will require appropriate matching of pharmacokinetic profiles (linked to drug potencies) and investigation of potential drug interactions.

Based on a validated review of available data, WHO recommends a single low-dose primaquine course (0.25 mg/kg) as a transmission-blocking agent, as it was determined to be safe, even in the absence of glucose-6-phosphate dehydrogenase (G6PD) testing. However, given the evidence for risk of serious side-effects of the 0.75 mg/kg primaquine regimen, the Cambodian Ministry of Health is reluctant to implement this policy, and the national ethics committee demands a safety study in G6PD deficient patients. Such a study would take too long to conduct due to the small number of eligible patients. In the context of DOT in community and health facility settings, where safety can be monitored (urine), the administration of a single low dose primaquine to all patients treated with an ACT for falciparum malaria seems to be both reasonable and feasible.

Recommendations

Clinical studies (phase I and II) to assess the safety, efficacy, and effectiveness of a 5-day dihydroartemisinin-piperaquine treatment course should be carried out to enable an evidence-based recommendation in the near future. Assessment of effectiveness is important given the potentially low adherence to a 5-day regimen.

There is a desperate need to accelerate the development of new chemical entities. When new blood schizonticides become available, it will need to be analyzed, whether they would be used to best effect in triple combination with current ACTs or in new combinations, possibly with fewer therapeutic principles, but ones not affected by resistance.

The primaquine 0.25mg/kg regimen should be adopted in Cambodia with close real-time monitoring of safety through protocols, which can be applied in routine DOT in community-based and health facility services and in therapeutic efficacy studies.

4.4 Update on K13 molecular markers

Presentation

Mutations in the *PF3D7-1343700* Kelch protein (K13) have been associated with artemisinin resistance in vitro and in vivo. More than 30 different mutations in the K13 gene have been reported so far, not all of them being located in the propeller domains, and different mutations seem to confer different resistance phenotypes. Mutant K13 alleles are more prevalent in Cambodian provinces where resistance is prevalent, and the increasing frequency of a dominant mutant K13 allele correlates with the recent spread of resistance in western Cambodia. Strong correlations between the presence of mutations, in vitro parasite survival rates, and in vivo parasite clearance rates indicate that K13

mutations are important determinants of artemisinin resistance. Genotyping of this gene will be hugely important for large-scale surveillance, although replication and validation studies in other regions, in particular sub-Saharan Africa will have to confirm the association of these markers with the slow clearance phenotype in other parasite populations. Replication of the genome-wide association study (GWAS) studies using a gene-scan approach (evaluating association with parasite clearance half-life of any polymorphism versus no polymorphism in all genes) has confirmed K13 mutations as a major determinant of clinical artemisinin resistance in Cambodia, Viet Nam and Myanmar. GWAS of TRAC study samples also confirmed the role of K13, while suggesting that there are possible "permissive" or compensatory background mutations which could themselves spread and facilitate de novo resistance of K13 mutations. Parasites with a mutation in any of the K13 domains (presently thought to include amino acid positions ≥ 440) displayed longer parasite clearance half-life than parasites with wild type alleles; only a single nucleotide polymorphism (SNP) seems to occur in any given K13 gene; no parasite strain has shown multiple SNPs thus far.

Haplotype analysis revealed evidence for spread of K13 mutations (such as C580Y), as well as for independent emergence of the same mutation on different genetic backgrounds from distinct geographic areas, indicating that resistance is both spreading and emerging independently. There is some evidence of spread between Cambodia and Viet Nam; in contrast, the predominant K13 mutant found in Myanmar does not appear to have spread from Cambodia but likely arose independently.

Discussion

TEG concluded that K13 SNPs provide a useful and powerful new molecular marker of artemisinin resistance; nevertheless, further validation studies are needed to clarify roles of specific mutations.

The significance of mutations outside the K13 propeller domains, and of very low numbers of infections with K13 mutations in several African countries was discussed. If "paternity testing" of these variants (i.e. analysing genetic markers flanking the K13 gene to ascertain shared or different ancestral lineages) determines that they have spread from South-East Asia, it was suggested that new policies (e.g. triple therapy) should be considered for Africa to protect the available ACTs. It was noted, however, that evidence is not yet on hand to determine whether these rare mutants represent spread or de novo emergences, whether they are a new phenomenon or have been occurring all along in the background, or whether they threaten ACT efficacy.

Recommendations

K13 analysis should be part of all future clinical studies and therapeutic efficacy studies on falciparum malaria. However, the science around this new marker is quickly evolving. Given the significance of the discovery and the quickly evolving information on K13 mutations, an evidence review group on the topic should be established to 1) to collect and review data; 2) to provide guidance on interpretation of local data on K13 (and beyond) 3) to propose an organizational structure (including a reference center) that can facilitate standardization of methods and information flow to national malaria control programs and WHO; this includes the development of mapping of the relevant K13 mutations 4) to identify remaining knowledge gaps for research.

4.5 Update on artemisinin resistance definition and tier maps

Presentation

With the identification of the K13 mutations as a marker for artemisinin resistance, there was agreement that this definition needs to be updated, but it was thought that the clinical phenotype of slow clearance should remain part of the definition. Early reports of a background prevalence of around 2% of slow clearance in African settings in the absence of artemisinin resistance were taken as a guide for assessing the proposed cut-offs. As with the previous working definition, a distinction is made between suspected and confirmed artemisinin resistance. Thus a new set of definitions of artemisinin resistance was proposed to the meeting by the WHO Secretariat as follows (including minor editorial amendments recommended by the meeting):

Suspected endemic artemisinin resistance is defined as:

- a prevalence ≥ 5% of infecting parasite strains carrying Kelch 13 resistance-associated mutations; **or**
- a proportion ≥ 10% of patients still parasitemic on day 3 by microscopy; **or**
- ≥ 10% of patients with a peripheral blood parasite half-life ≥ 5 hours following a treatment with ACT or artesunate monotherapy.

Confirmed endemic artemisinin resistance is defined as:

- a prevalence of ≥ 5% of infections with strains containing Kelch resistance mutations if the patients carrying these mutants also have persistent parasitaemia by microscopy on day 3 or a peripheral blood parasite half-life ≥ 5 hours following adequate treatment with ACT or artesunate monotherapy.

The term ACT resistance should be applied only when the therapeutic efficacy of ACTs start to fail in the context of resistance to both artemisinin and the partner drug(s). ACT failures > 10% should prompt a change in policy with another ACT.

Discussion

TEG considers the new definitions based on genotype and phenotype prevalence appropriate in an epidemiological context. The sensitivity, although good, may not be sufficient to trigger alarm signals. The definitions will likely need adaptation with more data becoming available. Further research is needed (e.g. transfection studies) to clarify roles and relative importance of specific mutations that confer artemisinin resistance. The question of whether containment activities should be activated on the basis of "suspected" resistance should take into consideration a number of confounding factors affecting parasite clearance rate, such as immunity, or drug absorption and metabolism. However, artemisinin resistance confirmed with molecular markers should prompt containment activities.

Recommendations

WHO should prepare new recommendations for national programmes on resistance monitoring based on the revised definitions.

There is a need for a limited number of reference laboratories accredited by WHO for K13 sequencing, and details of structure and mechanisms should be indicated by the proposed ERG on the topic. It is emphasized that at the current stage of technological development, it would be counterproductive to aim at the establishment of these techniques in all endemic countries, considering that it is easy to

conserve and send dried filter paper blood samples safely. Where robust PCR capabilities are already established, impediments to exporting clinical samples can be addressed by shipping PCR-amplified material to sequencing centers. WHO should facilitate the collaboration between national programmes and reference laboratories.

The new definitions will impact current tier classifications. WHO is awaiting data from clinical studies and molecular analyses from three provinces of Myanmar before issuing maps on tier 1 and 2. However, the probability of including northwestern provinces of Myanmar in tier 1 is high. Meanwhile, the temporal and spatial trends of all findings on artemisinin resistance indicate that all falciparum endemic areas in GMS countries, which are not already affected by artemisinin resistance, are at high risk. The TEG recommends that all such areas should be classified as tier 2. The strategies and interventions for these areas should be the same as for tier 1 areas, the only difference being a lower priority under financial and operational constraints.

5. Session 2: Modeling

5.1 Impact of spread of artemisinin resistance in Africa

Presentation

Using current artemisinin and partner drug resistance data from Asia and Africa, five potential resistance scenarios were used to estimate the impact of artemisinin resistance on the incidence of clinical malaria, severe malaria, and parasite prevalence, if it were to exist uniformly across the continent. In the model, artemisinin resistance was characterized by slow parasite clearance while partner drug resistance was associated with late clinical failure or late parasitological failure. An individual-based malaria transmission model was used. Scenarios with high levels of recrudescent infections (treatment failures) resulted in far greater increases in clinical incidence compared to scenarios with high levels of slow parasite clearance. Across Africa, when partner drug resistance levels were estimated to levels similar to those observed for sulfadoxine-pyrimethamine, 39 million additional cases could occur over a five-year period; this represents a 2.7% increase compared to a scenario with no resistance. This suggests that partner drug resistance may result in greater increases in malaria morbidity than if widespread artemisinin resistance alone were to develop at the levels currently observed in Pailin. However, if artemisinin resistance levels increase, these results are likely to change. Unlike partner drugs, there are no available alternatives to artemisinin. This means that if artemisinin resistance does appear in Africa (or elsewhere); containing it could potentially be much more challenging than addressing partner drug resistance alone. This model has, however, some limitations: it assumes that resistance is static and uniform across Africa; there was no modeling of resistant and sensitive parasites, and, there was no consideration of the potential for resistance developing to one component of the ACT putting resistance pressure of the other drug.

Discussion

This modeling confirms that protecting the partner drug is critical for Africa. Consideration of triple combination therapies is important also in this context, but this approach requires careful consideration of which drug(s) can be added to an ACT.

The question of adding low dose primaquine as transmission-blocking agent in Africa was discussed, but it was considered that primaquine would have little impact in areas of high endemicity. Firstly, in high

transmission areas, resistant strains will generally be more transmissible and less affected by primaquine than the sensitive ones; secondly, lower proportions of infections are treated; thirdly, in the presence of partner drugs resistance, recrudescence is frequent but the possibility of re-treatment with primaquine is limited, because many recrudescences are asymptomatic.

5.2 Multiple first-line treatments: outcome of recent modeling efforts

Presentation

In 2013 TEG discussed two mathematical models of implementation of MFLTs as a strategy to reduce risk of emergence of resistance. The two models yielded divergent results, since the two approaches were built on somewhat opposing principles. For one group, MFLT justification found its source in an evolutionary principle, assuming that an organism (malaria) cannot evolve too many different niches (drug types), whereas the other group assumes that malaria can simultaneously evolve to all these niches, i.e. develop multidrug resistance. This last model found that a policy of MFLT outlasts sequential application provided drug coverage levels are low to moderate, and appears not to drive widespread multidrug resistance. Inadequate dosing (poor adherence) is a more potent driver of drug resistance than the MFLT or sequential policy. When simulations were done at high drug coverage, sequential use was slightly better (5%) than MFLT in this model, but the difference was negligible. The other model found that the benefit of MFLT (occurring at any coverage level) was also modest, not exceeding 10%.

Discussion

In Africa, where less than 40% of infections are treated, MFLT may have an advantage provided operational issues are handled properly and quality drugs are used, but in low transmission areas where resistance has not emerged, there is no good reason to promote MFLT. It was noted that the two models are not too far apart, and given the uncertainty of the impact and the difficulty of changing policy, it is not justified to recommend implementation of one or the other.

Given the limited size of these effects MFLT is unlikely to have an impact one way or the other and further efforts to reconcile the two model outputs may be futile. Factors such as adherence, supply chains, cost and toxicity are probably more important than policy choice.

Recommendations

TEG does not currently recommend adopting MFLT as a general response to resistance or a strategy to prevent it. There are however situations, where MFLT is justified for operational reasons, for example to avoid drug stock outs. Under all circumstances, measures to ensure drug quality and adherence to treatment should be emphasized.

6. Session 3: Update on recent containment and elimination efforts

6.1 Emergency Response to Artemisinin Resistance project in the Greater Mekong subregion

Presentations

Initiatives for containment of artemisinin resistance

Different initiatives have been launched for elimination and containment of artemisinin resistance in the GMS. These initiatives include the WHO project for technical support and coordination (ERAR), the GFATM's RAI, and a newly established trust fund under the Asian Development Bank, and the Asia Pacific Leaders Malaria Alliance (APLMA).

WHO initiated the ERAR project with funding from the Australian Department of Foreign Affairs and Trade and Bill & Melinda Gates Foundation. The project aims to provide technical support, and support coordination of activities, for any initiatives and partners as needed. To do this, WHO has established a regional hub in Phnom Penh, Cambodia, and has staff in country and regional offices to provide technical support across the GMS. Key activities from the 2014 workplan were presented to the TEG for each of the six ERAR project objectives:

1. Strengthen leadership, coordination and oversight mechanisms;
2. Maintain and expand drug efficacy surveillance networks and accelerate priority research;
3. Improve access for migrant and mobile populations to quality services;
4. Facilitate the full implementation of the Myanmar Artemisinin Resistance Containment framework;
5. Strengthen the response to artemisinin resistance in Viet Nam;
6. Limit the availability of oral artemisinin-based monotherapy, substandard and counterfeit antimalarial medicine while improving quality of ACTs.

RAI is funding activities in five countries from 2014 to 2016, in addition to a regional component. RAI is overseen by a regional steering committee (RSC), supported by a secretariat located in the ERAR regional hub in Phnom Penh. APLMA was established to promote regional political leadership and collaboration against malaria in Asia and the Pacific. The alliance is hosted by the Asian Development Bank and has task forces on 1) quality medicines and other technologies, and 2) regional financing for malaria and other health threats.

Epidemiology

According to national estimates, a total of 47 million people are at risk of malaria across Cambodia, Lao PDR, Myanmar, Thailand and Viet Nam. The number of reported deaths, as well as the total number of reported cases (presumed and confirmed) has been falling. To a large extent, regional trends have been influenced by the significant reductions in incidence in Myanmar since 2011. In Cambodia, reported malaria cases have also been falling. In Lao PDR, malaria epidemics among migrant and mobile populations have occurred recently in the southern part of the country. In Thailand, data from partners working along the border with Myanmar have been included only since 2011 leading to an increase in the total reported cases. In Viet Nam, the number of cases has been falling slightly but appears relatively stable at a low level. Two of the six countries in the GMS have longer-term national strategies with formulated goals for national malaria elimination: China aims to eliminate malaria by 2020, and Cambodia aims to eliminate *P. falciparum* malaria by 2020, and all other malaria species by 2025. National strategies in the remaining four countries cover only the period until 2015 or 2016, and none of these strategies have explicit objectives for national elimination.

Discussion

TEG underlined the need for the ERAR hub to ensure effective coordination between initiatives to avoid duplication, to liaise with already funded activities such as the RAI, and build synergy where possible. The quality of epidemiological data continues to be in question: providers of ACT (public and private) could be included as a source of information. The ERAR hub was requested to prioritize a mapping for the whole GMS of which organizations are doing which activities in which areas targeting which

population and in which timeframe. This is a prerequisite for a further gap analysis regarding activities and funding.

Recommendations

Donor funding should not be limited to current tier 1 provinces. The priority is to have good services in tier 1 and the second priority is to have the same in tier 2 provinces. Information available on mobile and migrant population needs to be integrated into future strategies. The ERAR hub should report on its activities and progress at the next TEG meeting.

6.2 Update on the Regional Artemisinin Initiative

Presentation

In March 2013, the GFATM Board allocated US$ 100 million for three years in response to the need for a supra-national approach addressing artemisinin resistance in the GMS. The RAI includes US$ 15 million for an inter-country component and US$ 85 million for country components in Cambodia, Lao PDR, Myanmar, Thailand and Viet Nam. Total cost of LLINs represent 25% including the procurement and supply costs. The principal recipient (UNOPS) has disbursed first installments to Lao PDR, Myanmar and Thailand. Disbursements to Cambodia and Viet Nam are pending. The inter-country component is expected to start in July 2014. The GFATM sees APLMA as the political arm of the RAI while ERAR is seen as the technical arm. The RAI is overseen by a RSC consisting of representatives from: country coordinating mechanisms, national malaria control programmes, civil society, private sector, the Association of Southeast Asian Nations (ASEAN), the Asian Development Bank, development partners, WHO and academia. Following a RSC meeting in September 2014, the GFATM will negotiate year 2 workplans and budgets in November 2014. Any reprogramming suggested by the RSC can be included during in this process. As with any other grant, the principal recipient is responsible for monitoring and evaluation. The RSC also wants a higher-level monitoring and evaluation group working with the ERAR hub.

7. Session 4: Elimination of artemisinin resistance in the Greater Mekong subregion

7.1 Mass drug administration pilot studies in the Greater Mekong subregion

Presentation

The targeted malaria elimination project is a multinational trial of targeted MDA in areas of high malaria prevalence. Obtaining approval for implementing these studies was challenging. Community engagement must be a big part of the effort. Targeted malaria elimination project sites are located in three distinct regions: western Cambodia (Pailin), the border between Thailand and Myanmar, and Viet Nam. The rationale for MDA and preliminary results of the pilot studies in four villages located in Kayin state, Myanmar near the Thailand border were presented. The protocol consists of a monthly course of dihydroartemisinin-piperaquine with one dose of primaquine for three months (except in Cambodia where primaquine is not approved for blocking transmission). Two villages had the MDA intervention with treatment described above and two control villages had no intervention. Highly sensitive high-volume quantitative PCR (qPCR)-measured parasitaemia in venous blood samples, and clinical malaria was assessed at baseline and again after six months in both control and MDA intervention villages. The

proportion of the people actually in the village at the time of the survey that received MDA ranged between 93.9% and 97.3% in one village and between 59.6% and 81.3% in the other village. The coverage was much lower when the proportion of the people registered in the census list was considered. Treatment with dihydroartemisinin-piperaquine plus low-dose primaquine was well tolerated. One adverse event was reported for one patient with transient dark urine who had normal G6PD status. After 3 and 6 months, post-intervention results show an important decrease in *P. falciparum* prevalence to near zero (not in *P. vivax*), except for a few cases of domestically imported malaria. Data from Cambodia and Viet Nam are currently being gathered.

Discussion

Overall, this pilot study showed a considerable asymptomatic reservoir in low transmission settings. The prevalence depends on the sensitivity of the method, which is high with qPCR on a large blood volume (1 ml). Several questions remain unanswered, such as to what extent individuals with very low parasitaemia can transmit *P. falciparum*, or whether asymptomatic individuals carry the same proportion of resistant parasites. Maintaining high coverage is the major challenge and importation of new cases from outside target areas (vulnerability) may jeopardize the results. Further results are needed before more definite conclusions on the effectiveness of targeted MDA in eliminating falciparum malaria can be made. Improvement of coverage is clearly an issue to be addressed; those not registered or tested and treated could be a reservoir for future infections. The potential for bias in determining baseline prevalence should be considered carefully since the number of people who did not provide a blood sample is unknown and this group might be at higher risk than those who did, as mobile migrant population could be overrepresented among them (hidden reservoir), and on the other hand people who provided a blood sample may have received prior treatment. Serological assessments using pre-erythrocytic or erythrocytic antigens could be considered in evaluating MDA effectiveness.

A wide variety of possible scenarios regarding MDA can be modelled. This will remain important, but at this time the field evaluation of the currently selected scenarios should have priority. There is a rationale for MDA as long as it is not used as an isolated intervention, but is included in a package of quality interventions with the objective of eliminating falciparum malaria. Several questions must be addressed to optimize MDA trials, which include strategies for scaling up, blood volumes and sample sizes for screening and large scale community engagement. MDA remains a high-risk strategy, and the TEG has concerns that it could drive drug resistance further (last man standing). The concern is particularly strong, because the trials are conducted with dihydroartemisinin-piperaquine, which has a high failure rate in Cambodia resulting from resistance to both components. On the other hand it is recognized that there is no other regimen at present with sufficient data on safety and tolerability to be acceptable for MDA. Success depends on coverage achieved. The continued implementation will require an increased participation of national malaria control programmes and timely sharing of information with WHO. Policies for MDA must consider the balance between the need to eliminate and the risk of increasing levels of resistance.

Recommendations

More trials examining various aspects of this strategy should be conducted as soon as possible, and these should involve national programmes and WHO for planning and real-time monitoring. At the same time, more studies should be conducted to determine parasite genetic populations in relation to

population movements as well as to define the "reservoir". The reservoir should include parasites in mosquitoes and possibly infections that were detected but with insufficient DNA to determine the species. In the context of monitoring elimination and defining the "reservoir", monitoring transmissibility using serology testing in longitudinal studies may be useful.

In principle the treatment used for MDA should be different from the one used for first line treatment. In some settings however, this is not possible due to resistance to partner drugs. Whenever possible, rotating the drugs during MDA is desirable. Therefore, it is important to start trials with alternative MDA regimens, primarily to assess safety and tolerability.

7.2 Malaria elimination strategies in the context of artemisinin resistance

Presentation

Among those measures that are specific or particularly relevant to elimination, the prevention of onward transmission is critically important, and will be best achieved if the following conditions are met:

1) Strive for very early detection and treatment, including single primaquine dose for all *P. falciparum* cases;
2) Implement effective vector control in active transmission foci and keep malaria patients away from *Anopheles* mosquitoes, e.g. admit cases to hospital and keep in screened wards in non-endemic zone, and ensure use of LLINs in the hospital and after discharge;
3) Identify areas where patients have been since symptoms started;
4) Keep track of individual cases with a national patient register, and;
5) Identify and monitor delays in detection (patient or laboratory driven) and treatment and establish measures to improve timeliness.

The objective of malaria surveillance systems in the elimination phase is to ensure effective detection and treatment of all infections (symptomatic or not). This includes identification of all areas and foci of transmission. In low transmission settings, where people have no malaria immunity, most malaria infections are expected to produce fever; passive case detection should therefore lead to the detection of most malaria infections. However, in the GMS, recent unpublished studies have found high prevalence of asymptomatic carriers in some areas, a phenomenon which is thought to be related to recent reduction of transmission and burden. The continuous presence of health workers is required for good passive case detection in active transmission foci, and is preferable to periodic visits by mobile teams. Active case detection is a complementary strategy.

For elimination programmes, malaria case is defined as: any case in which, regardless of the presence or absence of clinical symptoms, malaria parasites have been confirmed by quality-controlled laboratory diagnosis. Quality of all facilities where malaria is diagnosed and treatment dispensed (pharmacy, non-governmental organizations, clinics, drug vendors) should be closely monitored. All positive cases should be promptly investigated for the purpose of classification, and the planning of adequate interventions in the localities where the infection originated from and where it may have spread. As a rule, case detection is considered effective if the total number of cases reported roughly matches the number of treatments used in the country. Active case detection should be used in populations that may have a high risk of infection to ensure that onward transmission is prevented.

In the elimination phase, the aim is to eliminate malaria in transmission foci. Focus investigations provide the necessary information on populations, vectors and the sites where transmission occurs, and then facilitate the selection of the most appropriate combination of interventions for controlling and eliminating malaria in a specific locality. The inclusion of MDA in an elimination strategy should be carefully planned in terms of timing and methods employed and should be restricted to well-defined areas.

A list of requirements for malaria elimination to be feasible was presented. These requirements include: issues relating to political commitment in the country, the situation of neighboring countries from which malaria may be imported, health regulations, health system infrastructure, financial and human resources. Before embarking on an elimination programme, a feasibility analysis should be carried out and problematic issues should be effectively addressed.

Discussion

TEG underlined the need for different approaches for regions, which progress from high endemicity to low endemicity, and those that were always low endemicity areas.

Recommendations

A practical plan for the elimination of *P. falciparum* in the GMS should be prepared based on the existing frameworks, which can help steering current initiatives.

7.3 Vector control strategies in the context of artemisinin resistance

Presentation

An evaluation of repellents as additional method to control residual transmission in malaria pre-elimination settings was presented. The term residual transmission is defined as all forms of transmission that persist despite full, effective coverage with LLINs and/or indoor residual spraying (IRS). Most malaria vector species are not fully susceptible to LLINs and/or IRS because they exhibit one or both sets of the following behavioral traits: 1) insecticide contact avoidance and early-exit behavior that minimize exposure hazards of vectors that preferentially feed indoors on humans, and 2) animal feeding and outdoor-feeding preferences, which are usually mutually associated, minimizing contact with insecticides targeted at the human habitat. Indeed 60% of vector species bite before sleeping time, and many infective bites occur before 22:00 and after 04:00, thus limiting effectiveness of LLINs and IRS. Other vector control methods, such topical repellents, are needed but evidence is lacking, as only few well-controlled trials have been conducted. The Malaria ResT project funded by the Bill & Melinda Gates Foundation was initiated to study the added value of repellents to LLINs for the control/elimination of malaria in Cambodia. This project has three major components:

1. entomological: evaluation of the mass effect of repellents on residual malaria transmission, and estimate the individual protective efficacy on wild mosquitoes;
2. epidemiological: assess the impact of repellents on the prevalence and incidence of malaria, other parameters important for malaria elimination and arboviroses;
3. sociological: assess the acceptability, adherence and adequacy of topical repellents.

The entomological study showed that the tested repellent (KBR3023) exhibits a dose-dependent effect against mosquito bites, providing an 80% protection (5 hours % repellency) from most vector genera and *Anopheles* species. The epidemiological study conducted in the province of Ratanakiri in 2012-2013

showed no impact of the repellent intervention on the prevalence (real-time PCR) of either *P. falciparum* or *P. vivax.* The sociological study showed very low adherence or misuse of repellent but the qualitative component of this study showed high acceptance of the trial and the product. From these preliminary results it is concluded that the lack of impact is due to lack of adherence. Analyses of serology, passive case detection, and per-protocol population data may provide further insight on the usefulness of repellent as part of an elimination strategy. As a collateral benefit, the study has generated an important database to identify hotspots, which are essential for understanding transmission dynamics and targeting control effort. It also identified the need to develop better sampling methods for entomological studies.

Discussion

The presence of residual transmission does not mean that distribution and promotion of LLINs should be stopped. On the contrary, it is important to continue implementing this intervention. However, based on good surveillance and geographic progress in interrupting transmission, the target population may be reduced and the efforts more concentrated. If LLINs coverage is adequate, there is in general no added value of IRS, except in specific settings where people are living in housing with sprayable walls, and they are up late at night. The potential of insect growth regulators was discussed and it was agreed that despite the limitations of larval source management in the GMS, this tool might have some potential, as there are several novel methods of applying it.

Recommendations

Mosquito nets are already an integral part of national malaria control programmes and must continue to be part of the containment and elimination strategies in the GMS. Personal repellents as programmatic interventions have insufficient evidence but can be an important tool for individual protection. More programmatic efforts should be put into the use of hammock-LLINs. Insect growth regulators should be investigated as a potential malaria vector control tool.

7.4 Ivermectin

Presentations

Ivervectin as a malaria elimination tool

Ivermectin is an endectocide drug that has activity against endoparasites (mainly nematodes) and ectoparasites (killing arthropods that blood-feed on a treated subject). Ivermectin is a macrocyclic lactone isolated from the bacterium *Streptomyces avermitilis.* In invertebrates it acts as a glutamate-gated chloride ion channel agonist, a mode of action that differs from those of insecticides used for LLINs or IRS, and thus could circumvent emerging insecticide resistance.

Ivermectin is one of the few drugs used in MDA campaigns, and more than one billion treatments have been delivered over the last few decades for controlling onchocerciasis, lymphatic filariasis, scabies and other neglected tropical diseases. While ivermectin has no in vitro or in vivo effect on blood-stage *Plasmodium* parasites, it can significantly reduce the survival and/or fecundity of several species of *Anopheles*, including *An. gambiae* s.s., *An. arabiensis, and An. stephensi*. Based on in vivo studies and a mosquito age-structured model of malaria transmission, different ways to apply ivermectin in malaria control efforts aimed at reducing transmission were presented and suggested for further investigations. Through current ongoing yearly anti-helminth MDA programmes, it was possible to show that

ivermectin MDA reduced survivorship of *Anopheles*, and suppressed sporozoite transmission for weeks. This effect is temporary and the degree and duration of these reductions must be thoroughly defined before considering repeated MDA as a malaria control intervention. In addition to direct anti-mosquito effects, expected changes in population structures (age grading), and third-order effects on entomological inoculation rate, vectorial capacity, the molecular force of infection and the malaria reproductive rate must be investigated. Current estimates of lethal concentration 50% (LC_{50}) of ivermectin for mosquitoes are based on membrane feeding assays. With simultaneous mosquito feeding and measurement of ivermectin concentration in plasma (capillary and venous blood), it is possible to establish a correlation and to calculate in vivo LC_{50} and the time post-treatment that the anti-mosquito/anti-sporogenic effect lasts. Additionally, studies have shown that sub-lethal ivermectin concentrations can affect *P. falciparum* transmission by inhibiting sporogony, suggesting that ivermectin MDA may reduce transmission for a longer period. Increasing the use of ivermectin is likely to lead to resistance in other parasites, which would compromise the success of other disease control programmes. Combination therapy with a second anti-helminthic drug, such as albendazole, may be considered. Co-administration of albendazole and ivermectin was shown to be safe in clinical trials. Other studies have shown that albendazole treatment does not interfere with the bioavailability of ivermectin in humans, with its anti-mosquito effect in vitro or in vivo or with its in vitro sporontocidal effect. In the GMS, ivermectin MDA could have a direct effect on exophagic and crepuscular feeding *Anopheles*. Data are available on LC_{50}s for *An. dirus*, *An. minimus*, *An. campestris*, and *An. sawadwongporni*, on re-feeding inhibition of *An. dirus* and *An. minimus,* and on sporontocidal effects on *P. falciparum* and *P. vivax* in *An. dirus* and *An. minimus.* Ivermectin may also be considered with the use of ACT (and primaquine) during MDA to simultaneously eliminate infectious vector and human reservoirs.

The potential impact of adding ivermectin to a mass treatment intervention to reduce malaria transmission.

To investigate the potential impact of ivermectin administered at the same time as MDA on malaria transmission, its effect on mosquito mortality was modeled in a three-stage process. Human pharmacokinetic data and mortality data for mosquitoes taking blood meals containing ivermectin were used to quantify the mosquitocidal effect of ivermectin. These were incorporated into a transmission model to estimate the impact of ivermectin used in combination with mass treatment strategies with artemether-lumefantrine. Adding ivermectin increases the reductions in parasite prevalence and delays the re-emergence of parasites compared to mass treatment alone. Ivermectin effectiveness depends on coverage, with the highest impact achieved if given to the whole population (all individuals above 5 years; coverage 90%) rather than only to those with detectable parasites. Results also suggest that ivermectin added in a mass treatment strategy can reduce the time taken to interrupt transmission as well as help to achieve transmission interruption in settings in which mass treatment strategies alone would be insufficient. It was also noted that adding ivermectin would not make parasites more resistant. However, mosquitoes could develop resistance to ivermectin. Ivermectin could also be given as MDA independently from an antimalarial drug MDA strategy. These previous results apply only for African settings. When the model was re-parameterized to characterize a “Cambodian-like” transmission setting, assuming 1% prevalence and a seasonality pattern, the impact of ivermectin was much lower. The effect of ivermectin could have been masked by the effect of MDA, which was always included in the

model. It was predicted that since MDA with ACT is likely to have a high impact in a low- prevalence setting, any additional interventions will not add much. However, when a Cambodia-like scenario is re-run without combination with ACT the results show that if ivermectin was to be given as stand-alone, once or twice (in three daily doses at 15 μg/kg) at the start of the rainy season, the impact on malaria incidence would be much more pronounced.

Discussion

Ivermectin is a promising tool, as it does not increase antimalarial drug resistance. MDA intervention with ivermectin and primaquine could possibly protect primaquine from resistance. As ivermectin treatment has no direct benefit related to malaria to the individual taking the drug, ethical issues must be taken into consideration.

Recommendations

The added value of ivermectin when combined with targeted MDA should be investigated. The TEG was encouraged by the widespread and apparently safe and effective use of this drug in MDA campaigns against onchocerciasis in western Africa. Entomological data from areas where ivermectin was deployed and safety data (in terms of highest tolerated doses) should be reviewed prior to MDA trials. Dosing and interaction with antimalarial drugs used in MDA will also need careful consideration. A comparative study of the combinations of ACT plus PQ versus ACT plus ivermectin is planned in Lao PDR. The TEG also recommends other field studies with ivermectin given as MDA, but not necessarily in combination with antimalarial drugs.

7.5 Use of community health/malaria workers and volunteers for improved surveillance and response to support malaria elimination

Presentations

The experience of Cambodia

The role of CHWs for improving surveillance and response to support malaria elimination was assessed and results presented. Both VMWs and CHWs have roles in several key areas of the response to malaria, particularly in the surveillance and information systems, in reaching mobile and migrant populations, or other hard to reach populations, for diagnosis, treatment and behavioral change communication. In Cambodia, tackling malaria in hard to reach villages (i.e. forests in the northeast) was initiated in 2001 by the National Malaria Center supported by the European Union, with a pilot project aimed at providing early diagnosis and treatment. The number of VMWs was increased to include low transmission villages of the northwest in 2009 as part of the artemisinin resistance containment project. With the support of GFATM, other donors, NGOs, and WHO, the VMW programme has been scaled up to about 1600 villages in 17 provinces covering 1 million people from 2001 to 2011 and has now been introduced to support mobile populations. A cross-sectional study employing quantitative and qualitative methods was conducted in 2012 to evaluate the performance of the VMW/mobile malaria worker (MMW) programme. Most indicators were in line with the expected performance target (80%), and some showed higher values. Strengthening the surveillance system will be important in order to reach the elimination goal by 2025. In this context, VMWs shall have a role in the malaria surveillance systems comprising the malaria case information system, day-3 positive alert systems, referral systems, and stock-out alert systems. A description of each system and the potential roles and responsibilities of VMWs in them was presented. The feasibility of surveillance of day-3 positive falciparum cases by

VMWs was tested in pilots. Although significant variations were observed between different partners, the system allowed detecting a day-3 positivity rate of about 21%. VMWs are responsible for a range of tasks including preparing blood slides on day 0, completing forms, administering DOT on days 0-2, obtaining follow-up slides on day 3 and transporting slides and paperwork to their supervising health center. Full engagement of VMWs and adequate financial compensation for specific tasks are needed for the good performance of the day 3 surveillance systems. While staff remuneration, computer literacy, frequent changes in health administrative structures, and mobile networks coverage are some of many challenges to be addressed, VMWs and MMWs have increased the capacity of national programmes and now constitute an essential component of a sustained efforts towards containing resistance and eliminating malaria.

The experience of Myanmar

Medical Action Myanmar, an NGO, supports a CHW project in Mon and Kayin States, eastern Myanmar. Villagers were trained to perform rapid diagnostic tests and dispense ACT + primaquine; they were available for patients in their village of residence or other villages nearby at a fixed time. CHWs received a small incentive for each rapid diagnostic test performed. A mobile monitoring team visited each village once a month to assess CHW performance, distribute LLINs, provide health education and obtain feedback of villagers. The CHW project monitoring proved to be expensive (approximately US$ 2000 per village per year), and time-consuming, due to the travel time required between villages. The project started in 2011 and expanded gradually. A retrospective cohort analysis stratified in two 6-month periods (January-June; July-December) was performed and indicated that CHWs were not always available, and that some villages had only few or no cases of malaria. Analysis of the villages with highest initial malaria incidence was presented. In general, falciparum positivity rate decreased in nearly all CHW project villages. In Myanmar, CHW are the only way to reach small remote villages. Success depends on the appropriate selection of CHW to make sure that he/she will be respected by villagers and will not compete with other health providers (e.g. quack), that they have appropriate incentives to maintain their motivation, and have the time to do the tasks in addition to their regular job.

Discussion

VMWs, CHWs and MMWs in Cambodia, in Myanmar, and in other countries have a major role in improving surveillance and response to support malaria elimination. VMWs have different mode of operations and conditions according to country. Differences in country context need to be taken into account in the design of CHW or VMW programmes. Countries have expressed concern over the sustainability of altering or creating community health programmes that are dependent on external funding. It was noted that in Viet Nam, 90 % of villages have VMWs. It was debated, if resources should be allocated for VMW and CHW to do DOT in the context of elimination.

Recommendations

Services provided by CHW or malaria volunteers should be considered an essential element of any malaria control or elimination strategy in GMS. While it is of very high priority to promote good adherence to standard treatment regimens, there is no hard evidence showing a clear benefit of DOT as a public health intervention on adherence at the population level. Therefore, TEG does not recommend a strong emphasis on efforts and funding support for DOT. Investing in research to identify additional methods to improve adherence was considered important. Depending on local conditions and

experience, DOT may be considered in the context of last stages of elimination phase, when there are only a few cases left, and in non-mobile populations.

7.6 RTS,S/AS01 in low transmission settings for targeted elimination

Presentation

An update on the assessment of the RTS,S/AS01 vaccine and the preparation of policy recommendations was presented. The pathways for WHO RTS,S vaccine policy recommendations include MPAC and the Strategic Advisory Group of Experts (SAGE) on immunization. Following regional consultations, SAGE and MPAC will communicate their specific recommendations to WHO Director General, after which a concept paper will be issued and released to countries for decision-making. The patient enrolment of a phase 3 randomized placebo controlled trial was completed 2011 in 7 African countries. The study included 15 460 children stratified in two age groups, 6-14 weeks old and 5-17 months old, at first immunization. The primary vaccination series consisted of three intramuscular doses given 4 weeks apart. Outcome measures include episode of clinical malaria during 12 months of follow-up in each age category. This multicenter study was conducted in a wide range of malaria transmission intensities (0.01 to 2.0 clinical episodes per child per year). Efficacy was measured in presence of other malaria control interventions: 86% LLINs coverage for infants aged 6 to 12 weeks, and 75% among children aged 5 to 17 months. Final results should be available in the summer of 2014 and will include a follow-up at 30 months in the two age groups, site-specific efficacy, and the effect of a booster dose given 18 months after the third dose.

Available results show no clear variation in efficacy according to transmission level. However, the benefits, in terms of number of episodes prevented, may be highest in high-transmission settings. A 3-fold higher immunogenicity for anti-CS IgG was observed in the older age group. From preliminary results, the assessment indicates that the efficacy is higher among 5-17 month olds than in 6 to 12 week olds. Efficacy wanes substantially by 18 months, and hence the booster dose data will be important for policy assessment. There is an increased frequency of febrile convulsions and meningitis in the vaccine group, compared to the control group, and this warrants further assessments by the Global Advisory Committee on Vaccine Safety. The policy recommendations, to be issued in 2015, will be geographically restricted to sub-Saharan Africa, as no RTS,S data are available from other regions. The EMA filing date is planned for June 2014, and the EMA regulatory decision timing should be Q3 2015, at the earliest.

Discussion

In the context of malaria elimination, all age groups would need to be vaccinated. The RTS,S vaccine has not been tested in South-East Asia. In the age groups that were studied, the vaccine shows benefit in terms of lower frequency of clinical episodes; however, to the knowledge of the TEG, its effect on asymptomatic parasitaemia was not studied. A specific concern raised by the TEG was whether RTS,S induced immunity can cause an increase in the asymptomatic but transmissible parasite reservoir. The TEG requested WHO to ask the PATH Malaria Vaccine Initiative and GSK whether data on this and other specific questions are available. The questions and answers are below.

Recommendations

Although the TEG has limited expertise on this vaccine, it considers that there is currently insufficient data to suggest a role of the RTS,S vaccine in containment/elimination strategies. The TEG considered it

important to invest in the development of a vaccine that interrupts malaria transmission, since this could prove an important additional tool in malaria elimination.

Post meeting note

Questions to PATH Malaria Vaccine Initiative and GSK*

a) *Do the trials show an impact of RTS,S on submicroscopic parasitaemia?*
   No data is available from field trials but the likely answer is yes, from the mechanism of action of RTS,S, which provides 50-60% or more sterile/complete protection in the controlled human malaria infection model.

b) *Do the trials show an impact in terms of delayed appearance of patent parasitaemia?*
   Yes, but limited field pediatric data is available only with AS02. AS01 is better so one can be confident that RTS,S/AS01 will do this.

c) *Are there data on the impact of submicroscopic gametocytaemia and transmissibility?*
   Gametocytaemia is being evaluated in the MAL055 Phase 3 trial; however, subpatent gametocytaemia or transmissibility has not been studied.

d) *Do the trials show an impact on reducing the genetic diversity of malaria infections?*
   Genetic diversity of malaria parasite infections is being evaluated in the MAL055 Phase 3 trial; one hypothesis is that RTS,S vaccination will be associated with reduced genetic diversity by reducing multiplicity of infections in the short term. The long-term effects are less clear.

e) *What will be the costs of conducting safety studies and efficacy studies in all age groups to enable possible deployment of this vaccine in the Mekong Region?*
   This has not been evaluated.

* These answers express the view of PATH Malaria Vaccine Initiative and GSK and were not commented by the TEG.

ANNEX1: QUESTIONS FROM MPAC FOR THE TEG TO DISCUSS AND GIVE RECOMMENDATIONS ON

1. ARTEMISININ RESISTANCE

a) *Should the definition of artemisinin resistance be updated and, if so, in which way?*
Yes, with the identification of the mutations in the resistance domains (amino acid positions ≥ 440) of the gene on chromosome 13 encoding for a Kelch protein (K13) as a marker for artemisinin resistance, there was agreement that this definition needed to be updated. However, it was agreed that the clinical phenotype of slow clearance should remain part of the definition. The committee recognizes that the definition might need adaptation as more data become available. As with the previous working definition, a distinction is made between suspected and confirmed artemisinin resistance at a population level. Suspected endemic resistance is defined as a prevalence ≥ 5% of infecting parasite strains carrying Kelch 13 resistance-associated mutations, **or** a proportion ≥ 10% of patients still parasitaemic on day 3 by microscopy **or** ≥ 10% of patients with a peripheral blood parasite half-life ≥ 5 hours following a treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy. Endemic artemisinin resistance is confirmed when there is a prevalence of ≥ 5% of infections with strains containing Kelch resistance mutations if the patients carrying these mutants also have persistent parasitaemia by microscopy on day 3 or a peripheral blood parasite half-life ≥ 5 hours following adequate treatment with artemisinin-based combination therapy (ACT) or artesunate monotherapy.

b) *Does the evidence support the inclusion of provinces in northwestern Myanmar in tier 1?*
WHO is awaiting data from clinical studies and molecular analyses from three provinces of Myanmar before issuing formal recommendations. However, the probability of including northwestern provinces of Myanmar in tier 1 is high.

c) *How should K13 be used in the surveillance of artemisinin resistance; in particular is an evidence review group on K13 needed (to review available data, reference center, SOPs, data analysis)?*
The committee agreed that K13 analysis should be part of all therapeutic efficacy studies on falciparum malaria. However, the science around this new marker is quickly evolving. More than 30 different mutations in the K13 gene have been reported so far, not all of them being located in the propeller domains, and different mutations may confer different resistance phenotypes. Moreover, a set of "permissive" mutations elsewhere in the genome may be a co-factor in emergence of K13-mediated resistance. Given the significance of the discovery and the quickly evolving information, the TEG recommended the establishment of an ERG on the topic to 1) to collect and review data; 2) to indicate which polymorphisms on K13 (and beyond) should have consequences, if detected in a given area, and describe these consequences; this includes a discussion on the development of integrated mapping of the relevant K13 mutations; 3) to propose organizational structures (such as a reference center) that can facilitate standardization of methods and information flow to national programs and WHO; 4) to identify remaining knowledge gaps for research.

d) *Which implications does the identification of the K13 mutation have on the response to artemisinin resistance?*
The identification of multiple K13 mutations and additional genetic analyses have shown the existence of multiple foci of de novo emergence of artemisinin resistance, in addition to its geographical spread. The "firewall approach" remains an appropriate and necessary containment measure in tier 1 and 2 but additional measures are necessary, which includes an effort for elimination of *P. falciparum* malaria in all affected countries in the GMS where artemisinin resistance has been detected, in addition to intensified measures in sub-Saharan Africa that include improved case detection and treatment of malaria,

uninterrupted supply of essential commodities, scaled up and sustained coverage with vector control measures, intensified efforts to eliminate monotherapy, counterfeit drugs and other substandard treatments, and enhanced therapeutic efficacy monitoring. Evidently, the K13 molecular marker will be an important additional tool for surveillance of artemisinin resistance.

2. RESISTANCE TO OTHER ANTIMALARIAL DRUGS

a) *What are the TEG's recommendations on the national treatment policies in particular in Thailand and Cambodia?*

In Thailand, the first line policy is still artesunate-mefloquine despite the evidence of high failure rate on the border between Thailand and Myanmar and Thailand and Cambodia. The TEG strongly recommends an urgent policy change in Thailand. The TEG will inform MPAC if no policy change is achieved in Thailand by September 2014. For western Cambodia, the TEG supports the implementation of artesunate-mefloquine as a short-term alternative to now failing dihydroartemisinin-piperaquine, but is concerned about the vulnerability of mefloquine. For the time being, it is recommended to use quinine and doxycycline over 7 days as rescue therapy in case of failure with artesunate-mefloquine, while waiting on the results of a study evaluating current efficacy of artesunate-pyronaridine in Western Cambodia. There was no consensus in the committee whether to recommend extension of dihydroartemisinin-piperaquine treatment from a 3 to 5 days course, because of potential safety issues regarding the increased piperaquine dose (QTc prolongation). However, clinical studies (phase I and II) to assess the safety, efficacy, and effectiveness of a 5-day dihydroartemisinin-piperaquine treatment course were recommended to enable an evidence-based recommendation in the near future.

b) *What should be the ideal profile of the next generation of antimalarial treatment?*

The TEG considered triple combinations of drugs with different modes of actions to be a target product profile for the next generation of antimalarial drugs either using current drugs or by adding a new compound to some of the existing ACTs. The selection of drugs will require appropriate matching of pharmacokinetic profiles (linked to drug potencies) and investigation of potential drug interactions. The absence of new drugs is a major impediment in fighting antimalarial resistance, and TEG expresses desperate needs to accelerate the development of new chemical entities.

c) *Should multiple first-line treatments for malaria be promoted as part of the response to resistance?*

The evidence examining multiple first-line therapies (MFLT) as a response to resistance is based on two modeling studies only, and those gave contradictory conclusions. In the study which was found to support MFLT, the potential benefit the potential benefit was estimated to relatively minor; likewise the model that did not support MFLT also showed a small effect. Therefore, TEG cannot currently recommend adopting MFLT as a response to resistance but recognizes the need to be flexible and does not oppose such practice, in particular when it is already in place or when used to avoid drug stock outs. The TEG acknowledged that increasing the complexity of treatment policy risks practices that exacerbate rather than mitigate the problem. The potential benefit of doing so seemed insufficient justify recommending it. Measures to ensure drug quality and treatment compliance should be also emphasized.

3. CONTAINMENT AND ELIMINATION - POLICY RESPONSE TO ANTIMALARIAL DRUG RESISTANCE

3.1. ONGOING ACTIVITIES

a) *Is regional Plasmodium falciparum malaria elimination a feasible, as opposed to desirable, goal? Consider assumptions, benefits and risks of options and timelines.*

The TEG considers malaria elimination to be feasible in the GMS, provided that sufficient funding is available, that the current and new tools are applied correctly, and that good coordination exists between

donors and implementers. The elimination goal must be translated into concrete action plans, with clear time lines and responsibilities. A pre-requisite for coordination is a good understanding of the availability of current and new tools, how these tools are used, and which groups are using them in which geographical area; this will require an accurate mapping of tools and resources for each targeted region of artemisinin resistance. Elimination goals and timelines will be set by country and/or regions. The following preliminary timelines have been proposed:

- Eastern Thailand, Cambodia, Viet Nam, Lao PDR, and China (Yunnan): 2020
- Eastern Myanmar and western Thailand: 2025
- Western Myanmar: 2030

b) *If not, what should be the optimal malaria strategy for Greater Mekong subregion (GMS) in a local and global perspective?*
See comments in 4 a)

c) *Should WHO work to have artemisinin resistance declared a "Public Health Emergency of International Concern" (PHEIC)?*
The TEG considers that artemisinin resistance does not constitute a PHEIC because the conditions for PHEIC introduced in the revised International Health Regulations (IHR, 2005)[*] are not met. As defined in IHR, a PHEIC is an "extraordinary event" that constitutes an acute public health risk, emphasizing "a serious and direct danger, to which a sense of urgency can be inferred" and "which may also require a coordinated response". IHR were designed to deal with acute (as opposed to chronic) public health conditions that are readily transmissible and disruptive to international trade. Declaration of a PHEIC by the WHO has far reaching consequences. While the committee considers artemisinin resistance as serious and severely threatening public health concern meriting a vigorous and coordinated response, it did not see it as meeting the criteria for a PHEIC as described above. The emergence of resistance to any class of drugs is not an "extraordinary event" but one that has occurred time and again with all other classes of antimalarial drugs over the past 100 years. Although the event is deeply worrying, it does not exceed reasonable expectations regarding parasite evolution in the face of important selection pressure. The TEG also recognized that in the context of artemisinin resistance, resistance to ACT partner drugs becomes equally or more critical than artemisinin resistance per se. The harm being caused by that distinct problem is not a hypothetical future – it is occurring today in the GMS – often resulting in treatment failures and illness rather than exhibiting modest delays in cure.

3.2. MASS DRUG ADMINISTRATION (MDA)

a) *Does the resistance situation in the GMS mean that MDA is no longer rational?*
There is a rationale for MDA as long as it is not used as an isolated intervention. MDA could be useful as part of an elimination strategy if included in the context of a package of interventions, such as a village health worker program for early diagnosis and treatment and, where appropriate, mosquito net distribution. However, a key problem is the lack of evidence to guide optimizing the approach in any given setting. Initial analysis of a pilot study using targeted MDA (3 rounds of a monthly full course of dihydroartemisinin-piperaquine) in villages with high malaria prevalence, show the expected results in reducing prevalent *P. falciparum*, but (as expected due to the untreated hypnozoite reservoir in the community) less so for *P. vivax*. Although not measured in that pilot work, success with MDA almost certainly depends on the coverage achieved, i.e. the proportion of people receiving therapy. The people most likely to be missed in MDA may also be the most likely to later reintroduce parasites into their

[*] WHO (2005). *International Health Regulation.* Geneva, World Health Organization.

communities, i.e. mobile and migrant populations, or those frequenting the forest. This potential pitfall implies that a sufficiently large area has to be covered when implemented. Several questions must be addressed to optimize targeted MDA trials, which include strategies for scaling up (such as blood volumes and sample sizes for screening, large scale community engagement and acceptance and support). MDA remains a high-risk strategy, since it has the potential to increase drug pressure on the parasite population driving increasing drug resistance (last man standing), so that efforts need to be maintained until elimination has been achieved. Until recently, opposition from countries has delayed the implementation of targeted MDA trials. The TEG recommends that more trials looking at various aspects of this strategy should be conducted as soon as possible and that national programmes and WHO should be involved in planning and evaluation with real-time sharing of information. Currently small-scale projects are being conducted or planned in Cambodia, in Myanmar near the border with Thailand, and in Viet Nam. Another study could be conducted in Bangladesh near the border with Myanmar, if funding is granted.

b) *If no, where does MDA have a role (socio-economic situations, epidemiological settings and resistance tiers)?*
Not addressed.

c) *Which drugs should be used in MDA?*
As a basic principle, the drug used for MDA intervention should be different from those used for first line treatment. In some settings however, this is not possible due to resistance to partner drugs. When possible, rotating the drugs used for MDA is recommended. The recommendation for targeted MDA is a balance between the need to eliminate falciparum malaria in an area with artemisinin resistance, and the risk of increasing drug resistance potentially losing the drug to full resistance. However, if MDA achieves permanent elimination, the antimalarial drug where applied will no longer be needed, and of course all of the parasites expose to the applied drug are, in principle, dead and gone.

d) *Are there other interventions with which MDA should be combined in a fixed way? If yes, which should be prioritized immediately in operations or in research?*
MDA is already part of a package of interventions. Research on how to include ivermectin in MDA should be prioritized.

e) *How should MDA be planned and monitored?*
Real-time data should be available, and WHO should be involved in planning and evaluation.

f) *What further inputs are needed from geneticists and modelers on MDA?*
A wide variety of possible scenarios regarding MDA can be modeled, but there are few real world data to inform the models or verify output. This will remain important, but at this time the field evaluation of the currently selected scenarios should have priority. The TEG acknowledges the need for more research on parasite population genetics in relation to population movement as well as research on a better understanding of the sub-patent parasite reservoir. In the context of monitoring elimination and defining the reservoir, monitoring transmissibility using serology testing in longitudinal studies may be useful in addition to the currently used genetic methods.

3.3. VECTOR CONTROL

a) *Which role should vector control interventions including ivermectin play in elimination/containment/control strategies in the GMS, considering effect, cost-effectiveness and alternative uses of the resources?*

Mosquito nets should be part of the containment activities and are already an integral part of national malaria control programme with high population coverage in many regions. Personal repellents as programmatic interventions have shown very limited impact, but can be important for individual protection. The choice of vector control interventions should be informed by understanding of both mosquito and human behaviors. Regarding ivermectin, research to investigate the added value of this vector control tool when combined with targeted MDA is recommended. Prior to larger studies involving ivermectin, entomological data from areas where ivermectin was deployed can be insightful. Dosing and interaction with antimalarial drugs used in MDA will also need careful consideration. A comparative study of the combinations of ACT plus primaquine versus ACT plus ivermectin is planned in Lao PDR. The TEG encourages implementation of other field studies with ivermectin. Research on other vector control methods to address residual transmission is also a priority.

3.4. ADDITIONAL TOOLS FOR MALARIA ELIMINATION

a) *What is the role of classical elimination tools such as focus-based interventions and active case detection in the context of artemisinin resistance in GMS?*
These tools are relevant, but need to be assessed and adapted to the epidemiological and operational realities of each country. However, the assessments that have been done offer little encouragement. The diagnostics technology that would enable such an approach is simply not available; the simple and quick methods are far too insensitive, and the complex and slow methods are more sensitive but, in any event, too expensive for consideration by NMCPs.

b) *What is the role of vaccination against malaria, especially RTS,S in the containment/elimination strategies?*
Although the TEG has limited expertise on this vaccine, it considers that there is currently insufficient data to suggest a role of the RTS,S vaccine in containment/elimination strategies. RTS,S was designed to prevent severe morbidity and mortality rather than infection per se. A specific concern raised by the TEG was whether RTS,S induced immunity can cause an increase in the asymptomatic but transmissible parasite reservoir. The TEG considered it important investing in the development of a vaccine that interrupts malaria transmission, since this could prove an important additional tool in malaria elimination.

c) *Is there any role for financial incentives to seek proper treatment in any areas?*
The TEG believes financial incentives for seeking proper treatments is ethically dubious and socially not sustainable.

d) *To which extent should funding be spent on implementation of directly observed treatments (DOTs) and follow-ups?*
Based on effectiveness studies and the tuberculosis experience there is no hard evidence showing a clear benefit of DOT as a public health intervention on treatment compliance at the population level. Therefore, TEG does not recommend more funding to support DOT. Investing in research to identify additional methods to improve adherence was considered important. DOT may be considered in the context of last stages of elimination phase when there are only a few cases left and in non-mobile populations. In other words, where there are many cases, DOT bears very high costs and little reward; but where cases are few DOT bears few costs and enormous reward.

e) *What actions, if any, should be recommended for groups such travelers and military entering or leaving areas with artemisinin resistance?*
This topic was addressed only partially but will be included on the agenda of the next TEG. It was agreed that military should be treated for preventing importation or exportation of resistant parasites in the GMS. Specific actions will be needed for UN. The TEG will review a set of recommendations for the UN through

email. Recommendations to travelers should be issued by the TEG on Chemotherapy in concert with the WHO division of International Travelers and Health. A regional meeting addressing the issues of malaria control in the military in the context of artemisinin resistance, organized by donors, WHO ERAR hub and the RSC RAI, will take place in Viet Nam 19-20 June.

f) *Does the TEG recommend the use of standby treatment for mobile populations?*
Under exceptional circumstances, when there are no malaria workers or health services, the TEG considers standby treatment for mobile populations acceptable provided the treatment is a quality-assured ACT. Drug should be provided as part of a kit containing nets and diagnostic tool(s). However, mobile malaria workers are a better solution and experience with them is accumulating.

g) *What other tools should be emphasized in the drive toward malaria elimination?*
Not addressed.

4. SUMMARY AND IMMEDIATE NEXT STEPS

a) *Since the development of the Global Plan for Artemisinin Resistance Containment (GPARC), research has provided additional information on artemisinin resistance, and resistance has been identified outside the area on the Cambodia-Thailand border. Is it now possible to identify a strategy for containment of artemisinin resistance i.e. to prevent or significantly and verifiably delay its spread beyond GMS biogeographic region or eliminate artemisinin resistant parasites?*
The area within the GMS affected by artemisinin resistance appears to have expanded significantly over the last few years. Genetic studies indicate that this is partially due to geographic spread but also de novo emergence of resistant mutants. It must thus be acknowledged, therefore that containment based only the "firewall principle" (preventing spread from a persistent focus) will unlikely be effective on its own. However, artemisinin resistance with clinical relevance is still confined to a relatively limited area of continental South-East Asia. Prevention of spread of artemisinin resistant falciparum malaria remains important, especially because the same strains are increasingly also resistant against the main partner drugs (lumefantrine, mefloquine, piperaquine) as well as atovaquone-proguanil. From a global perspective, there is therefore now a strong case for prioritizing falciparum malaria elimination in the GMS countries, in addition to the "firewall approach". Achieving this objective within a limited time could delay the emergence of multidrug resistance in other parts of the world, probably until or after new effective, safe and affordable antimalarial drugs become available. An additional argument is that, if falciparum malaria persists in the GMS countries, this subregion will be the first to need novel antimalarial drugs and will therefore again be the source of multidrug resistance to affect global control and elimination efforts.

However, malaria elimination in the GMS countries is severely hampered exactly by the widespread drug resistance. As in the past, this converges with highly exophilic vectors and extensive population movement. But there are also several factors that will facilitate falciparum elimination in this region: the vectorial capacity even in forest environments is not very high in this part of the world, meaning that interventions which can circumvent the outdoor transmission are likely to be highly effective; health systems are rapidly becoming stronger, as economies grow. In fact, the malaria burden has been greatly reduced in these countries over the last 20 years. Furthermore, national malaria control programmes now have at their disposal an array of interventions and information technologies, which were not known only a few decades ago. Although it is not possible at present to identify a definite, uniform strategy, which is guaranteed to lead to elimination within a few years, the TEG considers it likely that continued, fully scaled-up and improved implementation of the current standard interventions supplemented by

novel interventions specifically aiming at elimination, which are ready or almost ready to be validated through field research can lead to elimination of falciparum malaria in the GMS countries.

The assessment that time-limited elimination is feasible is based on the following assumptions:

1) that the effort is fully and continuously funded across the subregion until the objective has been achieved;
2) that there is continued excellent collaboration and coordination between countries, between countries and partners, between researchers and national malaria control programme managers and between partners;
3) that the remaining focal security problems will be solved rapidly and that no serious armed conflicts will emerge.

Progress in elimination of falciparum malaria in these countries will to a large extent serve as pathfinder for vivax malaria elimination. New tools are likely to become available for vivax malaria elimination within the next few years. Thus, vivax malaria elimination is likely to be achievable only a few years after falciparum malaria elimination in these countries. It is likely that a malaria elimination agenda, having more tangible objectives, will be more strongly supported by national and local governments as well as affected communities than containment plans have been in the past.

b) *If not, what is the TEGs role in ensuring that consensus is achieved and how should that role be fulfilled?*
Not addressed.

c) *What should the MPAC do to support the TEG further in its work?*
The TEG has recommended elimination of falciparum malaria in the GMS. With the support of a consultant, a subgroup of the TEG will prepare an analysis of the feasibility of malaria elimination in GMS, an estimation of the potential costs, and outline an elimination plan. This will be complemented by more detailed operational planning by the ERAR hub. As a matter of urgency, MPAC is requested to review this analytical work and provide any additional inputs. If MPAC deems elimination in GMS feasible with the proposed timelines from technical and financial viewpoints, it is requested to lend the proposed outline plan of action its full support, and then maintaining the political and financial momentum.

TECHNICAL EXPERT GROUP ON DRUG RESISTANCE AND CONTAINMENT

28-30 APRIL 2014, STARLING HOTEL, GENEVA, SWITZERLAND

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World Health Organization

TECHNICAL EXPERT GROUP ON DRUG RESISTANCE AND CONTAINMENT

28-30 April 2014 – Starling hotel, Geneva, Switzerland

Monday 28 April 2014		
09:00–09:15	Welcome **J. Reeder – ai Director GMP** **A. Dondorp – Chair TEG DRC**	
09:15–09:30	Declaration of interest, agenda, Global Technical Strategy **P. Ringwald**	
09:30–10:00	Minutes and action points last meeting **A. Dondorp**	
Session 1: Update on drug resistance		**Purpose of session and expected outcomes**
10:00–10:40	i) TRAC studies **A. Dondorp**	→ For information
10:40–11:00	**Coffee/tea break**	
11:00–12:30	ii) Artemisinin resistance confirmatory study in Suriname **S. Vreden** iii) Policy change in Cambodia **S. Sovannaroth**	→ For information and decision
12:30–13:30	**Lunch**	

13:30–15:30	iv) Update on K13 molecular marker **C. Plowe** v) Update on artemisinin resistance definition and tier maps **P. Ringwald**	→ For information and decision
15.30-16.00	**Coffee/tea break**	
Session 2: Modelling		**Purpose of session and expected outcomes**
16:00–18:00	i) Impact of spread of artemisinin resistance to Africa **H. Slater invited speaker** ii) Multiple first-line treatments: outcome of recent modelling efforts **I. Hastings** iii) The potential impact of adding ivermectin to a mass treatment intervention to reduce malaria transmission **H. Slater invited speaker**	→ For information and decision
18:30–20:00	**Reception**	
Tuesday 29 April 2014		
Session 3: Update on recent containment and elimination efforts		**Purpose of session and expected outcomes**
09:00–10:30	i) Emergency Response to Artemisinin Resistance (ERAR) project in the Greater Mekong subregion **C. Rasmussen** ii) Update on the Regional Artemisinin resistance Initiative (RAI) **S. Filler**	→ For information
10:30–11:00	**Coffee/tea break**	
Session 4: Elimination of artemisinin resistance in the GMS		**Purpose of session and expected outcomes**

11:00-12:30	i) MDA pilot studies in the GMS **A. Dondorp** ii) Malaria elimination strategies in the context of artemisinin resistance **A. Rietveld**	→ For information and decision
12:30–13:30	**Lunch**	
13:30-15:00	iii) Vector control strategies for malaria elimination in the context of artemisinin resistance **M. Coosemans invited speaker** iv) Ivermectin as an malaria elimination tool **K. Kobylinski invited speaker**	→ For information and decision
15:00-15:30	**Coffee/tea break**	
15:30-17:00	v) Use of community health workers (CHWs) and other volunteers for improved surveillance and response to support malaria elimination: - the experience of Cambodia: **S. Meek** - the experience of Myanmar: **F. Smithuis**	→ For information and decision
17:00-17:30	vi) RTS,S/AS01 in low transmission settings for targeted elimination **A. Bosman**	→ For information and decision
Wednesday 30 April 2014		
9:00-10:30	Formulation of TEG recommendations **A. Dondorp**	**Closed session**
10:00–10:30	**Coffee break**	
10:30-12:00	Adoption of TEG recommendations **A. Dondorp**	**Closed session**

12:30	Closing remarks **A. Dondorp/P. Ringwald**	**Closed session**
12:30–13:30	**Lunch**	

Feasibility of *Plasmodium falciparum* elimination in the Greater Mekong Subregion: technical, operational and financial challenges

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 11 September 2014

Technical Expert Group on Drug Resistance and Containment

World Health Organization

GLOBAL MALARIA PROGRAMME

Terms of reference

- This document was developed by a subgroup of the Technical Expert Group on drug resistance and containment (TEG), consultants hired by the Global Malaria Programme, and WHO for the Malaria Policy Advisory Committee outlining the technical, operational and financial feasibility and pre-requisites needed for Plasmodium falciparum malaria elimination in the Greater Mekong subregion

Methodology

- The mission was conducted through a series of consultations with main stakeholders involved in malaria control and elimination in South-East Asia, mainly by phone and email exchanges.
- In addition, the writing team reviewed and used existing literature, national strategic plans, reports, other relevant documents and scientific publications.
- Because of time constraints, it was not possible to undertake country visits.

Why the GMS, why now?

It’s the right time

- Emergence of multidrug resistance including artemisinin resistance in the region, leading to an unprecedented level of regional and national political will, international interest, external financing, technical assistance, regional coordination and national capacity for malaria control and elimination in the GMS.
- Clear demonstration of results in the short term needed to sustain the current level of support.
- This window of opportunity may be short, as political commitment tends to waver once the disease seems to linger on as a marginal problem.
- Missing this opportunity would mean losing much of the benefit of investments made to date.

There is considerable experience to build on

- Excellent progress has been made in addressing malaria across the GMS in the last decade by scaling up proven interventions.
- Efforts to address artemisinin resistance in the subregion have led to further intensification of malaria control activities, remarkably rapid increase in knowledge especially about resistance, population movement and the testing of innovative approaches.
- Mechanisms have been established for exchange of information, collaboration across borders and among partners.

We have no choice but to try

- There is a consensus that the best overarching strategy for stemming the emergence of further drug resistance in the subregion and its spread beyond is to aim for elimination of *P. falciparum*.
- The consequences of inaction would be the emergence of untreatable falciparum malaria, initially in the border area between Cambodia and Thailand.
- The global impact of multidrug resistance, should artemisinin-based combination therapies lose their effectiveness, has been estimated to include 150,000 additional deaths annually.

We have an imperfect but very good set of tools

- The world has at its disposal a set of proven tools for addressing malaria.
- It is likely that effectiveness of some current tools will diminish and few new tools are on the near horizon, so there is little to be gained by waiting.
- Some new tools will nevertheless be added.
- Much of the needed innovation will be in the application of tools. This will evolve fastest by applying them and learning as countries and partners move ahead.

The bill is manageable

- The estimated cost of eliminating malaria in the GMS will range from an USD 3.2 to 3.9 billion over 15 years.
- This represents an average of US$ 1.8 to 2.2 per capita for the population at risk of malaria in the GMS per year.
- While the total cost is significant, it is not out of reach.
- These costs should be weighed against the epidemiological and economic costs of inaction. According to modelling analysis, the economic impact of multidrug resistance could be in excess of US$4 billion annually, due mostly to productivity losses during illness and following deaths.

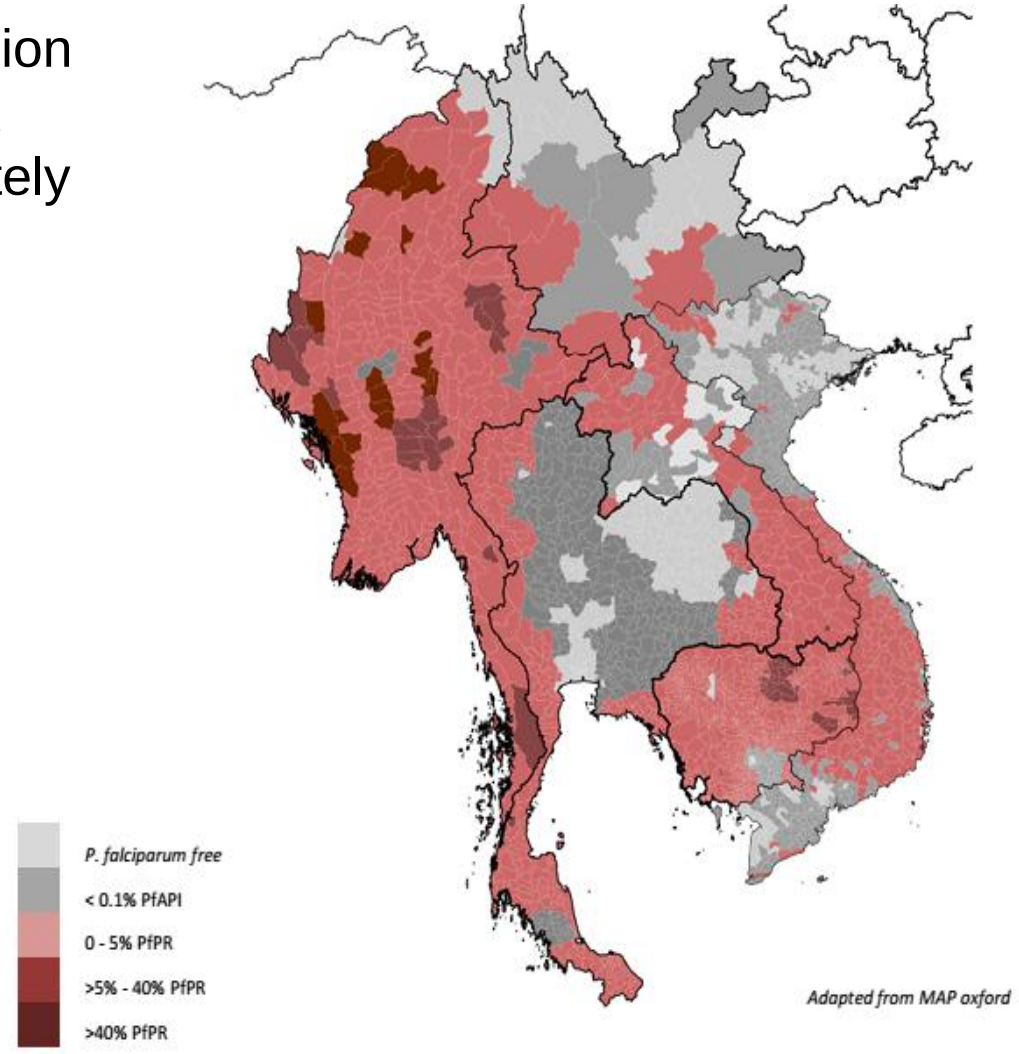
The biggest uncertainty for malaria elimination in the GMS is financial

- Technical and operational challenges can be overcome, yet without adequate and sustained financing the malaria elimination effort in the GMS will fail.
- The containment efforts undertaken in the GMS since 2008 have been hampered by a lack of financial continuity and uncertainty.
- Elimination of P. falciparum malaria in the GMS must be seen as a public good that warrants sustained funding from traditional development partners, especially through the Global Fund, as well as from emerging regional development partners.
- Although national governments, except China's, cannot be expected to shoulder all funding needs within the next decades, it is reasonable to foresee increasing allocations as part of the manifestation of high-level political commitment.

Technical feasibility assessment

GMS and endemicity

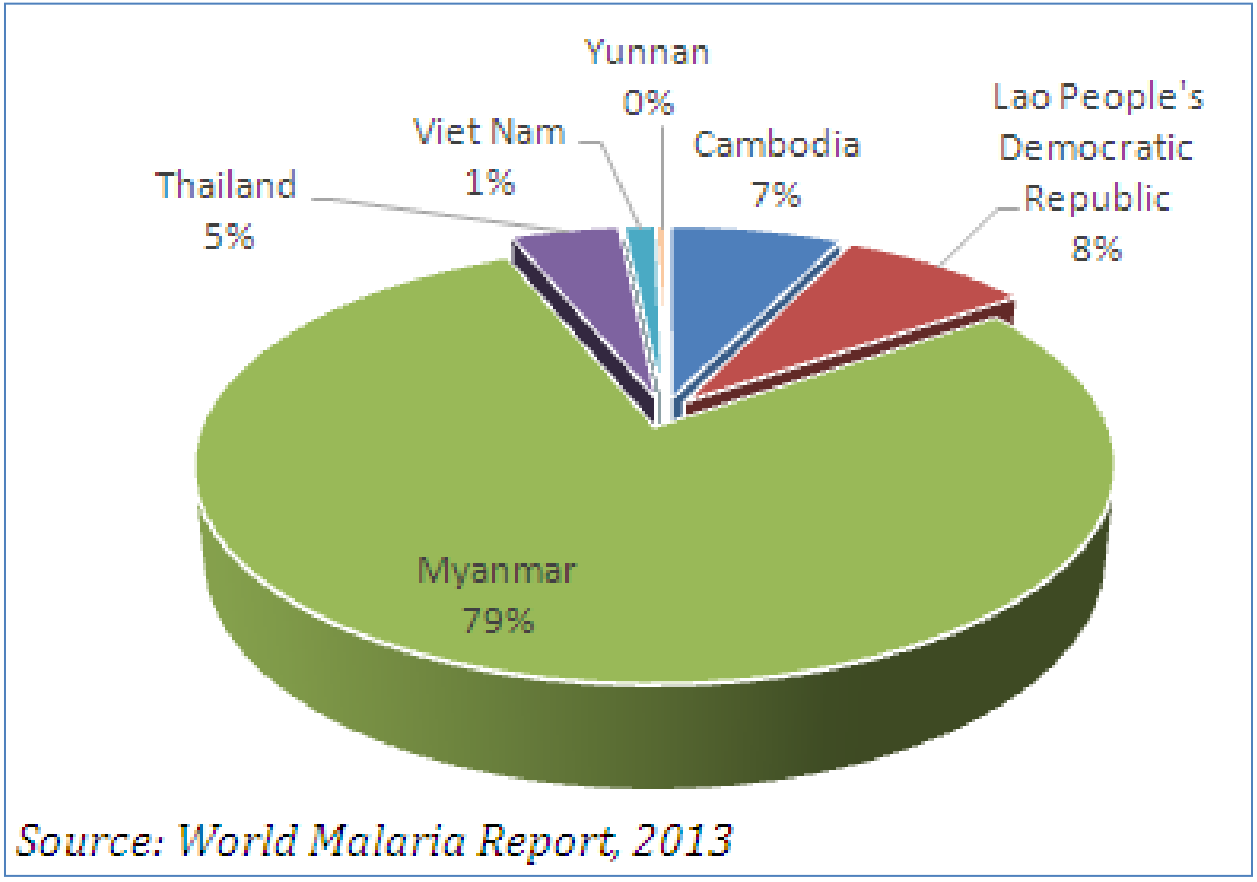
- The GMS covers 2.6 million km^2 and has a combined population of approximately 278 million



Malaria incidence and treatment-seeking in the GMS

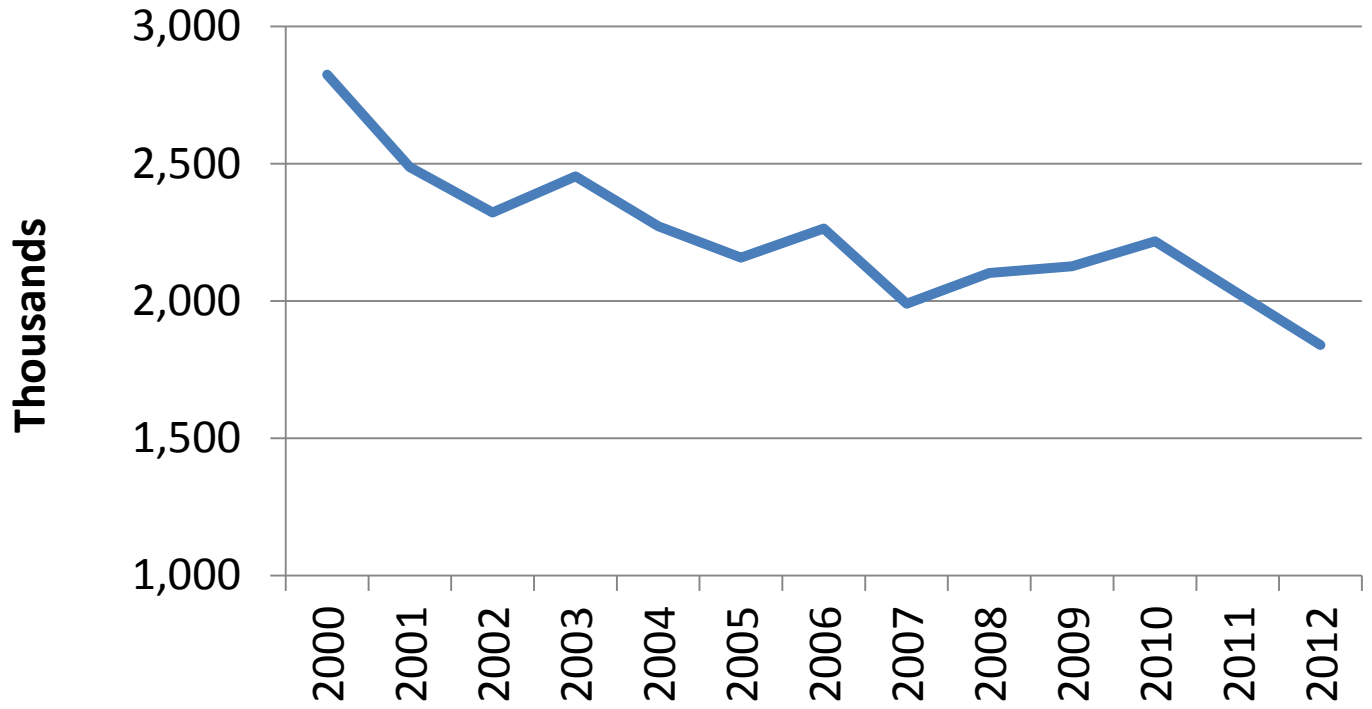
Country	Population at risk (millions)	Estimated malaria cases (upper, lower limits)	Estimated malaria incidence per 1000 population at risk	% patients seeking care in non-public sector
Cambodia	7.9	160000 (130 000–200 000)	20.3 (16.5-25.4)	59–80
Yunnan	9.2	3000 (2000–4000)	0.32 (0.22-0.43)	<5
Lao PDR	3.9	110 000 (89 000–140 000)	28.0 (22.7-35.7)	37–80
Myanmar	31. 7	1 400000 (1 200 000–1 800 000)	44.2 (37.9-56.8)	60
Thailand	33.4	140,000 (77 000–310 000)	4.2 (2.3-9.3)	Not available
Viet Nam	34	27 000 (24 000–30 000)	0.8 (0.7-0.9)	13–23
Total	120	1 840 000 (1 522 000–2 484 000)	15.3 (12.7-20.7)	

2012 GMS distribution of cases

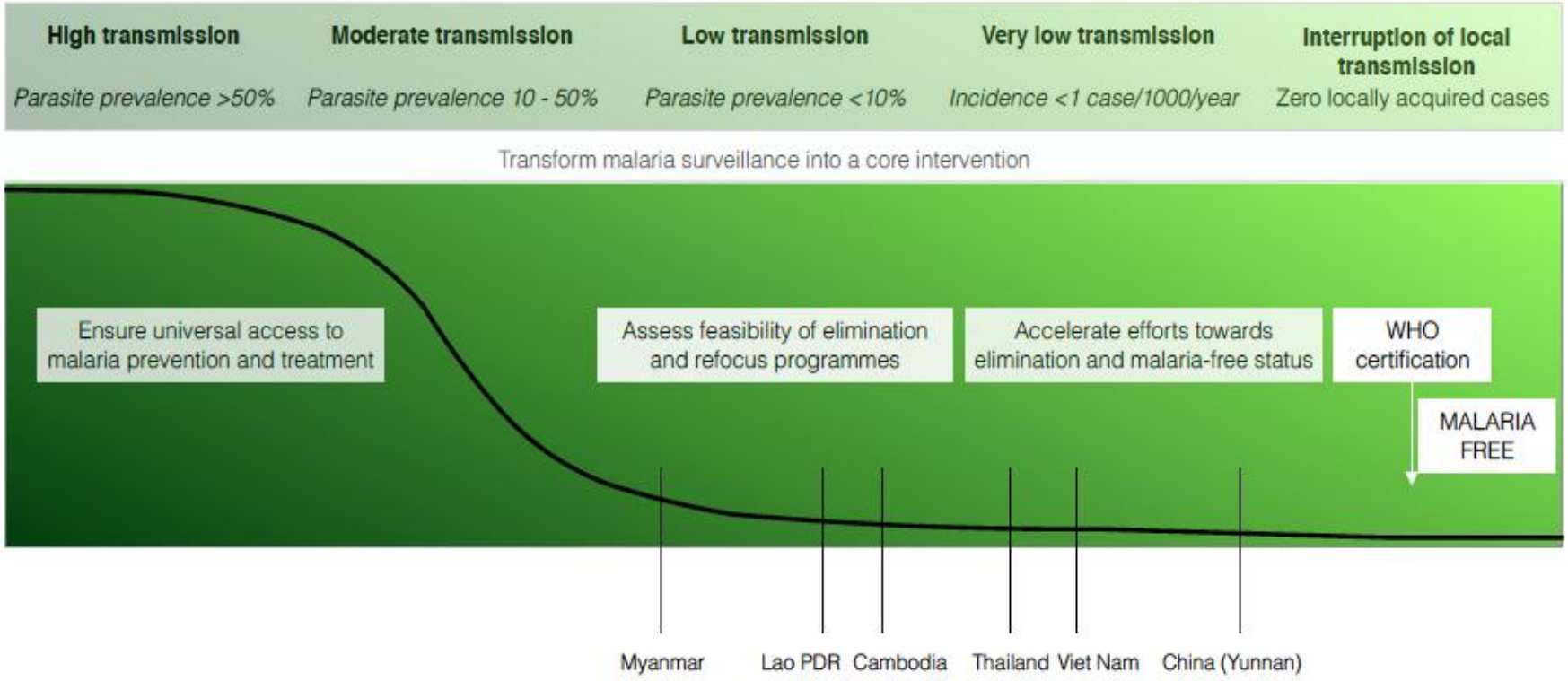


Source: World Malaria Report, 2013

Malaria cases in the GMS (estimated)



Progress toward elimination in the GMS



Current strategies and progress towards elimination

- Three of the six countries in the GMS have longer-term national strategies with formulated goals for national malaria elimination:
  - **China** aims to eliminate malaria in Yunnan province by 2020;
  - **Cambodia** aims to eliminate *P. falciparum* malaria by 2020, and all other malaria species by 2025.
  - **Viet Nam** aims to eliminate malaria by 2030.
  - **Thailand** has adopted a dynamic elimination perspective with a target of achieving interruption of malaria transmission in 60% of districts by 2016 and 80% by 2020.
- All countries, with the exception of China, are currently implementing an artemisinin resistance containment plan.

New tools

- A large arsenal of tools is available for malaria control, though not necessarily for *P. Falciparum* elimination.
- A number of new innovative tools are being developed. There is an urgent need to invest in innovative interim solutions

Technical feasibility issues

- The burden of disease in the GMS has been lowered to levels where most countries are considering, or have already committed to, elimination over the next 10–15 years.
- China is already undertaking elimination activities and from epidemiological as well as system viewpoints Thailand and Viet Nam could enter the elimination phase within the next 2–3 years.
- Cambodia and Lao will need to continue aiming for universal coverage of the population at risk for the next 3–6 years, at which point they could enter the elimination phase.
- Myanmar will have to continue scale up to universal coverage for the next 6–10 years before an elimination strategy can be implemented countrywide

Operational feasibility assessment

Introduction

- Is it possible to achieve minimum levels of effective coverage of those interventions needed to reduce malaria transmission to a very low level, from which elimination can be attempted?
- Operational feasibility depends on:
  - adequate information, both surveillance and operational, to understand potential and actual malaria transmission and to target and manage effective operations.
  - adequate capacity for service delivery – networks of service providers that can provide services to all people in need.
  - leadership and management – political and managerial commitment to elimination and the capacity to strategize, plan, target, organize, supervise, assure quality, monitor, evaluate and solve problems for operations that require a high level of rigor.
  - innovation – new delivery strategies and new partners to overcome the limitations of existing approaches and to deliver new interventions as they become available.

Information systems

Improvements should be made in:

- Accurate information on the burden and trends of malaria
- Information necessary to assess the operational feasibility of elimination
- Detecting the last cases of malaria in areas of very low transmission
- Timely detection of imported cases
- Information needed to manage elimination operations

Capacity for service delivery

Increasing effective coverage of interventions will require optimization of three channels of service delivery:

- public sector;
- private sector; and
- community level.

Opportunities and challenges for the public sector

- A critical role for the public sector in malaria elimination is that it takes the lead on strategy, policy, planning and evaluation of the elimination effort in a multi sectorial approach. While actual service delivery may be shared with the private sector and community level services, the public health authorities **must coordinate** and oversee malaria elimination.

Opportunities and challenges for the private sector

Too frequently, the private sector is viewed as a problem.

We must embrace with the private sector:

- The private sector delivering services to the population
- The private sector: employers of people working in malaria endemic areas
- The private health sector: Producers and importers of malaria control commodities

Innovation

- This means doing things either more effectively or more efficiently – better or cheaper. Innovations on the horizon include:
  - Targeted Mass Treatment (TMT);
  - Introduction of new treatment regimens (e.g. triple therapy) or multiple first-line treatments;
  - Deployment of primaquine;
  - identification of populations of asymptomatic carriers of parasites;
  - delivery of strategies to tackle outdoor biting by mosquitoes (e.g. repellents, personal or spatial, locally applied insecticides);
  - sustaining coverage and use of mosquito control in areas of risk;
  - use of technology in surveillance, mapping, data sharing, public communication and supervision.

Additional specific challenges to operational feasibility

- Multidrug resistance - **Artemisinin and partner drug resistance**
- Counterfeit and substandard antimalarial drugs
- Integration of malaria control activities into broader health services

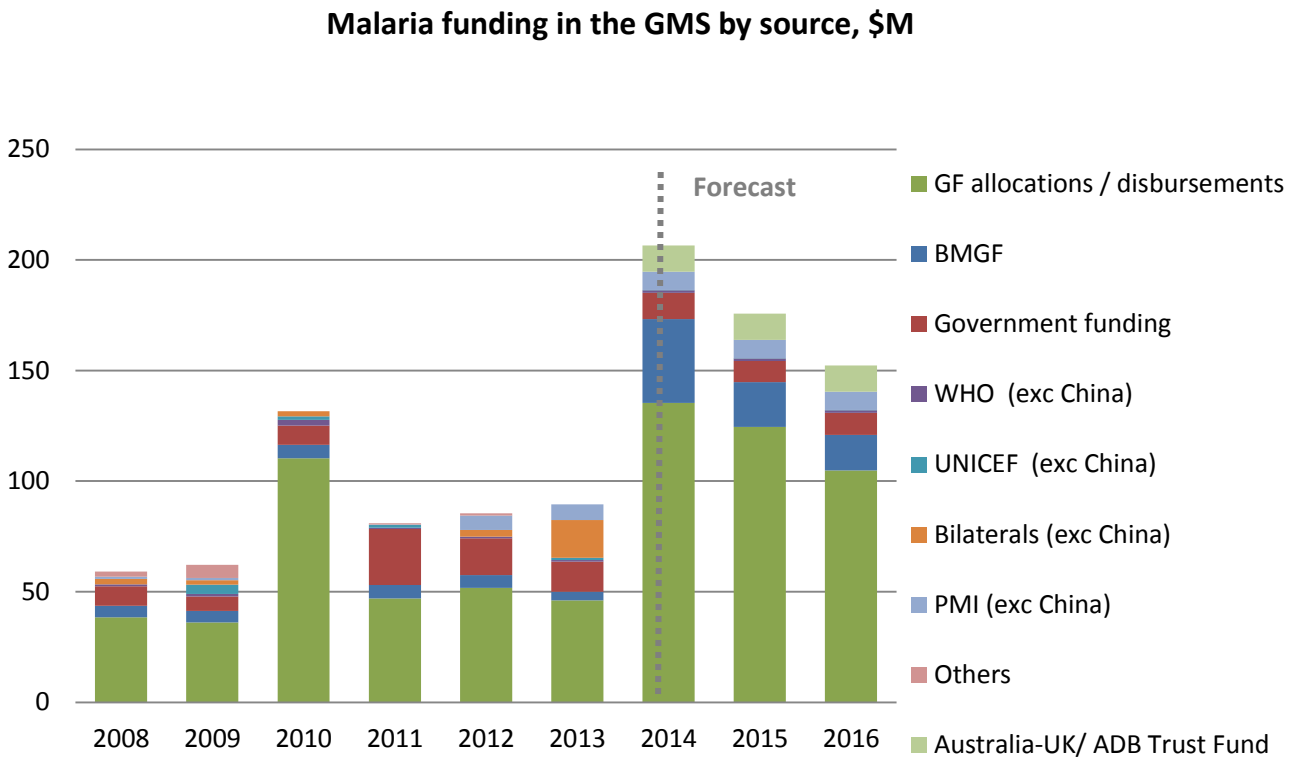
External determinants

- Urbanization
- Infrastructure development
- Security and stability
- Environmental factors

Most of these are on our side…

Financial situation

Malaria funding in the GMS by source

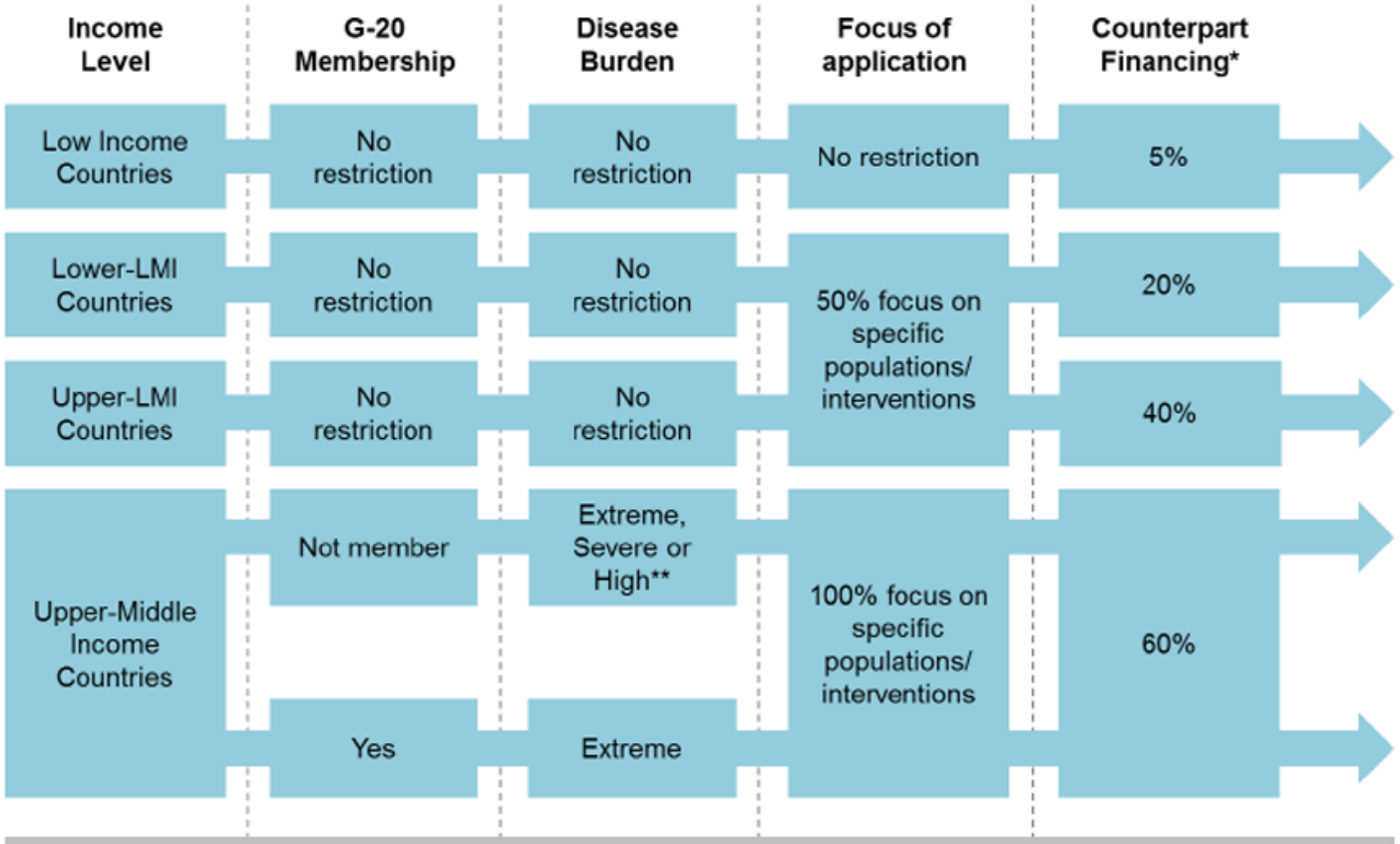


- *Sources: WHO world malaria report/ADB (NB: GFATM data until 2013 represents actual disbursements. Global data 2014-2016 represents fund allocation under new funding model including the US$ 100 million Regional Artemisinin Resistance Initiative grant).*

Anticipating funding from current malaria financiers post 2017

- It would be crucial for any country aiming for elimination to ensure adequate financial resources are made available during all phases of the elimination strategy.
- As observed in countries that have reached pre-elimination phase and failed to eliminate malaria (such as Sri Lanka in the 60's), when the number of cases is reduced to low levels, focus from decision makers and funding from financiers may become volatile due to other competing health priorities.
- With the exception of Myanmar, the GMS countries could see their burden of disease reduced to low or very low levels of transmission soon. Their income classification will also change.
- In this context, the funding from external resources and more particularly from the GFATM may scale down. The GFATM's current funding model allocates funding to countries based on their gross national income per capita and disease burden. As a consequence, the recipient countries will still be eligible for funding but their level of counterpart financing will have to increase.

Global Fund income classification



* *Minimum threshold: this is the minimum government contribution to the national disease program, as a share of the total of the government and Global Fund financing for that disease.*

** *Small Island Economies are eligible if they have a low or moderate disease burden.*

Innovative financing

- **Bonds** designed to front-load future donor commitments, issued in the financial markets, and paid back by donor governments and organizations;
- **Development impact bonds**, where the return on investment is linked to the achievement of programmatic results.
- **Debt-conversion mechanisms** by which a country's debt is written-off by the creditor, and converted into a fund disbursement;
- **Endowment funds** are capital provided by investors, where the returns on investment (though not the capital) will be used to fund malaria programmes;
- **Earmarked taxes**, to be levied on either the national or international level. Some suggestions for malaria elimination have included a national tourism tax or international airline tax.
- **Regional funds** would allow pooling of funds for financing of the malaria battle as a regional public good;
- **Private sector**: through corporate social responsibility initiatives or profit-sharing mechanisms;
- **Emerging country donors**: leveraging the trend of increasing overseas development aid of developing countries to encourage south-south development cooperation.
- **Voluntary public contributions** from developed countries, for example through lotteries or mobile phone solidarity contributions

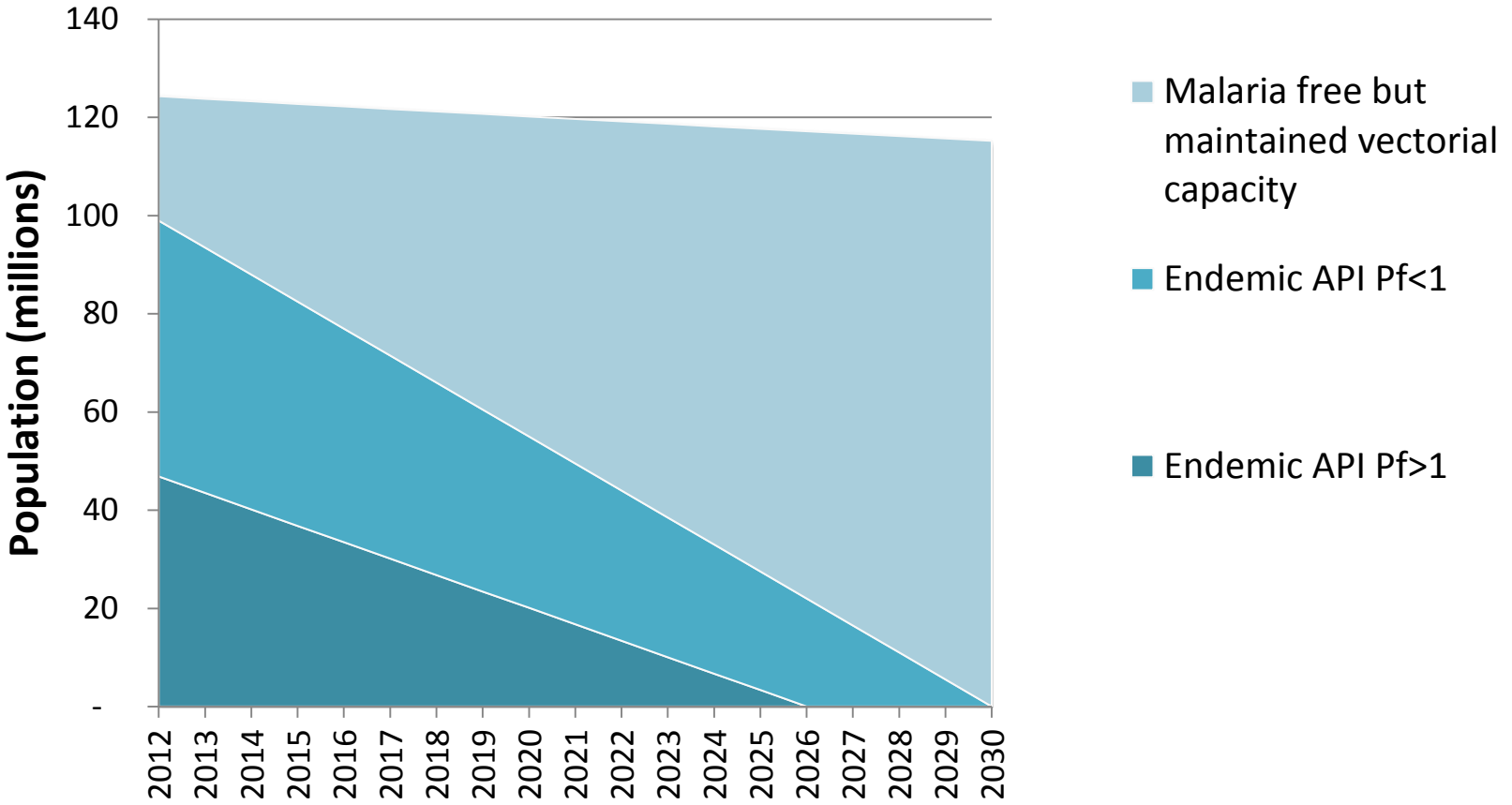
Costing

Costing key assumptions

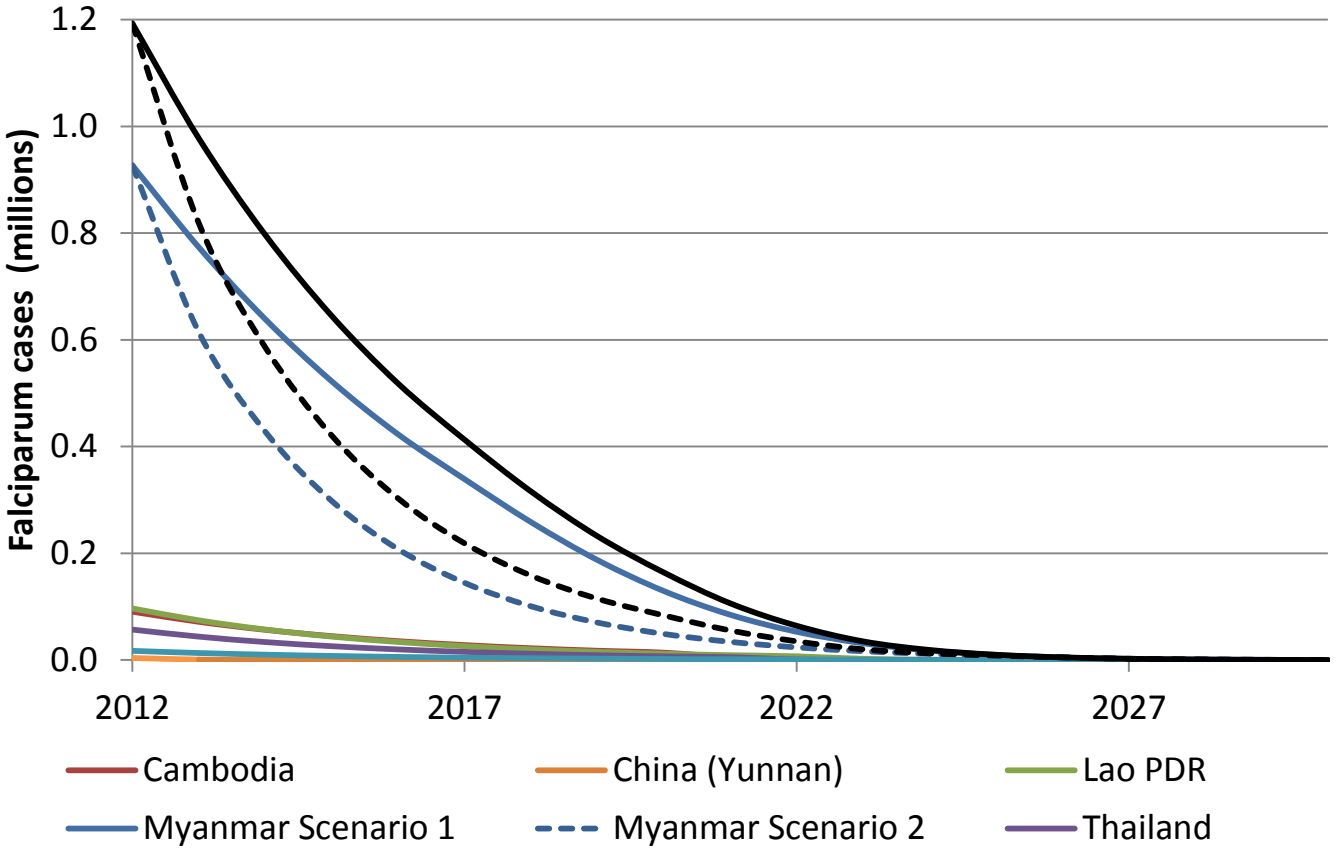
- The costing is based on assumed fall in the population at risk and the total number of falciparum malaria cases.
- It includes targets for interventions such as: proportion of the population at risk covered by vector control interventions, and coverage of volunteers/community health workers.

Risk population

- The population at risk in 2012 estimated on the basis of subnational data reported for WMR 2013 (2012 data).



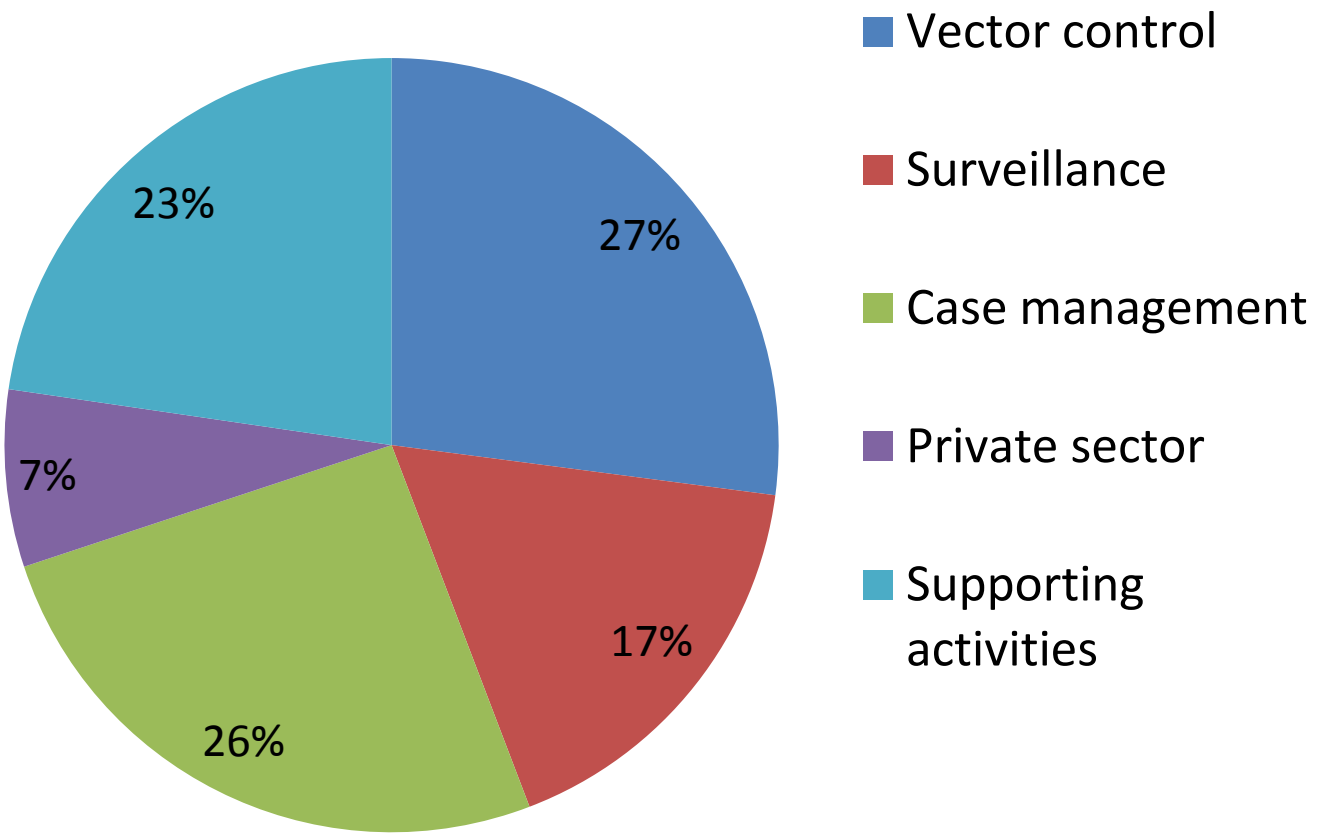
Assumed falls in falciparum cases



Costing scenarios

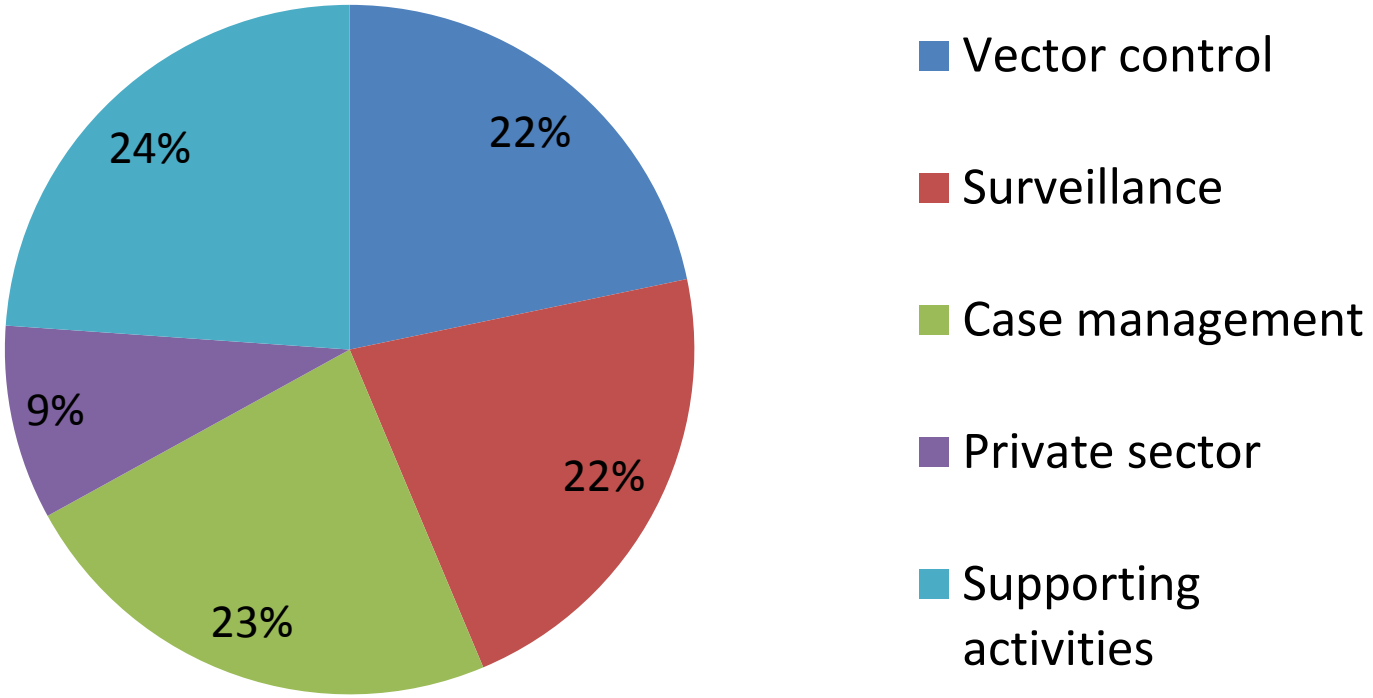
Scenario 1 = $3.9B

- high coverage of LLINs in high and low transmission areas.
- The slower projected fall in cases has been used in this scenario.



Scenario 2 = $3.2B

- high coverage of LLINs in high transmission areas and reduced coverage in low transmission areas with a gradual cost-sharing of CHW along the years as they become multipurpose agents.
- The faster projected fall in cases has been used in this scenario.



Costing TMT

- The cost of screening is estimated to be US$ 500 per village.
- In three countries (Cambodia, Lao PDR and Myanmar) 24,800 villages could potentially be targeted for screening.
- Two scenarios: villages eligible for TMT are 20% or 50% of those screened
- It is estimated that it will cost US$ 20 per person treated for three rounds of treatment and their management

Based on these two scenarios, the total cost for TMT in Cambodia, Lao PDR and Myanmar would be between US$ 82 and 186 million

Costing summary

- Range from an US$ 3.2 to 3.9 billion over 15 years, that is an average of US$ 1.8 to 2.2 per capita for the population at risk of malaria in the GMS per year.
- These costs should be weighed against the epidemiological and economic costs of inaction: According to modelling analysis, the economic impact of multidrug resistance could be in excess of US$ 4 billion annually, due mostly to productivity losses during illness and following deaths.

TEN Recommendations

Leadership

- High level political commitment to inter-country collaboration for health including malaria has been established by ASEAN
- National leadership of this regional elimination effort is essential and depends on national governments working together. **Each country should establish a national malaria elimination commission**
- The essence of leadership is not more governance but more **common spirit**
- WHO's role in the ERAR will be critical for technical guidance, rapid exchange of knowledge and subregional level surveillance
- A joint inclusive governance platform to monitor and coordinate implementation should be agreed upon by all parties involved (e.g. building on the current RAI-RSC)

Better information

- Current information on the burden of disease and its distribution and on malaria control operations is not sufficiently complete, accurate and detailed.
- Better information and analysis on trends over time are needed: Despite progress in micro-stratification, local situational analysis is often not sufficiently detailed to allow differentiation of strategies and approaches.
- In the elimination phase, surveillance systems must include accurate location information for all cases, and malaria should be made a notifiable disease.
- Surveillance should become a core intervention of the national strategies while countries move to elimination. It should gradually come to include not only case detection, but also case management and response.

New partners to address new challenges

- There is considerable potential to expand the breadth and scope of activities by engaging and empowering new partners to carry out specific roles under the coordination of the government authorities.
- This will only work if adequate funds are allocated to these partners to enable them to play their role.
- Reliance on the public sector alone to deliver malaria elimination is not likely to work; yet there is a significant challenge to the public sector as the leader on strategy, policy, planning and evaluation.

Private sector

- Too frequently the private sector is viewed as a problem that needs to be dealt with; it should rather be embraced as an essential partner in the elimination of malaria.
- This includes the private health sector delivering services to the population, the employers of people working in malaria endemic areas, and the producers of commodities for malaria control.
- The nature and scope of private sector engagement will vary across the GMS.

The role of community-based services

- Well-managed community-based health or malaria services have proven to be highly effective
- Community malaria worker networks should be rapidly expanded where needed and properly managed by local health authorities or NGOs
- As malaria incidence becomes very low it will be difficult to maintain workers exclusively dedicated to malaria – they should then become community health workers.
- The introduction of integrated community case management of malaria in some countries should be supported, but in a way that maintains a strong malaria component.

More expert attention needed for migrants, mobile populations, ethnic minorities and militaries

- Smarter and better organized programs to deal with migrants and mobile populations will be needed for elimination
- The best option to reach migrants with services is likely to be through those who already work with them
- Community malaria workers will also be part of the solution

- As malaria reaches very low levels in the region, more attention and support will be needed on the most remote static minority populations; though their numbers may be small, they are likely to be a critical residual source for malaria resurgence
- The military represents another priority population for malaria control because of mobility and deployment to areas where malaria transmission continues

Focus on where the problems are greatest

- Move away from only focusing on artemisinin resistance containment
- Within each country, the elimination strategy should aim for coverage of all areas with *P. falciparum* malaria; prioritisation of intervention areas should be guided by two determinants: multidrug resistance and high burden
- Two areas in the region should be prioritized: the border between Cambodia and Thailand where there is multidrug resistance and the high malaria burden areas in Myanmar
- The ERAR hub will work closely with the GMS countries to formulate their elimination action plans and priorities

Urgent research answers require quick answers

- Research is needed to validate new tools and interventions, including
  - TMT
  - Mass treatment with ivermectin
  - New vector control tools
  - Vaccination
- Most existing research funding mechanisms do not allow rapid disbursement of funds to quickly resolve questions as they arise
- It would be useful to have a moderate-sized rolling fund for urgent research managed by a panel of regional experts on malaria. This could address a mutually agreed set of known research issues as well as new questions as they arise.

Targeting asymptomatic carriers

- Strong vector control intervention will lower onward transmission from asymptomatic as well as symptomatic carrier.
- Targeting asymptomatic carriers to decrease the parasite reservoir can be achieved by TMT
- TMT is an option deserving of further active exploration and evaluation with a view to wider application
- Development and continuous refinement of clear standard operating procedures will be critical as well as training of teams that can oversee local health workers to implement TMT

The GMS is not malaria-free until all GMS countries are

- All countries of the GMS are vulnerable to importation of malaria from another GMS country. The only way to ensure elimination in the subregion is to eliminate malaria in all countries – and then be vigilant to importation from elsewhere.
- A subregional approach is needed that takes into account the malaria reality of each country.
- Myanmar is likely to be the last country of the GMS to be free of malaria. It can Myanmar benefit from lessons learned in the elimination phase in other countries of the GMS.

Conclusion

- The feasibility of malaria elimination raises the further question of “under what assumptions?” Also the inevitable answer “Yes, but only if….”.
- The **technical feasibility** of malaria elimination depends on the continued effectiveness of existing tools, for example in the face of the current threat of multidrug resistant malaria, and the development of new tools that can replace or, more likely, complement current tools. The push for elimination will itself help to limit the impact of multidrug resistance so that the speed and the rigor with which elimination efforts are implemented will themselves impact on technical feasibility.
- **Operational feasibility** depends to a large extent on whether health systems continue to develop in a way that improves their capacity to deliver services and their ability to organize and manage interventions with the scale and quality needed for elimination. This will also depend on the public sector’s willingness to engage with the private sector in service delivery and to seek assistance where needed with management tasks. Sustained high-level political commitment to elimination will be needed to maintain motivation and management of operations.
- **Overall feasibility** depend on financing; so much that insufficient or irregular funding becomes the greatest risk to malaria elimination

GMS countries have experienced an overall decline in cases

- In 2012, **Myanmar** accounted for 77% of the estimated cases in GMS and the regional trends in incidence in recent year have been dominated by the significant reductions in Myanmar since 2011.
- In **Cambodia**, reported malaria cases have also been falling.
- In **Lao**, malaria epidemics among migrant and mobile populations have occurred recently in the southern part of the country.
- In **Thailand**, data from partners working along the border with Myanmar have been included only since 2011 leading to an increase in the total reported cases.
- In **Viet Nam**, the number of cases has been falling but appears relatively stable at a low level.
- The number of deaths has also been falling and as with cases, the majority of estimated deaths occur in Myanmar

Results as per the ESP manual

- The population at risk that would require protection in order to achieve or maintain a prevalence of < 1% in 5–6 years was estimated using the ESP manual in conjunction with the estimates for key parameters in the section above.
- Overall, including those countries with <1% prevalence, **the ESP manual estimates that within the region 30–100% of the population at risk need to be effectively protected to achieve < 1% prevalence within 5–6 years.**
- This wide range reflects both the variability of transmission in the region, but also the limitations of using the tool for countries with such low prevalence rates.

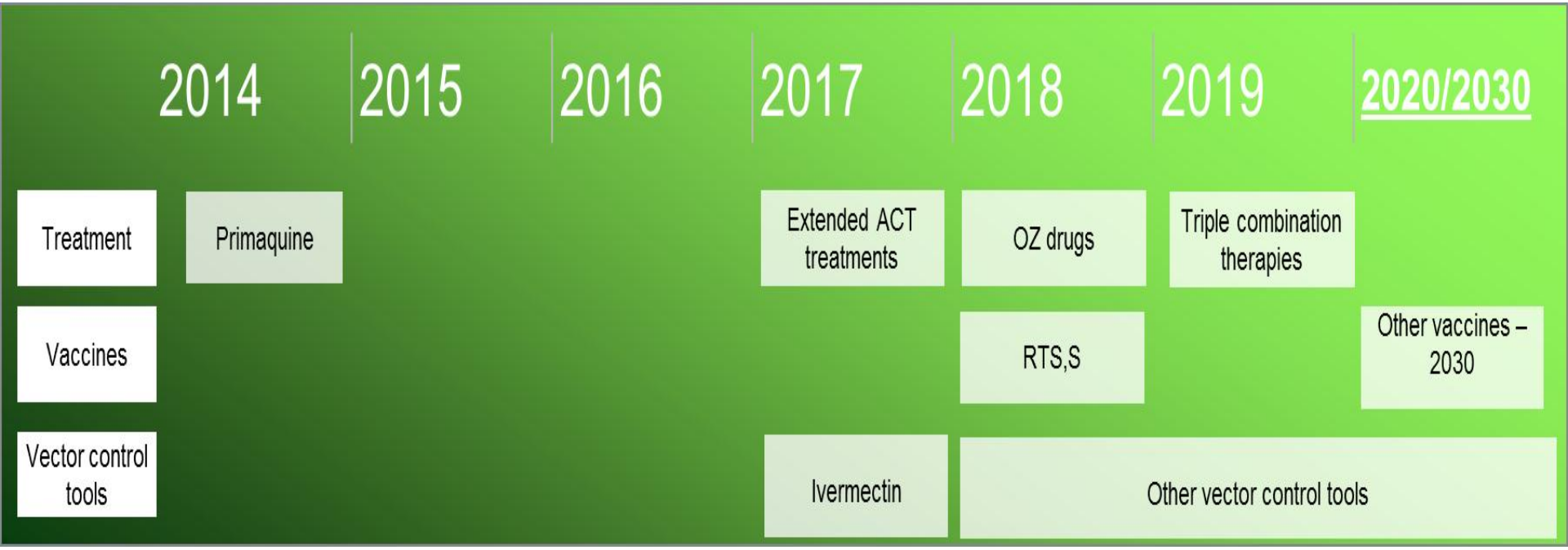
Estimated proportion of the population needing protection to achieve <1% P. falciparum prevalence

Country	Population at risk (millions)	Estimate falciparum malaria prevalence (%)	Fully effective ITN and LLIN coverage (%)	Estimated baseline prevalence prior to any control interventions (%)	Population at risk to be protected to achieve prevalence <1% within 5–6 years (%)
Cambodia	7.9	0.4	30	15	35–40
Yunnan	9.2	0.4	42	21	35–40
Lao PDR	3.9	12.5	73	50	70– 80
Myanmar	31. 7	4.1	20	10–30	30–70
Thailand	33.4	1.1[24]	20	10	30–100
Viet Nam	34	0.6	20	10	30–100
Total	120				

Limitations

- There are major limitations to using this tool, given it is parameterised for use in SSA, which differs significantly from the GMS epidemiological context.
- In addition, given that malaria prevalence is low, in some cases <1%, estimates are not likely to reflect the true situation in GMS.
- Finally, because the manual is parameterised for SSA, it does not take into account the likely reduction in effectiveness of LLINs because of the exophilic nature of vectors in the region.
- We have attempted to address this by estimating the potential reduction in effectiveness (~20%), taking the highest reported reduction in effectiveness from studies in Cambodia. However, the reduction could be greater, because the residual malaria problems occur exactly, where the effectiveness of conventional vector control methods is lowest. Given the diversity of vectors in the region and lack of data or evidence as to the true effectiveness of LLINs this should be considered an estimate only.

Potential timeframe for the development of new treatment, transmission blockers and vector control tools



Leadership & management

Without sustained inspiring leadership malaria elimination will not be possible:

- Prioritizing operations aiming at elimination of falciparum malaria as rapidly as possible
- Contracting out certain malaria control services should also be considered
- Managing malaria elimination activities among mobile and migrant populations may also require the establishment of mobile teams

Leadership and management

- Prevention of re-introduction of malaria to areas where it has been eliminated presents another set of management challenges
- Management of high priority research
- Cross border and inter-country management

Within the GMS, the suggested priorities at regional level are:

- Eliminating (or at least interrupting transmission) in the multidrug resistant area on the border between western Cambodia and eastern Thailand, where resistance is more advanced than anywhere else, and the disease is becoming untreatable;
- Reducing transmission in the high burden areas in Myanmar's eastern northern and western states and regions.

The priorities suggested at country level are:

- Reducing transmission as much as possible in areas of multidrug resistance;
- Flattening the epidemiological landscape by intensified control measures in areas of high transmission (sometimes referred to as hotspots);
- Local analysis may identify additional priorities such as measures targeting certain mobile populations.

Global context

- There is a global push towards refocusing efforts on elimination in countries where this seems within reach.
- The newly developed Global Technical Strategy and Global Malaria Action Plan 2 (still in draft) provides goals and milestones by 2030 for the global move towards a world free of malaria:

Table 1: Global Technical Strategy and Global Malaria Action Plan 2 goals and milestones for malaria elimination

Goals	Milestones		
	2020	2025	2030
To reduce malaria mortality rates globally compared to 2015	40%	75%	90%
To reduce malaria clinical case incidence globally compared to 2015	40%	75%	90%
To eliminate malaria from countries that had transmission in 2015, and ensure prevention of re-establishment in countries that are malaria-free	At least 10 countries	At least 20 countries	At least 30 countries

Elimination Field Manual Update

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 11 September 2014

Richard Cibulskis & Aafje Rietveld
Global Malaria Programme

World Health Organization

GLOBAL MALARIA PROGRAMME

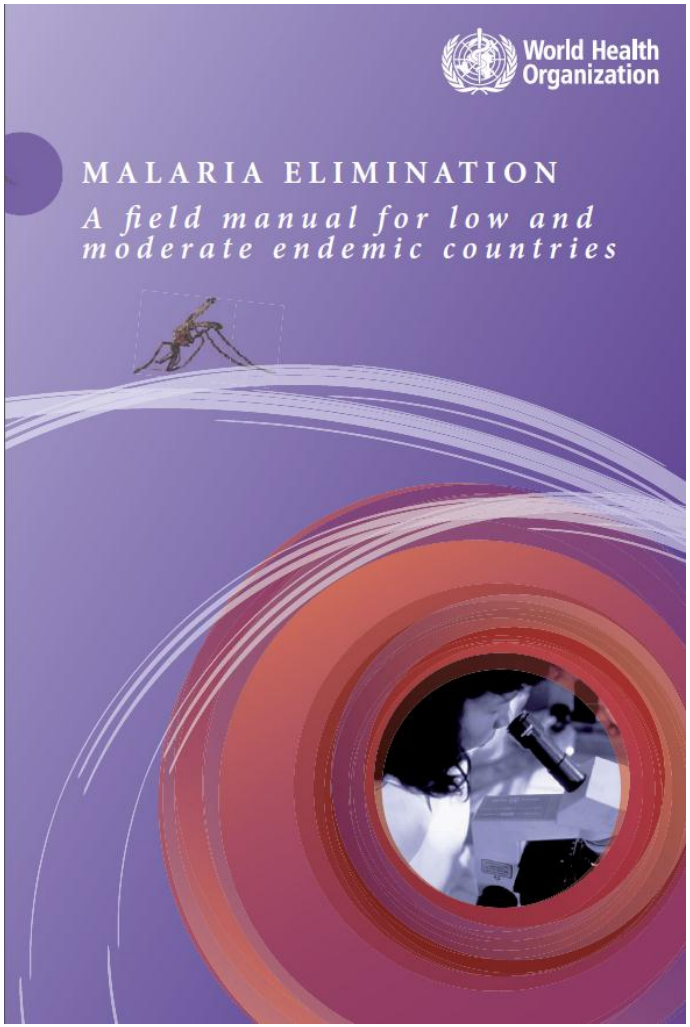
Elimination Field Manual

Produced 2007 to provide guidance on the implementation of effective elimination programmes to:

- NMCPs
- Partner and donor agencies
- Field managers

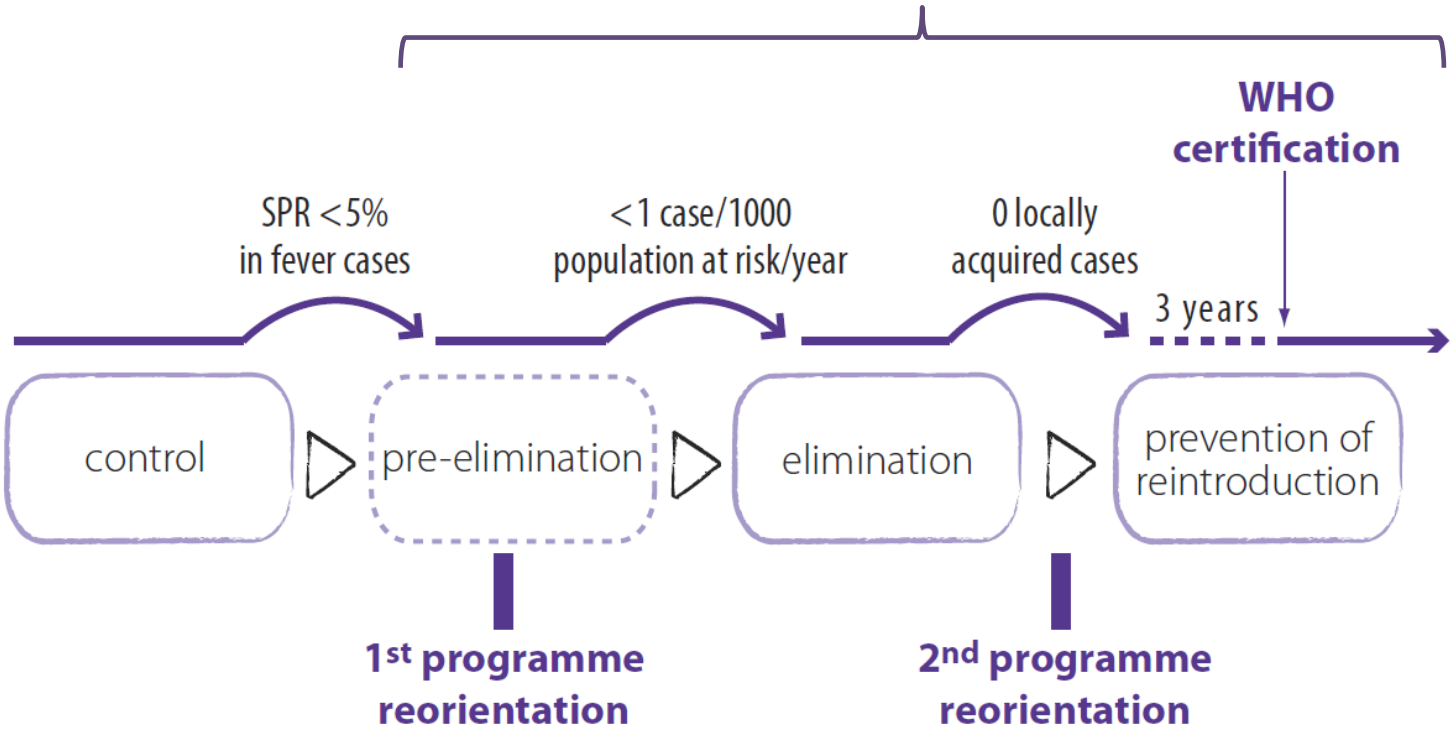
Definitions

- sustainable interruption of local malaria transmission by mosquitoes despite a continued presence of malaria vector mosquitoes and importation
- reduction to zero of the incidence of infection caused by a specified agent in a defined geographical area as a result of deliberate efforts



Programme reorientation in path to elimination

Field Manual



SPR: slide or rapid diagnostic test positivity rate.

[a] These milestones are indicative only: in practice, the transitions will depend on the malaria burden that a programme can realistically handle (including case notification, case investigation, etc.).

Enabling Environment

- Political commitment: official declaration
- Legal/ regulatory framework: malaria a notifiable disease, regulation of anti-malarial medicines
- Specific domestic funding earmarked
- Malaria elimination committee established
- Subnational malaria elimination cooperation strategy in place
- Cross-border agreements in place
- Reorient public and private health staff to the new goal of malaria elimination
- Ensure whole population have access to public or private health care facilities whatever their citizenship or conditions (refugees, displaced, temporary workers etc.)

Programme reorientation in path to elimination

	Pre-elimination	Elimination	Prevention of reintroduction
Malaria situation in areas with most intense transmission			(1) Recently endemic country with zero local transmission for at least three years; or (2) Country on the Register or Supplementary list that has ongoing local transmission*
Test positivity rate	< 5% among suspected malaria patients (PCD) throughout the year		
API in the district with the highest number of cases/1000 population/year (ACD and PCD)**, averaged over the last two years	<5 (less than 5 cases / 1000 population)	<1 (less than 1 case / 1000 population)	
Total number of reported malaria cases nationwide		A manageable number, e.g. <1000 cases nationwide (local & imported)	
Case management			Imported malaria. Maintain capacity to detect malaria infection and manage clinical disease
All cases detected in the private sector are microscopically confirmed	National policy being rolled out	Yes	Yes
All cases detected in the public sector are microscopically confirmed	National policy being rolled out	Yes	Yes
Nationwide microscopy quality assurance system covers public and private sector	Initiated	Yes	Yes
Radical treatment with primaquine for *P. vivax*	National policy being updated	National policy fully implemented	Yes
Treatment with ACT plus single dose primaquine for *P. falciparum*	National policy being updated	National policy fully implemented	Yes
Surveillance			Vigilance by the general health services
Malaria is a notifiable disease nationwide (<24–48 hrs)	Laws and systems being put in place	Yes	Yes
Centralized register on cases, foci and vectors	Initiated	Yes	Yes
Malaria elimination database	Initiated	Yes	Certification process (optional)
Active case detection in groups at high risk or with poor access to services ("pro-active" case detection)	Initiated	Yes	In residual and cleared-up foci; among high risk population groups
Case and foci investigation & classification (including "reactive" case detection and entomological investigation)	Initiated	Yes	Yes

* Ongoing local transmission = 2 consecutive years of local *P. falciparum* malaria transmission; or 3 consecutive years of local *P. vivax* malaria transmission in the same locality or otherwise epidemiologically linked.

** The API has to be evaluated against the diagnostic activity in the risk area (measured as the ABER). Low values of ABER in a district raise the possibility that more cases would be found with improved diagnostic efforts.

Programme reorientation in path to elimination

	Pre-elimination	Elimination	Prevention of reintroduction
Malaria situation in areas with most intense transmission			(1) Recently endemic country with zero local transmission for at least three years; or (2) Country on the Register or Supplementary list that has ongoing local transmission*
Test positivity rate	< 5% among suspected malaria patients (PCD) throughout the year		
API in the district with the highest number of cases/1000 population/year (ACD and PCD)**, averaged over the last two years	<5 (less than 5 cases / 1000 population)	<1 (less than 1 case / 1000 population)	
Total number of reported malaria cases nationwide		A manageable number, e.g. <1000 cases nationwide (local & imported)	

* Ongoing local transmission = 2 consecutive years of local *P. falciparum* malaria transmission; or 3 consecutive years of local *P. vivax* malaria transmission in the same locality or otherwise epidemiologically linked.

** The API has to be evaluated against the diagnostic activity in the risk area (measured as the ABER). Low values of ABER in a district raise the possibility that more cases would be found with improved diagnostic efforts.

Programme reorientation in path to elimination

	Pre-elimination	Elimination	Prevention of reintroduction
Case management			Imported malaria. Maintain capacity to detect malaria infection and manage clinical disease
All cases detected in the private sector are microscopically confirmed	National policy being rolled out	Yes	Yes
All cases detected in the public sector are microscopically confirmed	National policy being rolled out	Yes	Yes
Nationwide microscopy quality assurance system covers public and private sector	Initiated	Yes	Yes
Radical treatment with primaquine for *P. vivax*	National policy being updated	National policy fully implemented	Yes
Treatment with ACT plus single dose primaquine for *P. falciparum*	National policy being updated	National policy fully implemented	Yes
Surveillance			Vigilance by the general health services
Malaria is a notifiable disease nationwide (<24–48 hrs)	Laws and systems being put in place	Yes	Yes
Centralized register on cases, foci and vectors	Initiated	Yes	Yes
Malaria elimination database	Initiated	Yes	Certification process (optional)
Active case detection in groups at high risk or with poor access to services ("pro-active" case detection)	Initiated	Yes	In residual and cleared-up foci; among high risk population groups
Case and foci investigation & classification (including "reactive" case detection and entomological investigation)	Initiated	Yes	Yes

Advice sought

- Are there gaps in guidance in the Field Manual that need to be addressed in light of the GTS?
- Should the scope of manual be expanded – lower transmission countries in control phase?
- Ways forward: To create an Evidence Review Group?

	Pre-elimination	Elimination	Prevention of reintroduction
Malaria situation in areas with most intense transmission			(1) Recently endemic country with zero local transmission for at least three years; or (2) Country on the Register or Supplementary list that has ongoing local transmission*
Test positivity rate	< 5% among suspected malaria patients (PCD) throughout the year		
API in the district with the highest number of cases/1000 population/year (ACD and PCD)**, averaged over the last two years	<5 (less than 5 cases / 1000 population)	<1 (less than 1 case / 1000 population)	
Total number of reported malaria cases nationwide		A manageable number, e.g. <1000 cases nationwide (local & imported)	
Case management			Imported malaria. Maintain capacity to detect malaria infection and manage clinical disease
All cases detected in the private sector are microscopically confirmed	National policy being rolled out	Yes	Yes
All cases detected in the public sector are microscopically confirmed	National policy being rolled out	Yes	Yes
Nationwide microscopy quality assurance system covers public and private sector	Initiated	Yes	Yes
Radical treatment with primaquine for *P. vivax*	National policy being updated	National policy fully implemented	Yes
Treatment with ACT plus single dose primaquine for *P. falciparum*	National policy being updated	National policy fully implemented	Yes
Surveillance			Vigilance by the general health services
Malaria is a notifiable disease nationwide (<24–48 hrs)	Laws and systems being put in place	Yes	Yes
Centralized register on cases, foci and vectors	Initiated	Yes	Yes
Malaria elimination database	Initiated	Yes	Certification process (optional)
Active case detection in groups at high risk or with poor access to services ("pro-active" case detection)	Initiated	Yes	In residual and cleared-up foci; among high risk population groups
Case and foci investigation & classification (including "reactive" case detection and entomological investigation)	Initiated	Yes	Yes

* Ongoing local transmission = 2 consecutive years of local *P. falciparum* malaria transmission; or 3 consecutive years of local *P. vivax* malaria transmission in the same locality or otherwise epidemiologically linked.

** The API has to be evaluated against the diagnostic activity in the risk area (measured as the ABER). Low values of ABER in a district raise the possibility that more cases would be found with improved diagnostic efforts.

Contents

Proposal for an Evidence Review Group on MDA, MSAT and FSAT

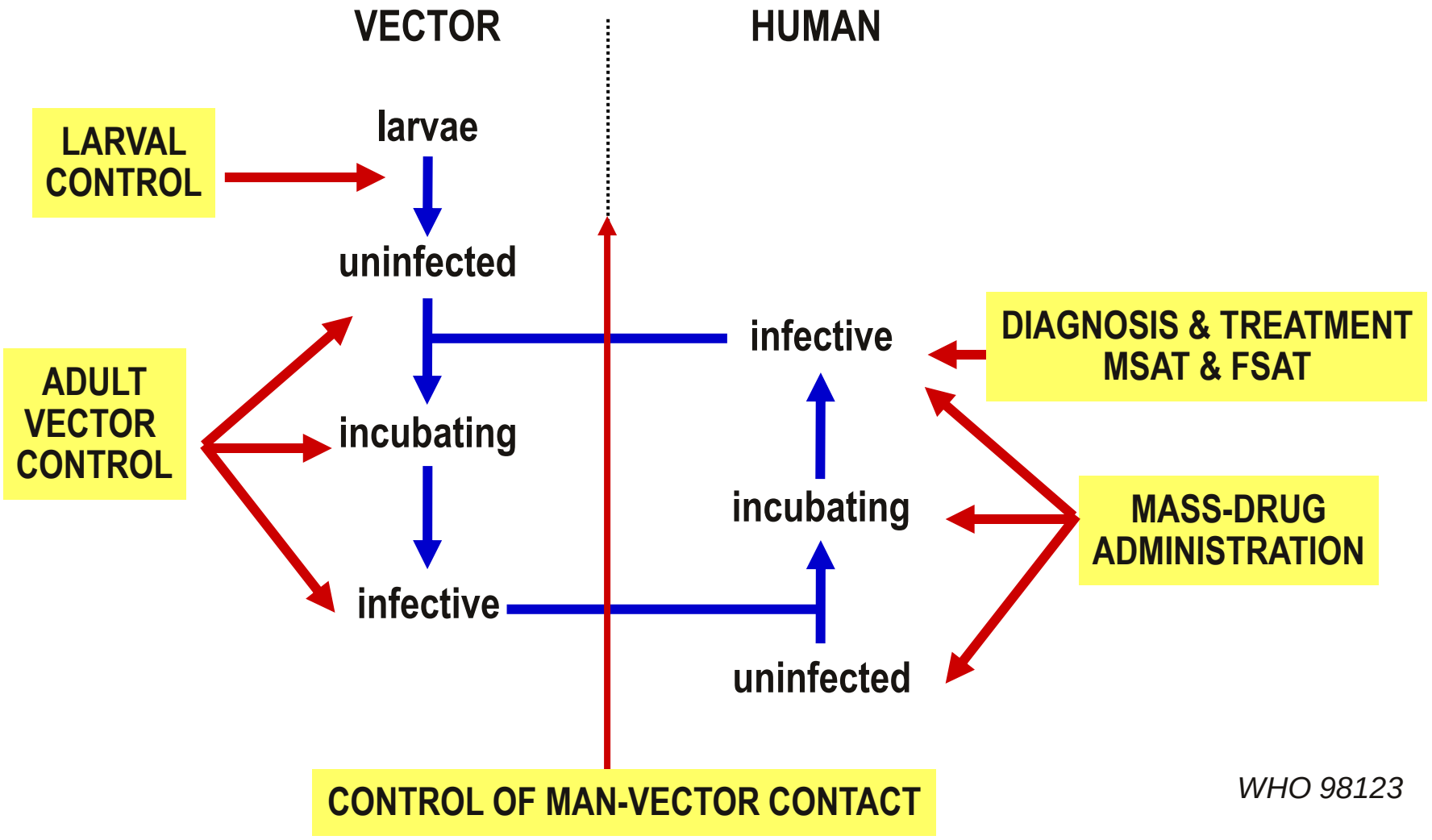
Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 11 September 2014

Dr A. Bosman and Dr P. Ringwald

World Health Organization

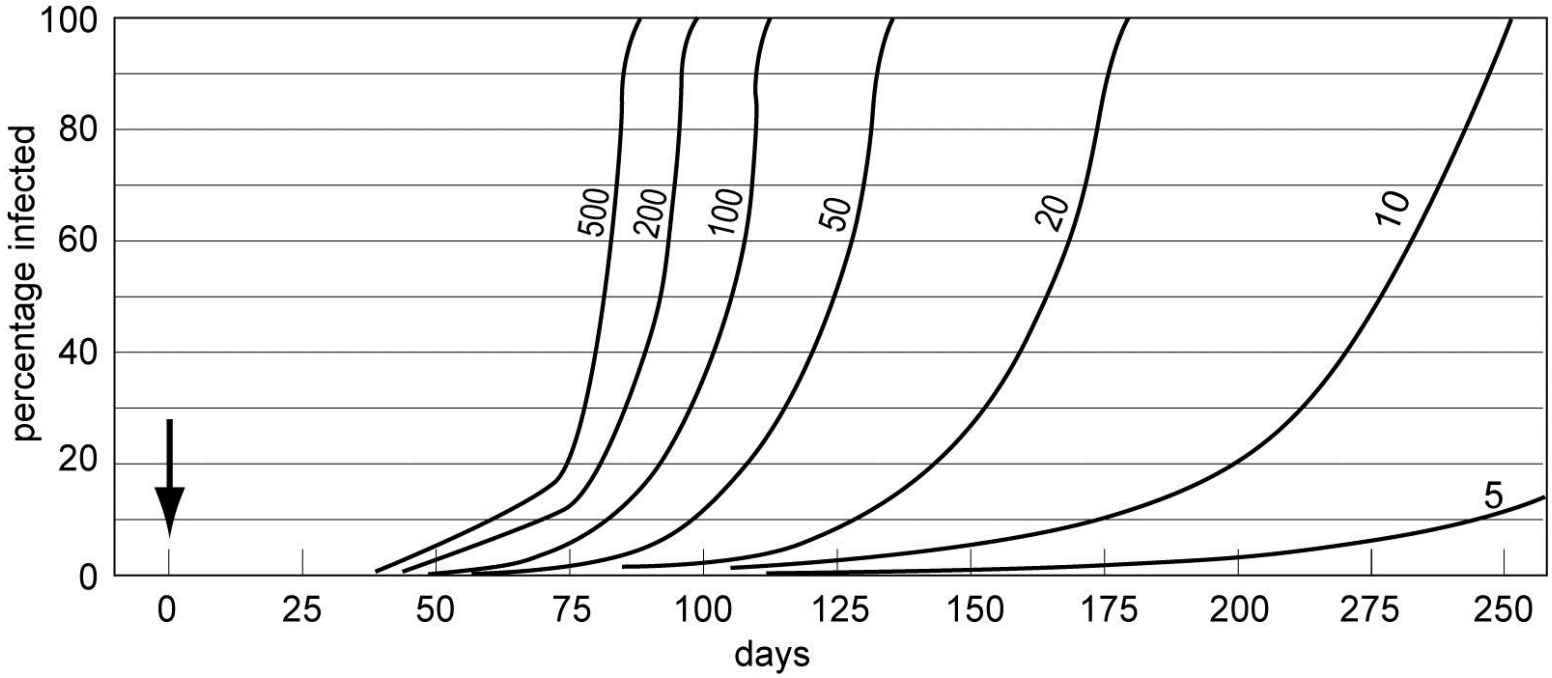
GLOBAL MALARIA PROGRAMME

Impact of MDA, MSAT and FSAT on malaria transmission



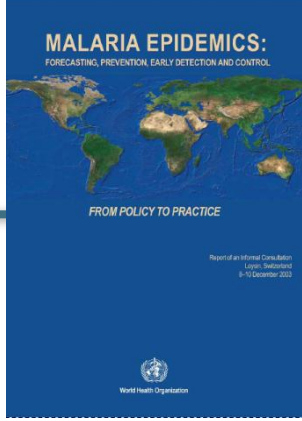
WHO 98123

Resilience of malaria transmission



The curves show probable growth of falciparum infection rates in epidemics assuming primary cases at time 0 (arrow) as 0.1 per cent of the population with falciparum infection, an incubation interval of 35 days, under the influence of different reproduction rates for malaria. (Adapted from the *Bulletin of the World Health Organization*, 1956, vol. 15:380)

Current WHO recommendations



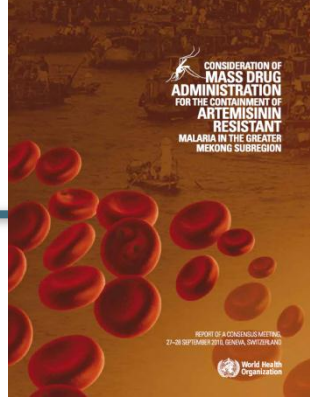
MDA – mass treatment of all, or a large section, of the population whether symptoms are present or not

Based on the review of results of 19 MDA projects during the period 1932–1999 by von Seidlein and Greenwood [1] and a Technical Consultation held in 2003 [2] , WHO concluded that there is little evidence that MDA is effective in reducing transmission although reduction in parasite prevalence and transient reduction in mortality and morbidity have been documented in some cases.

1 von Seidlein L, Greenwood BM (2003). Mass administration of antimalarial drugs. *Trends in Parasitology, 19*: 452–460.

2 Malaria epidemics: forecasting, prevention, early detection and control From policy to practice. Report of a WHO Informal Consultation, 8–10 December 2003.

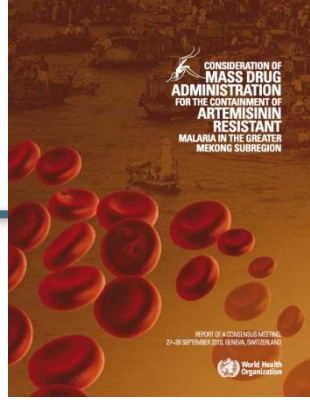
Current WHO recommendations



In 2010 a WHO consultation [3] reviewed the potential role of MDA in the context of artemisinin resistance in the Greater Mekong subregion based on evidence of impact of existing interventions, operational and modelling considerations. The consultation recommended immediate planning of a pilot MDA operation in western Cambodia or eastern Thailand and the collection of essential information on the safety and efficacy of the candidate drugs for MDA.

[3] Consideration of mass drug administration for the containment of artemisinin resistant malaria in the Greater Mekong Subregion. Report of a WHO consensus meeting, 2010.

Current WHO recommendations



- The same consultation also reviewed the role of mass screening and treatment (MSAT/FSAT – people in a broad/defined geographic area are screened, regardless of whether they have symptoms of malaria, providing treatment for those who test positive).
- MSAT generates important information on the epidemiology of malaria that can be useful for further containment efforts, but it is resource-intensive and logistically challenging - lack of field-ready, high-throughput, highly sensitive diagnostic tests.
- FSAT operationally more feasible than MSAT, this is not delivered in all villages simultaneously, and, therefore, it is unlikely to contribute significantly in elimination efforts.
- The contribution of MSAT and FSAT effective in reducing transmission needs to be confirmed.

Background

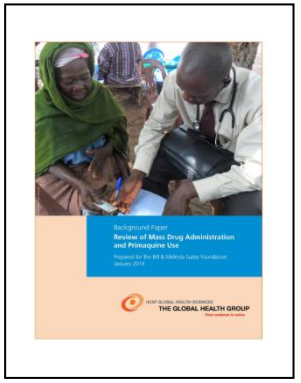
- A recent systematic review [4] of 32 studies assessed MDA in areas with different endemicity, with different medicines and dosages, different timings and number of rounds and concomitant implementation of vector control measures. The review concluded that MDA appears to quickly reduce malaria parasitaemia and several clinical outcomes, but more studies are required to assess its impact after 6 months, the barriers for community uptake and the potential contribution to the development of drug resistance.

The Cochrane Collaboration
Trusted evidence. Informed decisions. Better health.

4. Poirot et al., Mass drug administration for malaria. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD008846. DOI: 10.1002/14651858.CD008846.pub2.

Background (continued)

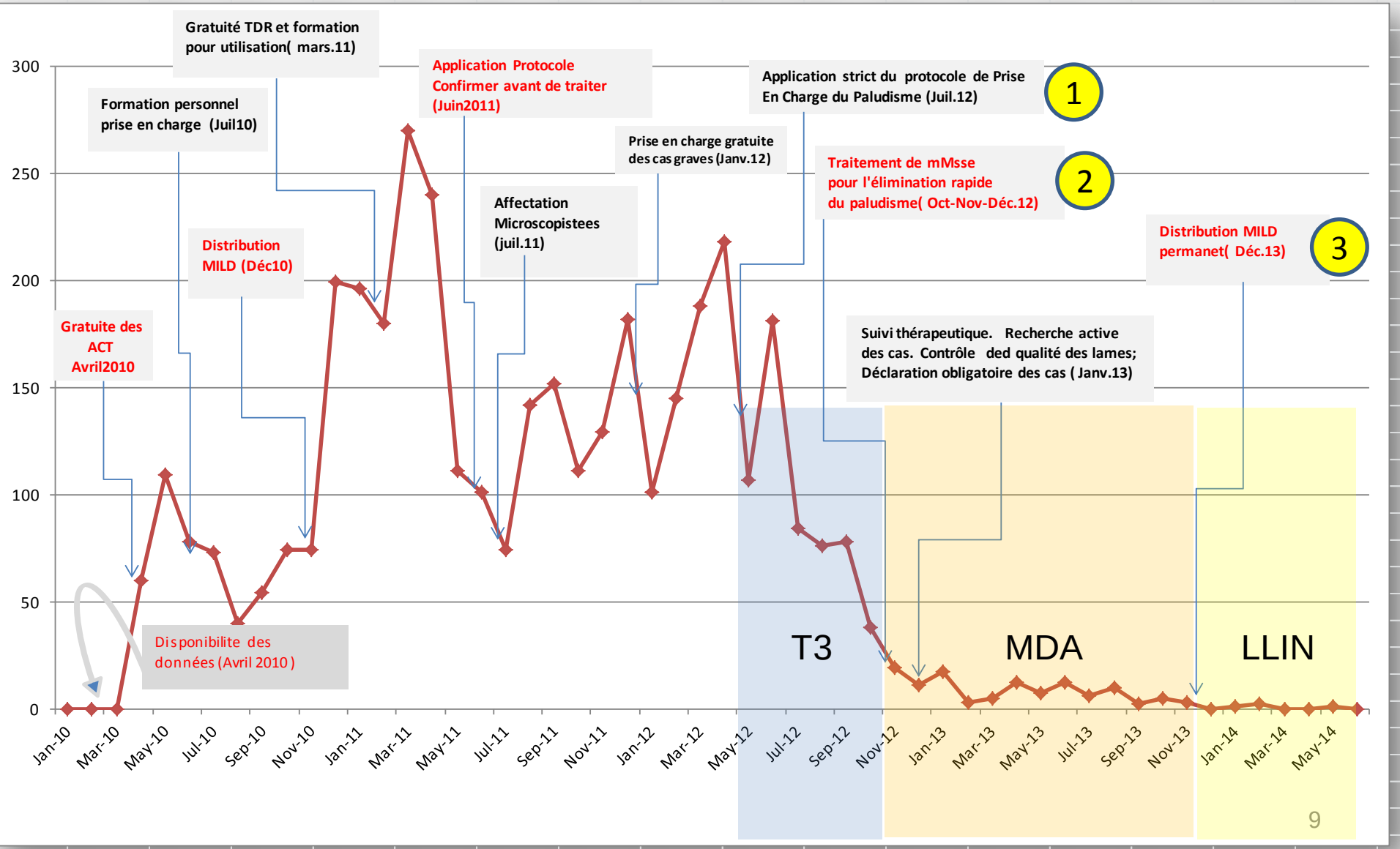
- A subsequent review of the literature [5], including unpublished studies, identified 12 MDA studies demonstrating zero indigenous malaria cases in the target population maintained over six months after the end of drug administration.



- Over the last few years implementation research on MDA and FSAT have been conducted in Cambodia , and in other countries for which results are not yet in the public domain (e.g. FEMSE in Comoros, MDA in Zanzibar, MSAT in Zambia and MDA at Thai-Myanmar border).

5. UCSF Global Health Sciences. Review of mass drug administration and primaquine use: background paper prepared for the Bill & Melinda Gates Foundation, 2014 (unpublished document).

Impact of T3, MDA and LLINs in Anjouan Island (Comoros)
Malaria reported cases: April 2010 – Dec 2013



ERG preliminary list of questions (1- 4)

1. Is there evidence of impact on malaria transmission at six month and one year following implementation of MDA, MSAT and FSAT?
2. What are the key determinants of "durable impact" on malaria of MDA, MSAT and FSAT?
3. What are the optimal conditions for application of MDA, MSAT and FSAT to reduce malaria transmission in terms of endemicity levels, combination of medicines and dosages, use of diagnostics, timings and number of MDA rounds, concomitant deployment of vector control interventions, IEC and pharmacovigilance?
4. What are the major limitations and challenges faced by multiple groups in the successful application of MDA, MSAT and FSAT to reduce malaria transmission?

ERG preliminary list of questions (5 – 8)

5. What is the specific role of MDA, MSAT and FSAT in the advanced phase of malaria elimination?
6. What is the specific role of MDA, MSAT and FSAT for the elimination of artemisinin resistant falciparum malaria?
7. What are the main knowledge gaps and what data need to be collected to recommend wider deployment of MDA, MSAT and FSAT as part of initiatives to reduce malaria transmission?
8. Which of methodological aspects and ethical requirements need to be considered by research groups and national ethical review boards for planning and assessment of studies on the durable impact of MDA, MSAT and FSAT on malaria transmission?

Discussion points for MPAC

- Refine ERG questions to be addressed
- Systematic reviews, and recent unpublished studies to be reviewed
- Methodological aspects and timing of ERG
  (tentative: 8-10 December 2014)
- Investigators/programme managers to include as presenters and reviewers
- Co-Chairpersons (from MPAC members) and Rapporteurs
- AOB

Proposal for an Evidence Review Group on MDA, MSAT & FSAT*

Dr A. Bosman and Dr P. Ringwald

Short summary of current WHO recommendations

Mass drug administration (MDA – mass treatment of all, or a large section, of the population whether symptoms are present or not) has been implemented by malaria control programs in the past, as a way of controlling epidemics most often in conjunction with insecticide residual spraying. Based on the review of results of 19 MDA projects during the period 1932–1999 by von Seidlein and Greenwood [1] and a Technical Consultation held in 2003,[2] WHO concluded that there is little evidence that MDA is effective in reducing transmission although reduction in parasite prevalence and transient reduction in mortality and morbidity have been documented in some cases. Mass treatment of symptomatic febrile patients was recommended for epidemic and complex emergency situations, with active search for febrile patients to ensure that as many cases are treated.

This intervention has received renewed interest over the last decade in the context of malaria elimination initiatives and as part of artemisinin resistance containment efforts. In 2010 a WHO consultation reviewed the potential role of MDA in the context of artemisinin resistance in the Greater Mekong subregion based on evidence of impact of existing interventions, operational and modelling considerations.[3] The consultation recommended immediate planning of a pilot MDA operation in western Cambodia or eastern Thailand and the collection of essential information on the safety and efficacy of the candidate drugs for MDA.

The consultation also reviewed the potential role of mass screening and treatment (MSAT – all the people in a broad geographic area are screened, regardless of whether they have symptoms of malaria). While MSAT generates important information on the epidemiology of malaria that can be useful for further containment efforts, this approach is resource-intensive and logistically challenging, especially in view of the lack of a field-ready, high-throughput, highly sensitive diagnostic test. The strategy, when applied in a defined geographical area is named focused screening and treatment (FSAT – screening all the people in a defined geographical area and providing treatment for those who test positive). While operationally more feasible than MSAT, this is not delivered in all villages simultaneously, and, therefore, it is unlikely to contribute significantly in elimination efforts. The contribution of MSAT and FSAT effective in reducing transmission needs to be confirmed.

Background and Rationale

A recent systematic review of MDA has been published including areas with different endemicity, various medicines and dosages, different timings and number of MDA rounds and concomitant

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* This document was prepared as a pre-read for the September 2014 meeting of the Malaria Policy Advisory Committee (MPAC) and is not an official document of the World Health Organization.

1. von Seidlein L, Greenwood BM (2003). Mass administration of antimalarial drugs. *Trends in Parasitology, 19*: 452–460.

2. Malaria epidemics: forecasting, prevention, early detection and control From policy to practice. Report of a WHO Informal Consultation, 8–10 December 2003.
(http://whqlibdoc.who.int/hq/2004/WHO_HTM_MAL_2004.1098.pdf)

3. Consideration of mass drug administration for the containment of artemisinin resistant malaria in the Greater Mekong Subregion. Report of a WHO consensus meeting, 2010.
(http://whqlibdoc.who.int/publications/2011/9789241501644_eng.pdf)

implementation of vector control measures.[4] The review concluded that MDA appears to quickly reduce malaria parasitaemia and several clinical outcomes, but more studies are required to assess its impact after 6 months, the barriers for community uptake and the potential contribution to the development of drug resistance. A subsequent review of the literature, including unpublished studies, identified 12 MDA studies with follow-up periods of greater than six months showing zero indigenous malaria cases in the target population maintained over six months after the end of drug administration.[5] Over the last few years implementation research on MDA and FSAT have been conducted in Cambodia [6] [7], and in other countries for which results are not yet in the public domain (e.g. FEMSE [8] in Comoros, MDA in Zanzibar, MSAT in Zambia and MDA at Thai-Myanmar border).

There is continuous interest by national malaria control programmes on the potential role of MDA, MSAT and FAST for malaria elimination, and growing interest of the scientific community and major funders for potential role of MDA in combination with other interventions also in areas with moderate-to-high transmission.[9] The availability of new evidence on impact and operational requirements in different epidemiological situations from unpublished studies provides an opportunity to extract lessons and define further guidance for policy makers and research groups which are investing in the evaluation of these interventions.

In view of the above and of the urgency of implementing cost-effective interventions for elimination of artemisinin-resistant falciparum malaria, WHO/GMP is proposing to the Malaria Policy Advisory Committee to establish and Evidence Review Group (ERG) on the role of MDA, MSAT and FSAT for malaria transmission reduction and elimination.

Objectives of the Evidence Review Group

The ERG could be held on 8-10 December 2014 with the following objectives:

a) review all available published and unpublished reports on the impact of MDA, MSAT and FSAT on malaria transmission, building on the most recent Cochrane Review;

b) review results of experiences/unpublished studies of large-scale implementation of MDA in Comoros, at the Thai-Myanmar border and Zanzibar, of MSAT in Zambia and other relevant initiatives;

c) evaluate the role of concomitant administration of low-dose primaquine (0.25 mg base/kg) as gametocytocide of *P. falciparum* together with the ACT deployed for MDA;

d) define the specific conditions of application of MDA, MSAT and FSAT to reduce malaria transmission in terms of endemicity, medicines and dosages, diagnostics, timings and number of MDA rounds, concomitant implementation of vector control measures and best strategies to ensure community uptake and pharmacovigilance;

e) identify research gaps and provide recommendations on data requirements, study methods and ethical considerations for research groups and policy makers interested in further evaluating the role of MDA, MSAT and FSAT in reducing malaria transmission.

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4. Poirot et al., Mass drug administration for malaria. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD008846. DOI: 10.1002/14651858.CD008846.pub2.
5. UCSF Global Health Sciences. *Review of mass drug administration and primaquine use: background paper prepared for the Bill & Melinda Gates Foundation*, 2014 (unpublished document).
6. Song. et al., Rapid and effective malaria control in Cambodia through mass administration of artemisinin-piperaquine. *Malaria Journal* 2010, 9:57
7. Hoyer et al., Focused Screening and Treatment (FSAT): A PCR-based strategy to detect malaria parasite carriers and contain drug resistant *P. falciparum*, Pailin, Cambodia. *PLOS ONE* 2012, e45797
8. Fast Elimination of Malaria by Eradicating Source (FEMSE)
9. http://www.irinnews.org/report/100365/kenya-to-pilot-community-wide-malaria-treatments

WHO/GMP secretariat is proposing that the ERG will be convened to develop draft recommendations on the impact of MDA, MSAT and FSAT on malaria transmission for review and endorsement by the MPAC in March 2015.

Proposed questions to be addressed by the Evidence Review Group

1. Is there evidence of impact on malaria transmission at six month and one year following implementation of MDA, MSAT and FSAT in endemic settings?
2. What are the key determinants of positive impact on malaria transmission at six month and one year following implementation of MDA, MSAT and FSAT?
3. What are the optimal conditions for application of MDA, MSAT and FSAT to reduce malaria transmission in terms of endemicity levels, combination of medicines and dosages, use of diagnostics, timings and number of MDA rounds, concomitant deployment of vector control interventions, IEC and pharmacovigilance?
4. What are the major limitations and challenges faced by multiple groups for the successful application of MDA, MSAT and FSAT to reduce malaria transmission?
5. What is the specific role of MDA, MSAT and FSAT in the advanced phase of malaria elimination?
6. What is the specific role of MDA, MSAT and FSAT for the elimination of artemisinin resistant falciparum malaria?
7. What are the key gaps in knowledge and what data need to be available for review to enable a wider deployment of MDA, MSAT and FSAT as part of initiatives aiming at malaria transmission reduction ?
8. Which of methodological aspects and ethical requirements need to be considered by research groups and national ethical review boards for the preparation and assessment of studies on the durable impact of MDA, MSAT and FSAT on malaria transmission?

Suggested timetable

i. September 2014: identify ERG members and contact researcher(s) to present evidence to ERG
ii. October: compile and analyse recent literature (including grey literature)
iii. October-November: preparation of short reports of recent/ongoing studies
iv. End November: dissemination of pre-reads to ERG members
v. December: meeting of ERG
vi. January –February 2015: finalization of ERG meeting report
vii. End February: sharing ERG meeting report with MPAC members
viii. March 2015: present outcome of ERG review to MPAC

Declaration of Interests

All ERG members to complete a DoI form which will be evaluated by WHO Secretariat and the summary of the assessment included in the ERG report and published on the MPAC website for public record.

WHO-FIND Malaria RDT Evaluation Programme: Product Testing Round 5

Malaria Policy Advisory Committee Meeting
WHO HQ Geneva, 11 September 2014

Jane Cunningham
Global Malaria Programme

World Health Organization

Global Malaria Programme

Overview

- **Background**
- **Overview of Product testing process**
- **Round 5 results – what's new ?**
- **WHO procurement criteria**
- **Market trends and impact on manufacturers**
- **Future**
  - Product testing and lot testing based on recombinant Ag panels

Field trials are expensive, not possible across many products, specific in time and population

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chinkhumba 2010	481	464	26	346	0.95 [0.93, 0.97]	0.43 [0.39, 0.46]
Ishengoma 2011	3343	1695	436	12739	0.88 [0.87, 0.89]	0.88 [0.88, 0.89]
Lemma 2011a	402	114	51	1855	0.89 [0.85, 0.92]	0.94 [0.93, 0.95]
Lemma 2011b	377	97	76	1872	0.83 [0.79, 0.87]	0.95 [0.94, 0.96]
Mubi 2011	282	442	48	657	0.85 [0.81, 0.89]	0.60 [0.57, 0.63]
Premji 1994	213	24	40	103	0.84 [0.79, 0.88]	0.81 [0.73, 0.88]
Ratsimbaosa 2012	94	12	4	80	0.96 [0.90, 0.99]	0.87 [0.78, 0.93]
Tiono 2013	276	109	6	125	0.98 [0.95, 0.99]	0.53 [0.47, 0.60]

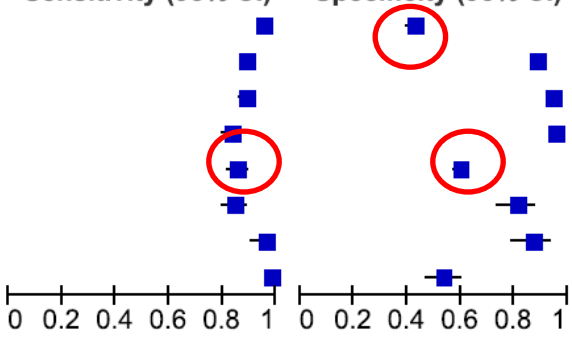
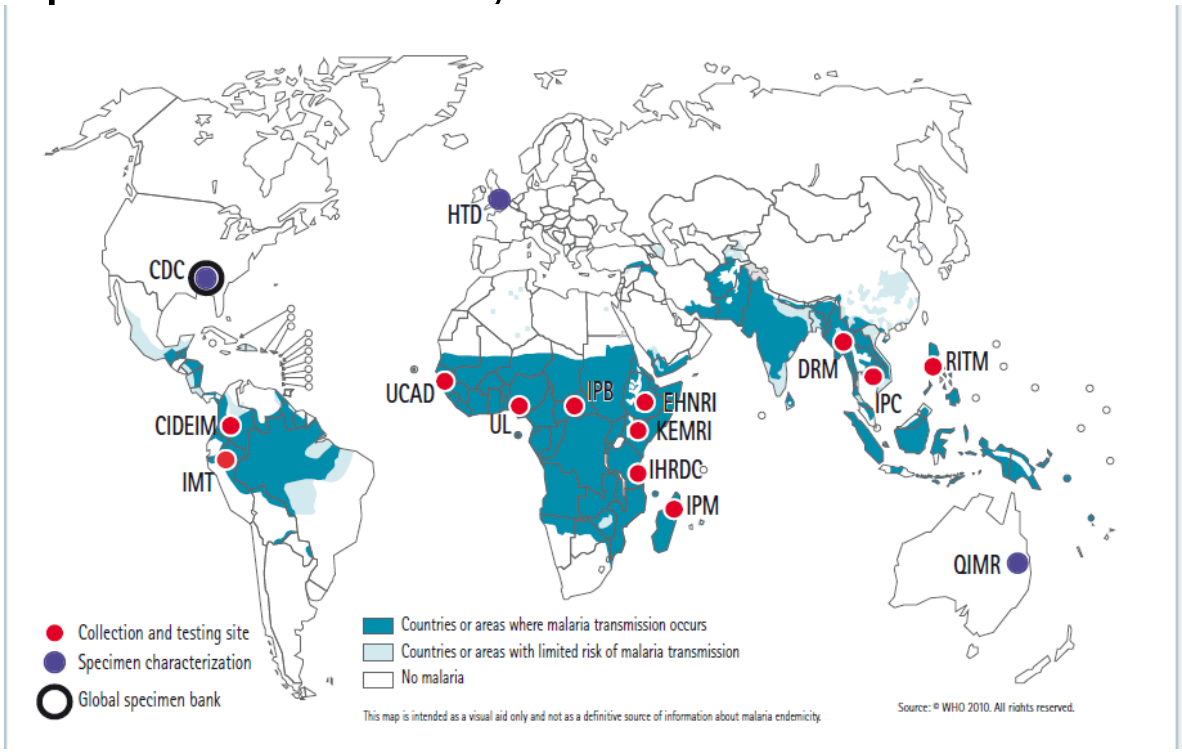


Figure 10 Forest plot of RDT performance when performed by CHWs (no subgroup analyses). Lemma 2011a = Paracheck Pf, Lemma 2011b = Parascreen pan/p.

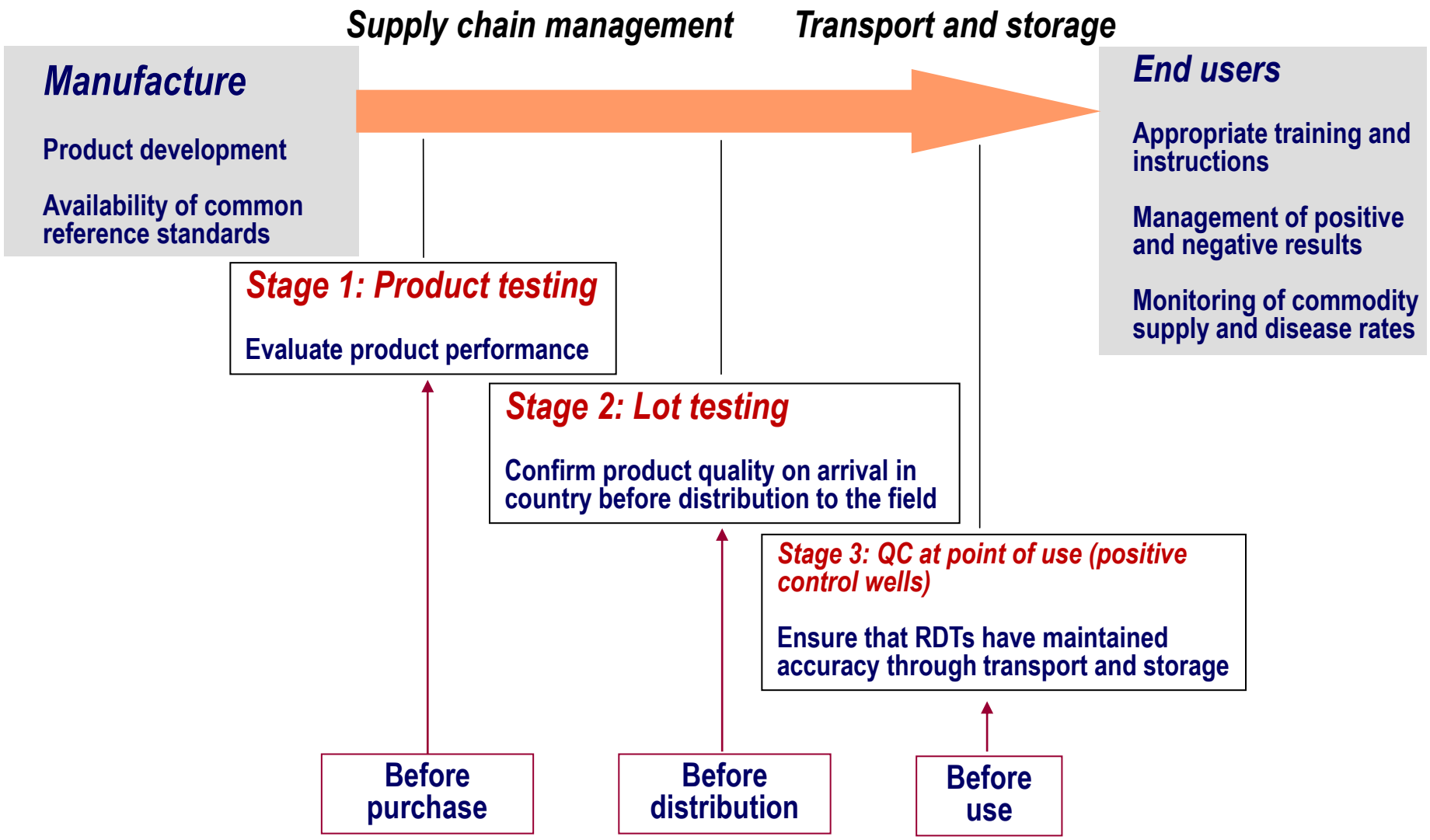
200+ malaria RDT in the market; 60+ manufacturers)

International collaboration

- Between 2002-2008, WHO, TDR, FIND, US CDC and other partners developed methods, characterized (microscopy, PCR, ELISA), diluted and stored wild type *P. falciparum* and *P.vivax* clinical samples from Africa, South America and South East Asia

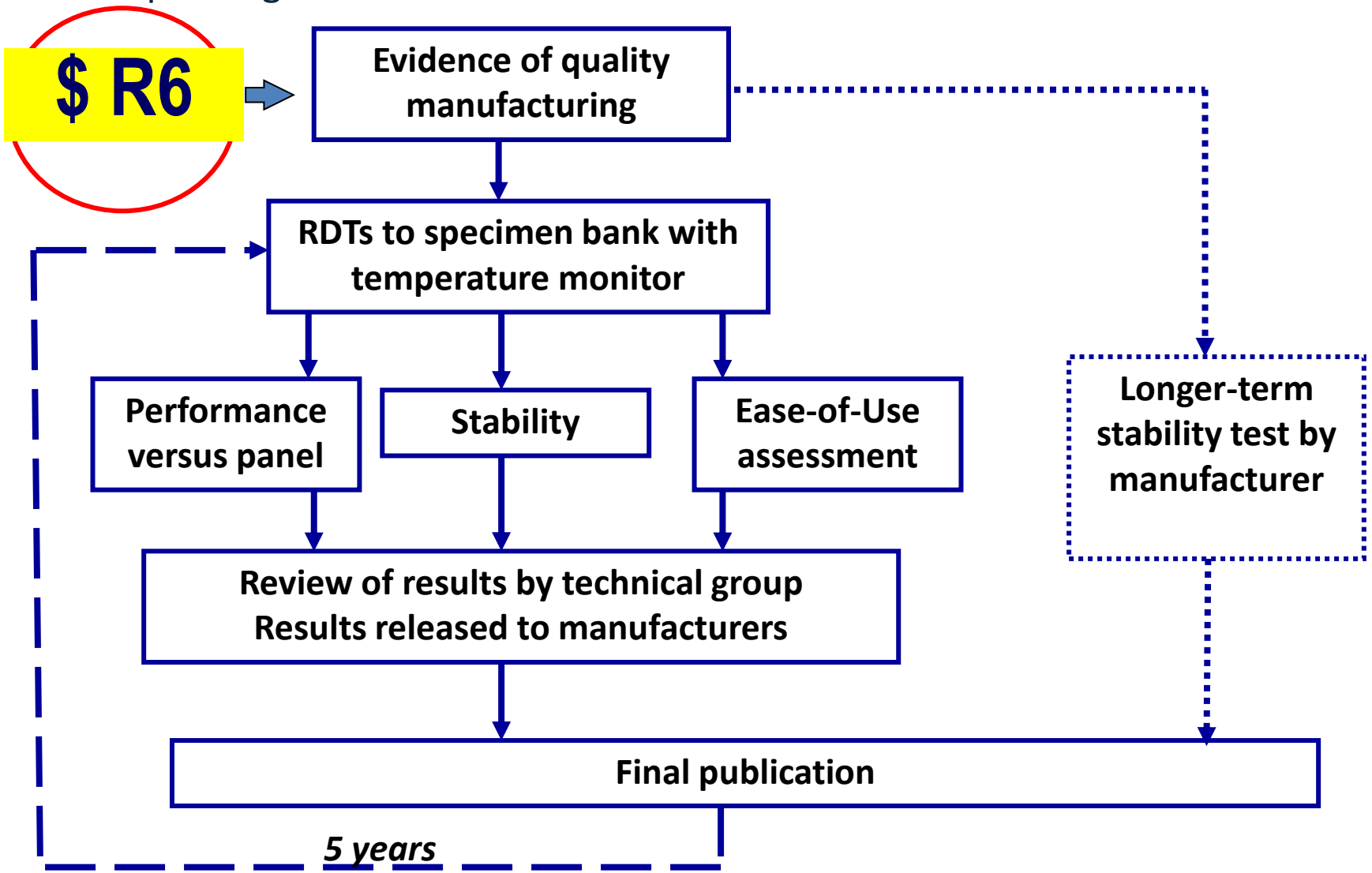


WHO-FIND strategy for QA of RDT-based diagnosis



Current Product Testing

Comparative evaluation of commercially-available antigen-detecting malaria rapid diagnostic tests – RDTs.



Product Testing (at US CDC)

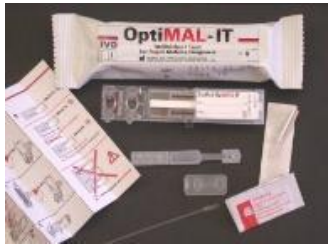
- **Performance** – panel detection score, false-positive and invalid rates
  - Phase 1 – 20 cultured *P.falciparum* samples; 2 lots; 1 RDT/lot @2000p/µl ; 2 RDT/lot @ 200p/µl + 20 clean negative samples in R6
  - Phase 2
    - *P.falciparum* (100), *P.vivax* (35), 2 lots; 1 RDT/lot @2000p/µl ; 2 RDT/lot @ 200p/µl
    - 1000 negative samples (mixed clean and other disease conditions)
- **Heat stability** (4°C, 35°C, 45°C; 75% humidity x 60 days)
- **Ease of use assessment**
  - blood safety, instructions quality, no. timed steps, RDT anomalies

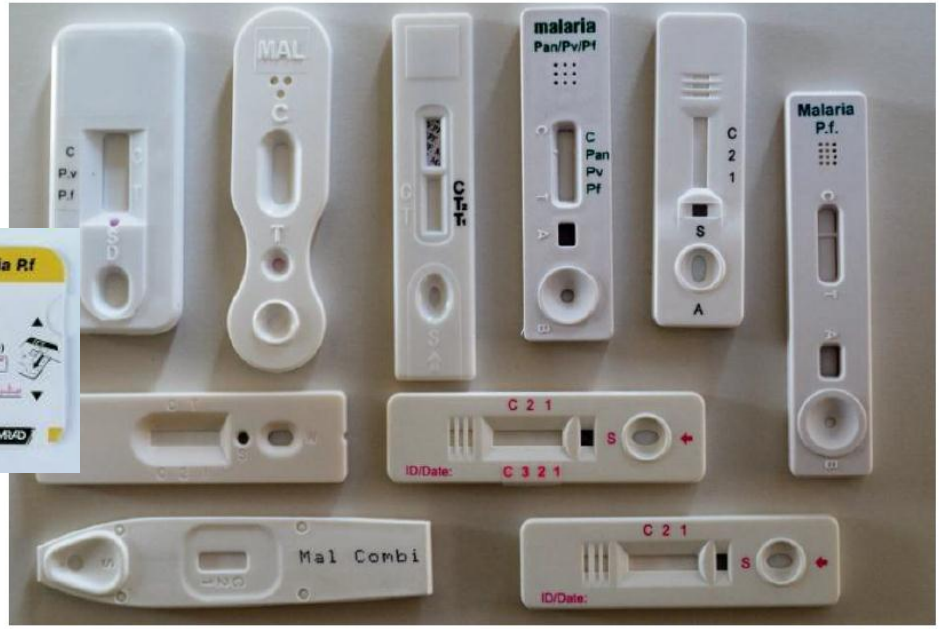
Malaria Antigen Targets for RDTs

Table 3. Antigen targets of rapid diagnostic tests for malaria

Plasmodium species	HRP2	pLDH				Aldolase
		pLDH-Pf	pLDH-pan	pLDH-Pvom	pLDH-Pv	
P. falciparum	X	X	X			X
P. vivax			X	X	X	X
P. malariae			X	X		X
P. ovale			X	X		X

HRP2 – histidine-rich protein 2
pLDH – *Plasmodium* lactate dehydrogenase
Pf – *P. falciparum*
pan – all *Plasmodium* species
Pvom – *P. vivax, ovale* and *malariae*
Pv – *P. vivax*





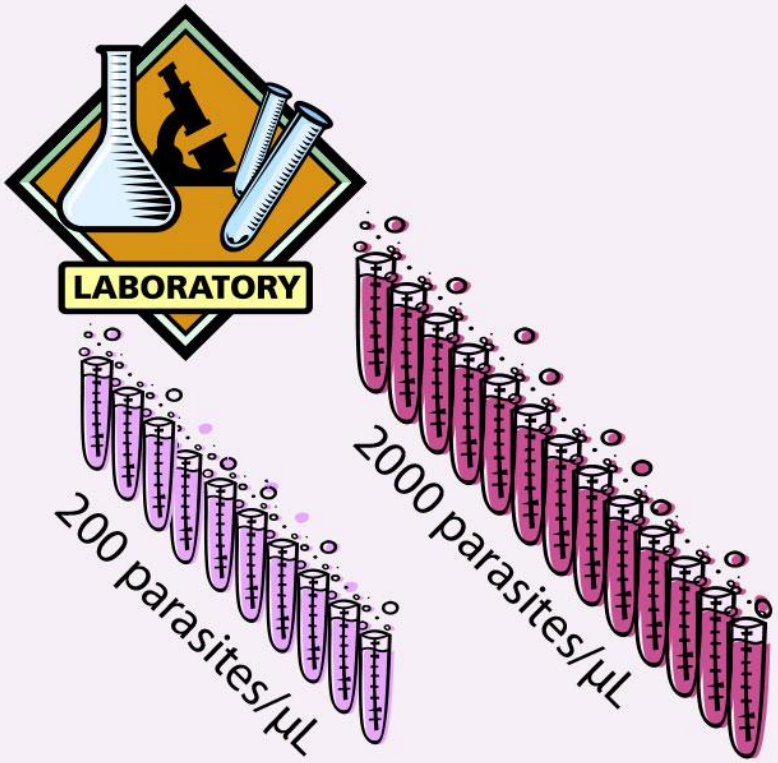
Source: *Gillet P. Malaria Rapid Diagnostic Tests: Laboratory aspects in the diagnostic setting, 2011 (Doctoral dissertation, Maastricht University).*

World Health Organization

Box 2: Performance measures in WHO product testing and in field settings: PDS versus clinical sensitivity

WHO Malaria RDT Product Testing

Primary performance measure: PDS indicates which products are likely to be more sensitive in the field, particularly in populations with low-density infections.



Reference panels: two fixed parasite densities allows discrimination in RDT performance.

Malaria endemic setting

Performance measure: sensitivity is the proportion of the population studied who have malaria for whom the test is positive.

- high, moderate, low transmission
- immune, non-immune
- vulnerable groups

Patients have varying parasite density. Most RDTs for *P. falciparum* and *P. vivax* perform well for a parasite density > 2000 parasites/µL, but clinically significant densities < 200 parasites/µL may be missed. The "overall" test performance will nevertheless be classified as very good in a field evaluation.

Antigen concentrations (HRP2,pLDH, aldolase) in panel samples Rounds 1-5

Figure AS1.1: Box-and-whisker plot of distribution of *P. falciparum* HRP2 concentration (ng/mL) in product testing phase 2 (wildtype) panels.

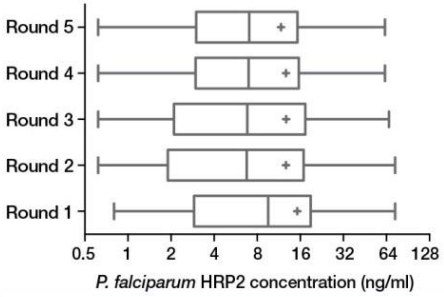
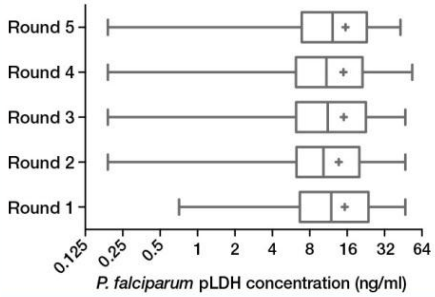


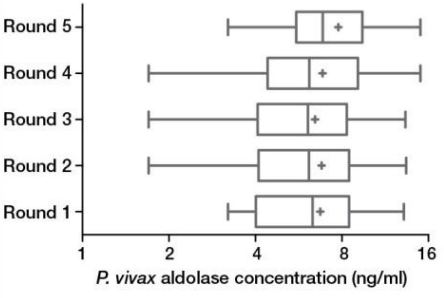
Figure AS1.2: Box-and-whisker plot of distribution of *P. falciparum* pLDH concentration (ng/mL) in product testing phase 2 (wildtype) panels.



Box 4. Explanations for variable antigen concentrations in samples with the same parasite density

- variation in antigen expression among isolates
- different durations of infections (accumulating antigens)
- different parasite growth stages at the time of collection (expressing different levels of antigens)
- presence of circulating HRP2 from previous cycles of growth
- HRP2 produced by parasites sequestered in the host's vascular tissues that cannot be accounted for in the estimate of parasite density on the blood slide (29)

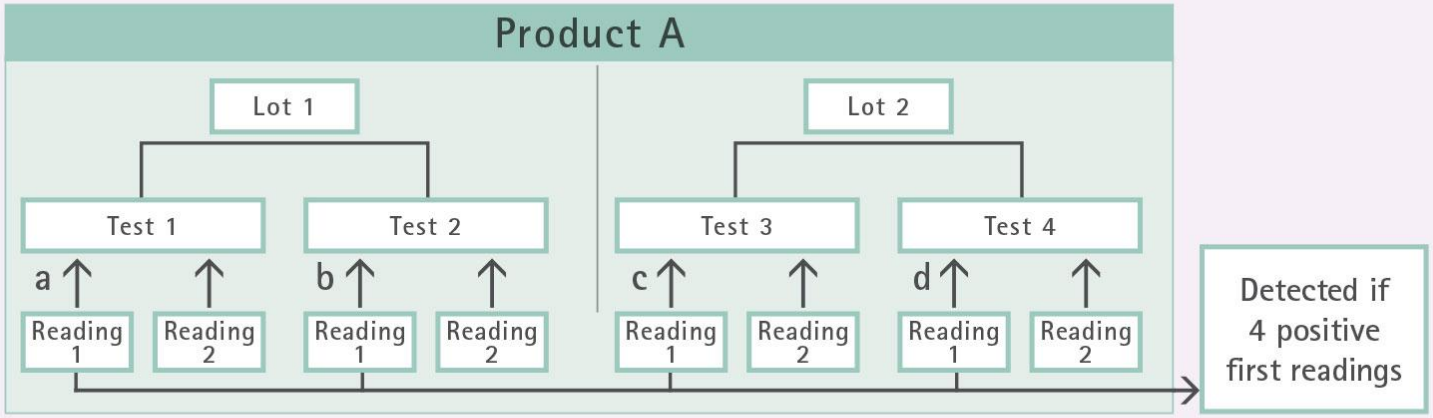
of *P. vivax* aldolase concentration (ng/mL) in product testing phase 2 (wild-type) panels.



Performance measure: Panel detection score

Box 1: Example calculation of panel detection score and positivity rate for product A against a sample density of 200 parasites/µL

The first reading was at the minimum time specified by the manufacturer; the second reading was up to 30 min later[a]. A sample is considered detected only if all first test readings, from both lots, are positive, i.e. readings a, b, c and d must be positive.



[a] second reading results are for internal use only

P. falciparum sample	a	b	c	d	
1	+	–	+	+	Sample NOT detected
2	+	–	–	+	Sample NOT detected
3	+	+	+	+	Sample detected

In this example, only one of three samples was positive all four times it was tested; the PDS is therefore 1/3 = 33%.

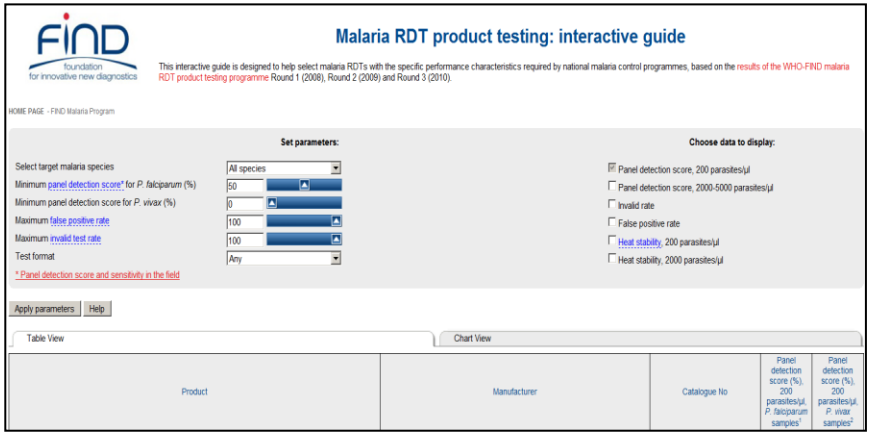
The positivity rate is calculated as the percentage of all tests of a particular product that returned a positive test result at the manufacturers' recommended minimum reading time when tested against a *P. falciparum* or *P. vivax* sample.

In the above example, the positivity rate is: 9/12 = 75%.

The positivity rate is always greater than the PDS, except when the PDS and the positivity rate are both 100%.

Rounds 1-5

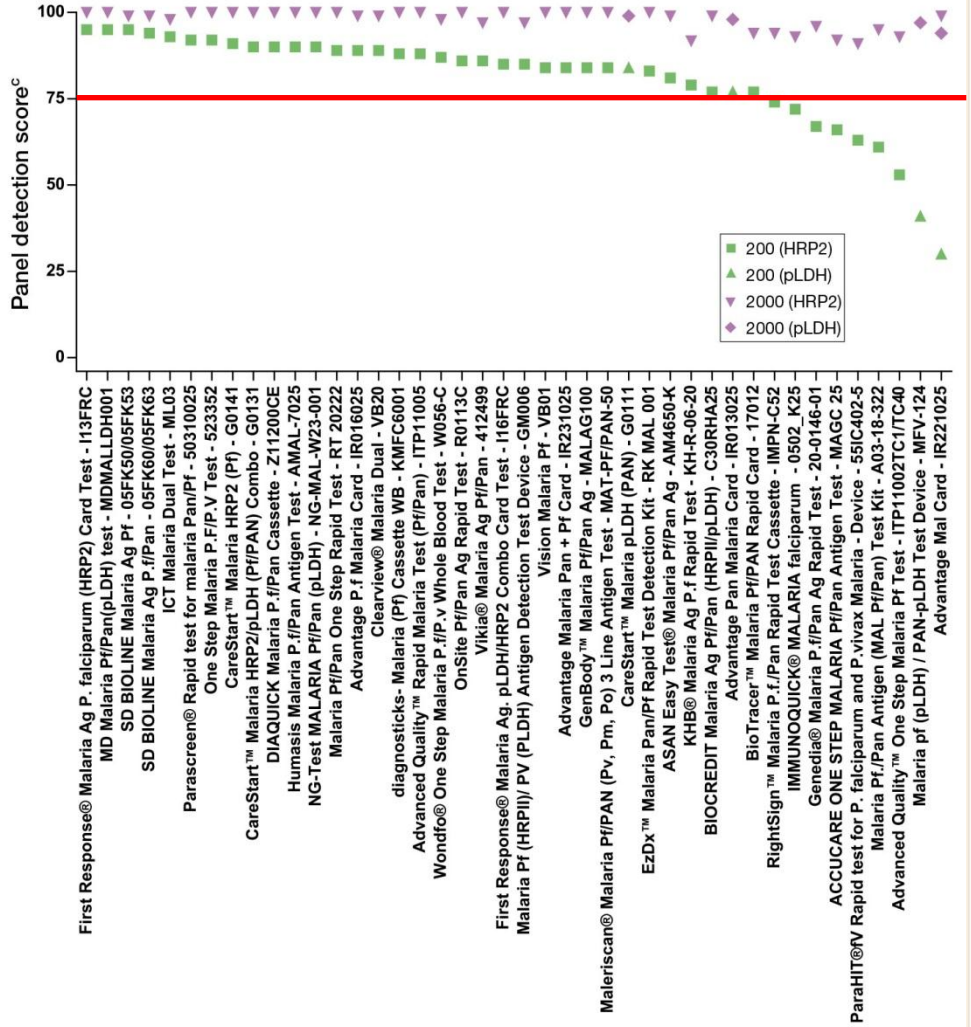
- Published Rounds 1- 5
  - 206 RDTs evaluated (147 unique products)
- Round 5 : 42 RDTs (23 resubmissions (10 compulsory)
  31 combo, 9 Pf, 2 pan (34 manufacturers)



- Round 6
  41 RDTs (30 combo, 11Pf (22 manufacturers))

Results: PDS @ 200 and 2000p/µL

Figure 10: Phase-2 *P. falciparum* panel detection score of malaria RDTs at low (200) and high (2000[a]) parasite density (parasites/µL) according to target antigen type (HRP2 or pLDH)[b]

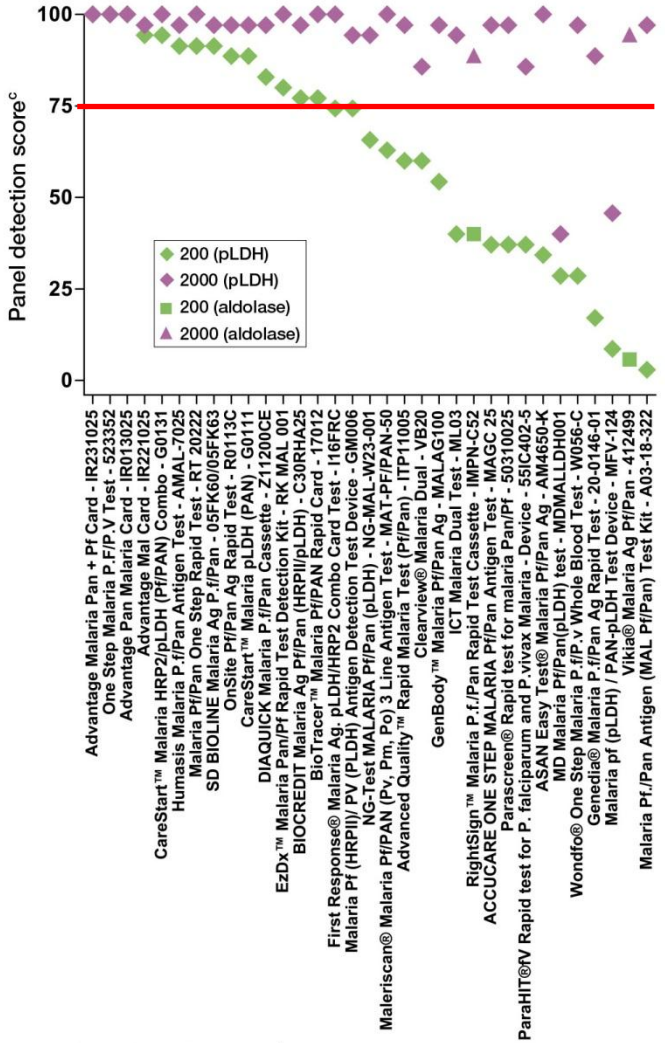


[a] 4 (4%) of the 100 *P. falciparum* dilution samples sets had 200 and 5000 parasites/µL and 2 (6%) of the 35 *P. vivax* dilution sample sets had 200 and 5000 parasites/µL.

[b] Phase-2 evaluation panel consisted of 100 clinical blood samples containing wild-type *P. falciparum*. RDTs performed = 2 tests x 2 lots at 200 p/µL and 1 test x 2 lots at 2000 p/µL.

[c] A sample is considered detected only if all RDTs from both lots read by the first technician, at the minimum specified reading time, are positive.

Figure 11: Phase-2 *P. vivax* panel detection score of malaria RDTs at low (200) and high (2000[a]) parasite density (parasites/µL) according to target antigen type (aldolase, pLDH)[b]



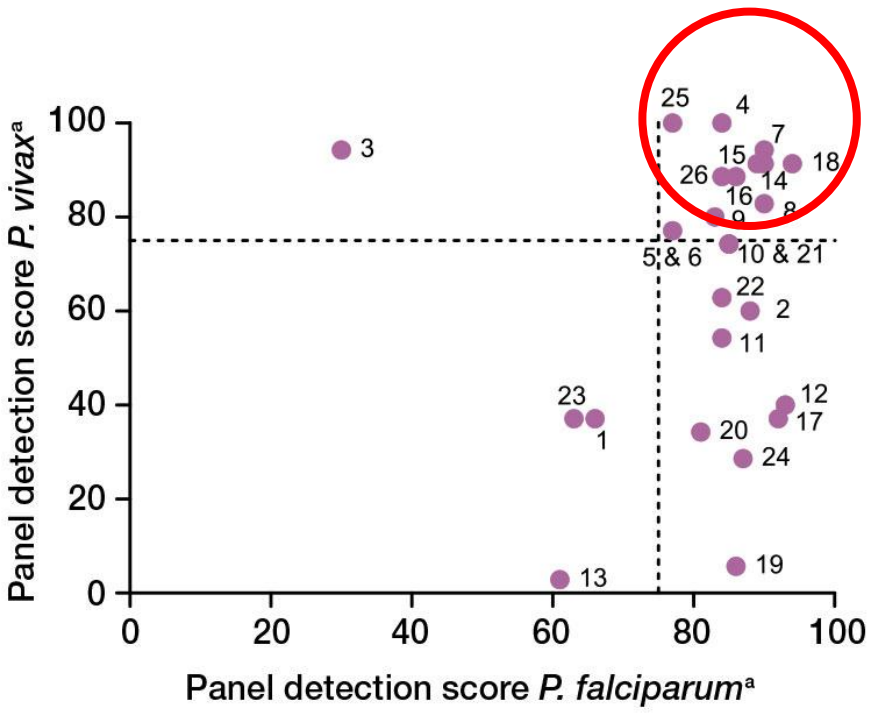
[a] 2 (6%) of the 35 *P. vivax* dilution sample sets had 200 and 5000 parasites/µL.

[b] Phase-2 evaluation panel consisted of 35 clinical blood samples containing wild-type *P. vivax*; RDTs performed = 2 tests x 2 lots at 200 p/µL and 1 test x 2 lots at 2000 p/µL.

[c] A sample is considered detected only if all RDTs from both lots read by the first technician, at the minimum specified reading time, are positive.

Combined Pf and Pv PDS

Figure S3: Panel detection score of malaria combination RDTs, meeting WHO procurement criteria for false-positive and invalid rates, in phase 2 of rounds 2-5 against wild-type (clinical) samples containing *P. falciparum* and *P. vivax* at low (200) parasite density (parasites/µL)



1 ACCUCARE ONE STEP MALARIA Pf/Pan Antigen Test
2 Advanced Quality™ Rapid Malaria Test (Pf/Pan)
3 Advantage Mal Card
4 Advantage Malaria Pan + Pf Card
5 BIOCREDIT Malaria Ag Pf/Pan (HRPII/pLDH)
6 BioTracer™ Malaria Pf/PAN Rapid Card
7 CareStart™ Malaria HRP2/pLDH (Pf/PAN) Combo
8 DIAQUICK Malaria P.f/Pan Cassette
9 EzDx™ Malaria Pan/Pf Rapid Test Detection Kit
10 First Response® Malaria Ag. pLDH/HRP2 Combo Card Test
11 GenBody™ Malaria Pf/Pan Ag
12 ICT Malaria Dual Test
13 Malaria Pf./Pan Antigen (MAL Pf/Pan) Test Kit
14 Malaria Pf/Pan Antigen Test
15 Malaria Pf/Pan One Step Rapid Test
16 OnSite Pf/Pan Ag Rapid Test
17 Parascreen® Rapid test for malaria Pan/Pf
18 SD BIOLINE Malaria Antigen Pf/Pan
19 Vikia® Malaria Ag Pf/Pan
20 ASAN Easy Test® Malaria Pf/Pan Ag
21 Malaria Pf (HRPII)/ PV (PLDH) Antigen Detection Test Device
22 Maleriscan® Malaria Pf/PAN (Pv, Pm, Po) 3 Line Antigen Test
23 ParaHIT®fV Rapid test for P. falciparum and P.vivax Malaria - Device
24 Wondfo® One Step Malaria P.f/P.v Whole Blood Test
25 Advantage Pan Malaria Card
26 CareStart™ Malaria pLDH (PAN)

[a] Panel detection score - A sample is considered detected only if all RDTs from both lots read by the first technician, at the minimum specified reading time, are positive.

PT results are the basis for WHO procurement criteria

Box 3: WHO selection criteria for the procurement of RDTs

Products should be selected in line with the following set of criteria, based on the results of the assessment of the WHO Malaria RDT Product Testing Programme:

(A) For the detection of *Plasmodium falciparum* (Pf) in all transmission settings the panel detection score (PDS) against Pf samples should be at least 75% at 200 parasites/µL.

(B) For the detection of *Plasmodium vivax* (Pv) in all transmission settings the panel detection score (PDS) against Pv samples should be at least 75% at 200 parasites/µL.

(C) The false positive rate should be less than 10%.

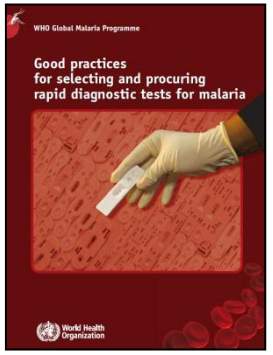
(D) The invalid rate should be less than 5%.

Only products meeting performance criteria outlined in A,B,C and D are recommended for procurement

Eligible for tender: 58 RDTs (24 Pf, 31 combo, 2 pan; 1 Pv only)

Further considerations:

- **Stability**
- **Ease of use and training requirements**
- **Price**
- **Lot testing**



Compulsory resubmission – 10/22

Table 1b: Products due for compulsory resubmission in round 5

Manufacturer	Product name	Catalogue number	Participation in round 5[a]
Access Bio, Inc.	CareStart™ Malaria pLDH (PAN)	G0111	Yes
	CareStart™ Malaria HRP2/pLDH (Pf/PAN) COMBO	G0131	Yes
	CareStart™ Malaria HRP2 (Pf)	G0141	Yes
Acon Laboratories, Inc	Malaria Plasmodium falciparum Rapid Test Device (Whole Blood)	IMA-402	No
Amgenix International, Inc.	OnSight - ParaQuick (Pan, Pf) Test	536-25DB	No
Biosynex	Immunoquick Malaria Falciparum	0502_K25	Yes
	Immunoquick Malaria +4	0506_K25	No
Diagnostics Automation/Cortez Diagnostics Inc.	Malaria *P.F/Vivax*	172110P-25	No
Human GmbH	Hexagon Malaria	58051	No
	Hexagon Malaria Combi	58024	No
IND Diagnostic Inc.	One Step Malaria Antigen Strip	820-1	No
Innovatek Medical Inc.	Quickstick Malaria Antigen Test[b]		No
Intec Products, Inc.	ADVANCED QUALITY TM MALARIA (p.f) POCT	ITP11002TC1	Yes
Inverness Medical Innovations, Inc.	Binax Now Malaria	IN660050	No
J. Mitra & Co. Pvt. Ltd	Advantage P.f. Malaria Card	IR016025	Yes
	Advantage Pan Malaria Card	IR013025	Yes
	Advantage Mal Card	IR221025	Yes
Premier Medical Corporation Ltd.	First Response® Malaria Ag HRP2	II3FRC	Yes
Span Diagnostics	Parahit-Total Device Rapid Test for *P. falciparum* and Pan malaria species	25989	No
Standard Diagnostics	SD Bioline Malaria Ag Pf	05FK50	Yes
Unimed International	FirstSign – Malaria Pf Card Test	-	No
	FirstSign – ParaView-2 (Pv + Pf) Card Test	2102CB-25	No

[a] The results of the first tests of the products in this list that were not retested in round 5 have been removed from tables S2 and S3 and figs S1 and S2.
[b] Co-listed with IND Diagnostics - One Step Malaria Antigen Strip (820-1)

- PDS*Pf* and PDS*Pv* were significantly lower in compulsory resubmissions as compared to voluntary resubmissions

GLOBAL MALARIA PROGRAMME

RDT anomalies

Figure AS2.1: Malaria RDT anomalies encountered in production lots

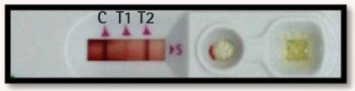
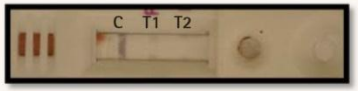
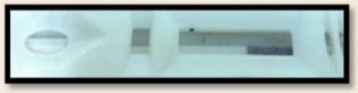
a) Observations on the test strip		
Red background		Background staining is relatively common. In this example, the result is positive as test lines are positive; however, a more intense red background may obscure weak positive test lines, giving false-negative results
Incomplete clearing	 	Poor clearing of blood may obscure weak positive test lines, giving false-negative results. In this example, the result is positive as the test line is visible
b) Observations of flow problems		
Failure to flow		Blood and buffer c of the strip
Irregular migration that obscures test line(s)		One portion of the test band was not dry during wicking, tion of blood/buff that may obscure
Irregular migration		One portion of the test band was not dry during wicking, tion of blood/buff In this example, the test line is clearly
c) Observations on test lines		
Ghost test lines		*White lines on a st example, the resul line is not dark and*
Patchy broken test line(s)		*The test line is visible but interrupted (broken).*
Diffuse test line(s)		*Test line wider than control, without clearly defined edge.*
d) RDT structural problems		
Strip misplaced in the cassette		*Strip can be seen only partially in the results window.*
Specimen pad not seen in sample window		*Normally, the colour of the conjugated antibody can be seen in the sample window (commonly purple, pink or blue).*

Table 8: Observations on RDT production lots that might affect interpretation of the results

Observations/anomalies	No.(%) of products with at least one recorded observation
Red background	42 (100)
Incomplete clearing	42 (100)
Failure to flow	26 (61.9)
Shift or misplacement of strip	10 (23.8)
Ghost lines	7 (16.7)
Diffuse test lines	2 (4.8)
Patchy broken test line	2 (4.8)

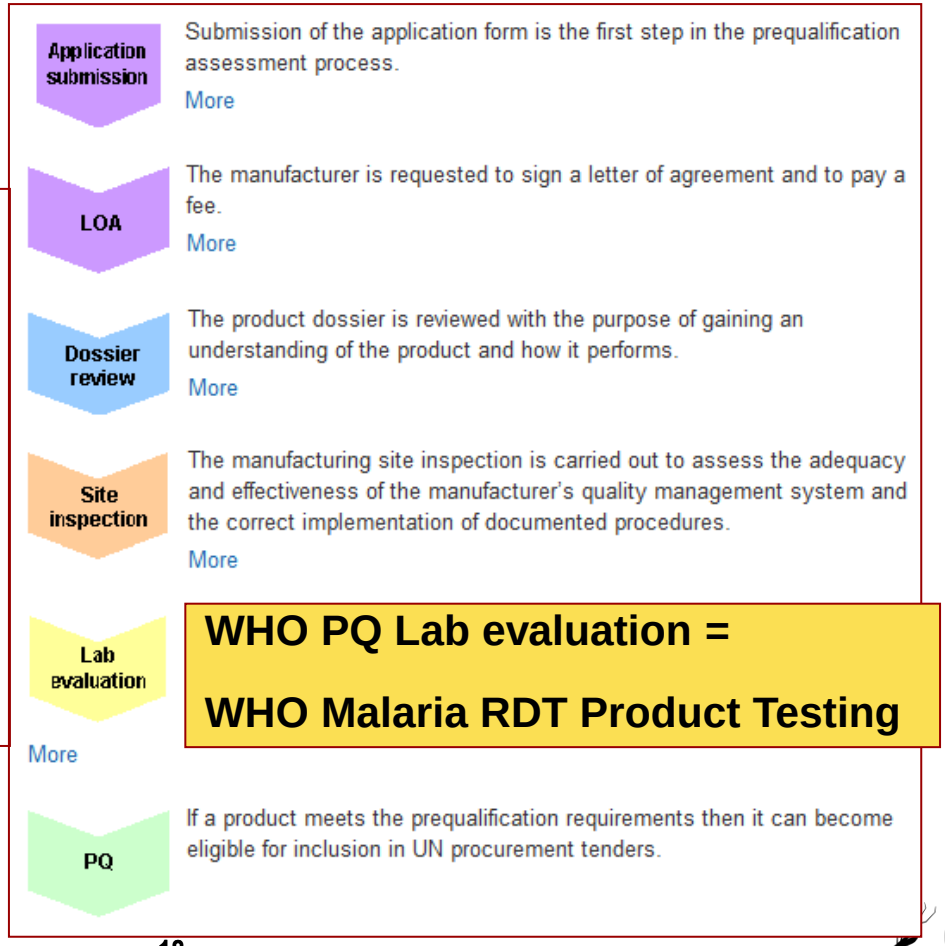
WHO Prequalification of malaria RDTs

WHO has started in 2007 the prequalification of malaria RDTs according to the following procedure:

So far the following RDTs

has been prequalified:

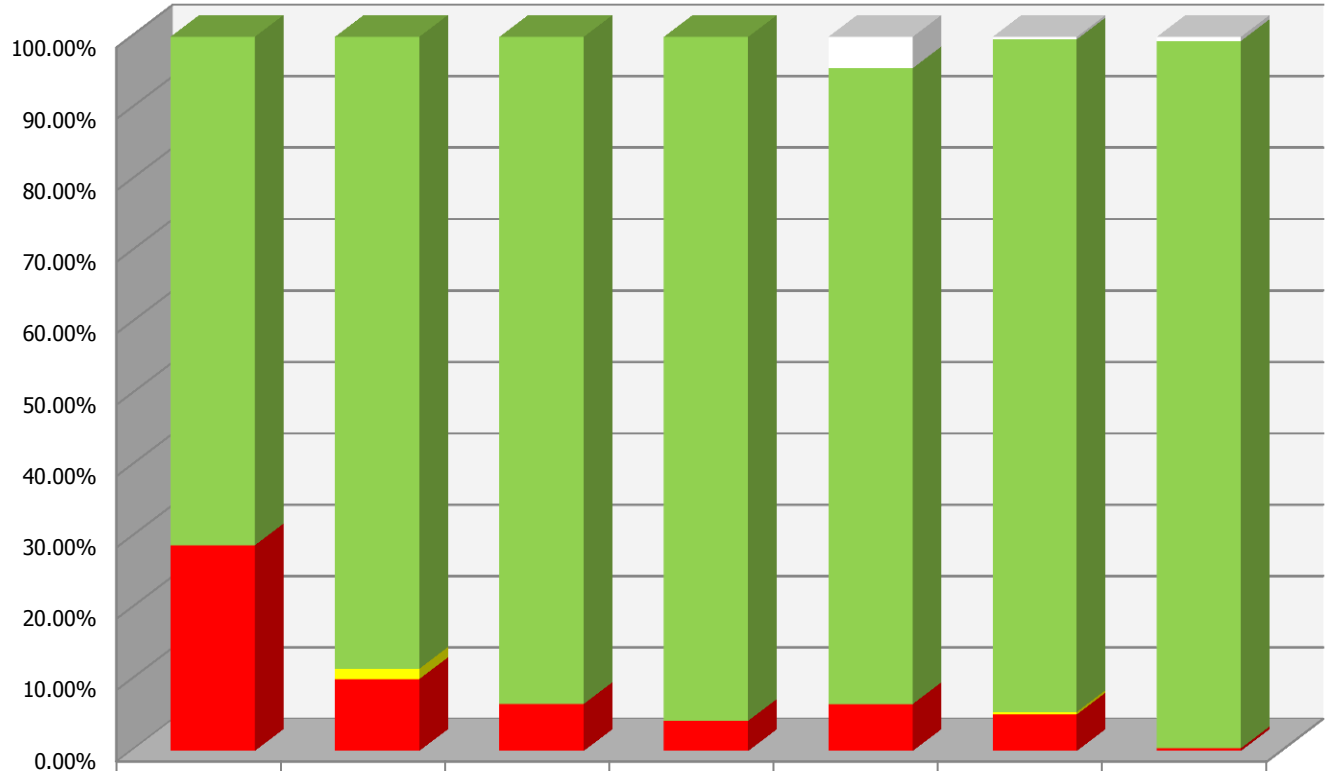
- **SD BIOLINE Malaria Ag P.f (05FK50/05FK53)**
- **SD BIOLINE Malaria Ag P.f/Pan (05FK63 and 05FK60)**



WHO PQ Lab evaluation =

WHO Malaria RDT Product Testing

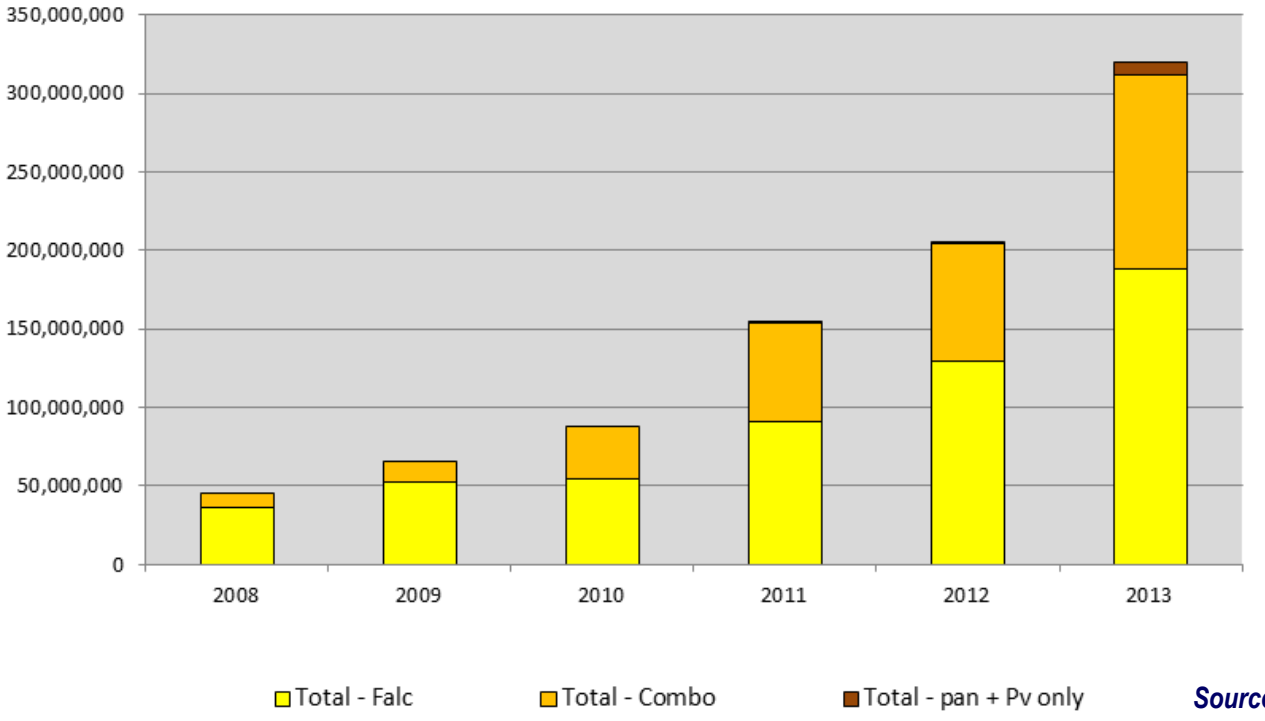
Panel Detection Score (PDS) of Malaria RDT submitted for lot-testing (for pre/post procurement)



	2007	2008	2009 Rd 1 Apr.	2010 Rd 2 May	2011 Rd 3 Dec	2012 Rd 4 Dec	Jan-Jun 2013
Not submitted to Product Testing					4.38%	0.35%	0.58%
PDS* ≥75% (high performance criteria)	71.19%	88.49%	93.42%	95.76%	89.04%	94.18%	99.04%
PDS* ≥50% (WHO medium performance criteria)		1.44%	0.00%			0.35%	
PDS* <50% including False Positive (outside WHO criteria)	28.81%	10.07%	6.58%	4.24%	6.58%	5.11%	0.38%

RDT trends (2008-2013)

Data provided by 29 manufacturers eligible for participation in the WHO RDT Product Testing Programme



Source: WHO/GMP manufacturer survey 2014

Based on Global Fund and PMI data (compiled by CHAI and UNITAID)

- Three manufacturers won 90% of tenders in 2012
- Four won 98% in 2013
- 90% of public sector supplies depends on 2 manufacturers

Impact on manufacturers

- **Following Round 5**
  - One prequalified product – **Immunoquick Malaria falciparum (0502_K 25,50,100 Dipstick**) (**Biosynex)** is delisted (PF PDS <75% and ++ red background
  - One market leader combination test , **First Response pLDH-HRP2 Combo Test, I16FRC (Premier Medical Corporation)** scored *P.vivax* PDS 74.3% (Pf PDS 85%).
    - Comparable to scores in Rounds 1 and 2 – PDS 75%.
      - 2014 NOT eligible for WHO tender or procurement
      - Procured by Ethiopia, Tanzania, DRC, Madagascar, Rwanda, India, Pakistan, Myanmar, Cambodia, Indonesia

Limitations of current system

- **Need to reduce costs ++ to ensure sustainability and reasonable manufacturer payments**
- **Need to standardize panels across time and space**
- **Need to make panels available to manufacturers (same as are used for product testing and lot-testing)**
- **Need to provide countries with standard, reliable, acceptable materials for lot-testing (there will be increased requirement for in-country testing of RDTs in the future)**

Recombinant antigen based system

Identification of candidate antigens

- Acquisition of recombinant antigens from other institutions
- Procurement of commercially available recombinant antigens
- Synthesis and expression of new recombinant antigens

Quality evaluation

- Calculation of protein concentration by absorbance
- Evaluating purity by polyacrilamide gels
- Assessing immunodetection and concentration curves by ELISA
- Testing storage and temperature stability

Performance evaluation

- Equivalence testing by RDTs to compare PDS (Panel Detection Score) between selected recombinant antigens and parasites

2013-2017 plan funded by UNITAID

	2003 -2011	2011-2014	2015-2016	2017
	Step 1: Start	**Step 2: Develop**	**Step 3: Roll-out**	**Step 4: Implemented**
	Establish patient-derived sample panels	Develop and evaluate recombinant antigen panels	Scale-up and launch recombinant antigen panels	Manufacture and distribute reference materials
	Establish lot testing process	Ongoing lot testing based on cultured parasites	Roll-out lot testing based on recombinant antigens	Local lot testing financed by purchaser
	Product testing round 1 to 3	Ongoing product testing round 4 & 5	Product testing based recombinant panel and partly financed by IVD suppliers	Product testing financed by IVD suppliers
Cost:	**$$$$**	**$$$$$**	**$$$**	**$**

FUNDED

Thank you !

- FIND
- US CDC
- Hospital for Tropical Disease, UK
- Queensland Institute of Medical Research, Australia
- Army Malaria Institute, Australia
- Research Institute Tropical Medicine, The Philippines
- Institute Pasteur Cambodia
- Collection sites: CIDEIM (Colombia), DMR (Myanmar), KEMRI (Kenya), EHNRI (Ethiopia), IHRDC (Tanzania), IMT (Peru), IPB (Central Africa Republic), IPM (Madagascar), UCAD (Senegal), UL (Nigeria)

Malaria Rapid Diagnostic Test Performance

Summary results of WHO product testing of malaria RDTs: Round 1-5 (2008-2013)

World Health Organization

FIND
foundation for innovative new diagnostics

CDC

Malaria Rapid Diagnostic Test Performance

Summary results of WHO product testing of malaria RDTs: Round 1-5 (2008-2013)

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The WHO Programme of Prequalification of Diagnostics and Medical Devices uses the results of the WHO Malaria RDT Product Testing Programme as the laboratory evaluation component of the prequalification process for malaria RDTs. Although not currently a requirement for WHO procurement, manufacturers are encouraged to apply for WHO prequalification. A regularly updated list of WHO-prequalified diagnostics, including malaria RDTs, is available at *http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/*.

WHO recommendations for procurement of malaria RDTs are currently based on the attainment of a set of minimum performance criteria in the WHO Malaria RDT Product Testing Programme. These recommendations were established by the WHO Malaria Policy Advisory Committee in 2012 , are outlined in this report and presented in full in a WHO information note (available at *http://www.who.int/malaria/publications/atoz/rdt_selection_criteria_en.pdf?ua=1*).Products that do not meet the full set of minimum performance criteria are not eligible for procurement by WHO.

The lists of RDTs included in this report are not exhaustive lists of malaria RDTs. These lists reflect those products which have been submitted for evaluation in Rounds 2-5 of the WHO Malaria RDT Product Testing Programme, and indicate to what extent these products, as manufactured by the listed companies, were -at the time of their evaluation- found to meet the above mentioned set of minimum performance criteria. The evaluation results indicated in the figures and tables apply only to the specific product as listed with its unique product code / catalogue number and as manufactured by the listed company.

The improper storage, transport and handling of malaria RDTs may affect their level of performance.

The fact that certain products are not included in the lists and figures in this report indicates that they have not or not yet been submitted for evaluation in the WHO Malaria RDT Product Testing Programme, or that their evaluation has not yet been completed and published in [a new edition of this report]. It does not however indicate anything in respect of such products' performance. The lists and figures are updated regularly, and malaria RDTs are added to the lists and figures as and when (following the voluntary participation in the WHO Malaria RDT Product Testing Programme) their evaluation against the above mentioned set of minimum performance criteria has been completed.

Although the malaria RDTs listed in the tables and figures are regularly re-evaluated, and updated evaluation results are published by WHO, WHO cannot represent that products included in the lists and figures will continue to meet the performance criteria in the same manner as indicated. WHO recommends therefore that before procurement of a malaria RDT, each lot of that product undergoes lot testing at one of the two following lot-testing laboratories: Institut Pasteur du Cambodge (IPC), Cambodia or Research Institute for Tropical Medicine (RITM), The Philippines.

WHO disclaims any and all liability and responsibility whatsoever for any injury, death, loss, damage, or other prejudice of any kind that may arise as a result of or in connection with the procurement, distribution and use of any product included in this report and the figures and tables listed on page IV.

This report may not be used by manufacturers and suppliers for commercial or promotional purposes.

Contents

FIGURES

TABLES

1. SUMMARY OF PERFORMANCE OF RAPID DIAGNOSTIC TESTS FOR MALARIA: WHO PRODUCT TESTING ROUNDS 1–5

1.1. Introduction

WHO estimates that half the world's population is at risk of malaria. In 2012, there were an estimated 207 million cases (with an uncertainty range of 135 million to 287 million) and an estimated 627 000 deaths (with an uncertainty range of 473 000 to 789 000). Approximately 90% of all malaria deaths occur in sub-Saharan Africa, and 77% occur in children under 5 years. Malaria remains endemic in 104 countries, and, while parasite-based diagnosis is increasing, most suspected cases of malaria are still not properly confirmed, resulting in over-use of antimalarial drugs and poor disease monitoring (*1*).

WHO recommends that malaria case management be based on parasite diagnosis in all cases (*2*). The use of antigen-detecting rapid diagnostic tests (RDTs) is a vital part of this strategy, forming the basis for extending access to malaria diagnosis by providing parasite-based diagnosis in areas where good-quality microscopy cannot be maintained. The number of RDTs available and the scale of their use have increased rapidly over the past few years; however, limitations of field trials and the heterogeneous nature of malaria transmission have limited the availability of the good-quality data on performance that national malaria programmes require to make informed decisions on procurement and implementation, and it is difficult to extrapolate the results of field trials to different populations and times. Therefore, in 2006, the WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FIND) launched a programme to systematically evaluate and compare the performance of commercially available malaria RDTs. The results of WHO's malaria RDT product testing have been published annually since 2009 and form the basis of the procurement criteria of WHO, other United Nations agencies, the Global Fund to Fight AIDS, Tuberculosis and Malaria, national governments and nongovernmental organizations. The data have guided procurement decisions, which, in turn, have shifted markets towards better-performing tests[1] and are driving overall improvements in the quality of manufacturing.

This summary presents an overview of the results of rounds 1–5 of malaria RDT product testing and key concepts for understanding and using the results. It is published in conjunction with the release of the full report on round 5. The results of all rounds of testing should be considered as a single data set. The separate, full reports of each round (*3–6*) should be consulted for further details of methods, product performance and interpretation of the results.

1.2. The WHO product testing programme

The RDT evaluations summarized here were performed in collaboration by WHO, TDR, FIND, the United States Centers for Disease Control and Prevention (CDC) and other partners.[1] All companies that manufacture according to the ISO 13485:2003 quality system standard were invited to submit one to three products for evaluation in the programme. In each round of testing, products are evaluated against geographically diverse, cryopreserved *Plasmodium falciparum* and *P. vivax* clinical samples diluted to 200 and 2000 parasites/μL and with consistently comparable concentration ranges of histidine-rich protein II (HRP2), *Plasmodium* lactate dehydrogenase (pLDH) and aldolase determined by quantitative enzyme-linked immunosorbent assay (ELISA) (Annex S1). In the first round of testing, 41 products from 21 manufacturers were evaluated against prepared blood panels of cultured *P. falciparum* parasites, while 29, 50, 48 and 42 products from 13, 23, 27 and 34 manufacturers were evaluated in rounds 2, 3, 4 and 5, respectively. Of these 210 products, 206 progressed to testing against panels of patient-derived *P. falciparum* and *P. vivax* parasites and a parasite-negative panel. Thermal stability was assessed after 2 months of storage at elevated temperature and humidity, and a descriptive assessment of ease of use was made. Many manufacturers have decided voluntarily to submit products to one or more rounds of testing, and, in round 5, a requirement was instituted to resubmit products for re-evaluation within 5 years of original testing (Table S1). Of the 206 fully evaluated products, 32 have been evaluated twice, 11 have been evaluated three times and two evaluated four times in rounds 1–5. Of the 147 unique products tested in the programme, 36 detect *P. falciparum* alone, 101 detect and differentiate *P. falciparum* from non-*P. falciparum* malaria (either pan-specific or species-specific for *P. vivax* or *P. vivax*, *ovale* and *malariae*), 9 detect *P. falciparum* and non-*P. falciparum* malaria without distinguishing between them, and one product was designed to detect *P. vivax* only. Manufacturers submitted two lots of each product for evaluation. When the same products (*7*) were resubmitted in subsequent rounds of testing, the second set of results replaced those from the earlier round. Thus, the performance of some tests in the results below differs from that reported in rounds 1–4.

Of the 22 products due for compulsory retesting in round 5, 10 were submitted (Table S1). Round 1 products that were not

[1] See full reports of rounds 1–5 (3–6) for lists of collaborating partners.

resubmitted have been removed from the figures and tables in this summary performance document.

The aim of the evaluation is to provide comparative data on the performance of the submitted production lots of each product. These data will be used to guide procurement decisions by WHO, other United Nations agencies and national governments and constitute the laboratory evaluation component of the WHO prequalification process for malaria RDTs (*8*). Product testing is part of a continuing programme of work to improve the quality of RDTs in use and to ensure reliable malaria diagnosis in areas where malaria is prevalent. A sixth round of product testing will begin in June 2014.

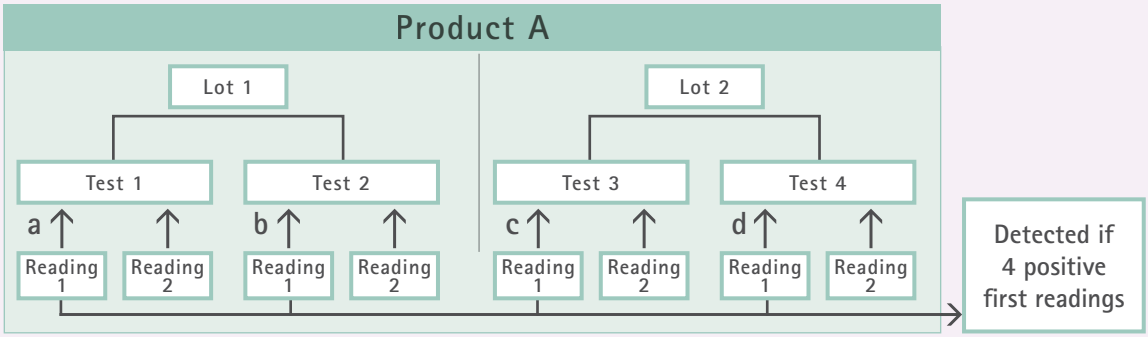
1.3. Panel detection score and other results of the evaluation

The results (summarized in Figs S1–S3 and Tables S2 and S3) provide comparative data on two lots of products against a panel of parasite samples diluted to a low parasite density (200 parasites/µL) and a higher parasite density (2000 or 5000 parasites/µL). The former is well below the mean parasite density found in many populations with endemic malaria and is considered close to the threshold that must be detected in order reliably to identify clinical malaria in many settings (*9*). For the purposes of this report, the main measure of performance is the panel detection score (PDS);[1] for each RDT evaluated, the PDS is measured separately at the

[1] Termed "detection rate" in the full report of round 1, published in 2009.

Box 1: Example calculation of panel detection score and positivity rate for product A against a sample density of 200 parasites/µL

The first reading was at the minimum time specified by the manufacturer; the second reading was up to 30 min later[a]. A sample is considered detected only if all first test readings, from both lots, are positive, i.e. readings a, b, c and d must be positive.



[a] second reading results are for internal use only

P. falciparum sample	a	b	c	d	
1	+	–	+	+	Sample NOT detected
2	+	–	–	+	Sample NOT detected
3	+	+	+	+	Sample detected

In this example, only one of three samples was positive all four times it was tested; the PDS is therefore 1/3 = 33%.

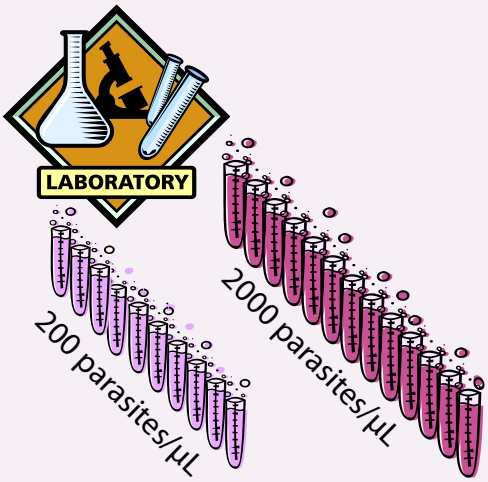
The positivity rate is calculated as the percentage of all tests of a particular product that returned a positive test result at the manufacturers' recommended minimum reading time when tested against a *P. falciparum* or *P. vivax* sample.

In the above example, the positivity rate is: 9/12 = 75%.

The positivity rate is always greater than the PDS, except when the PDS and the positivity rate are both 100%.

Box 2: Performance measures in WHO product testing and in field settings: PDS versus clinical sensitivity

WHO Malaria RDT Product Testing
Primary performance measure: PDS indicates which products are likely to be more sensitive in the field, particularly in populations with low-density infections.



Reference panels: two fixed parasite densities allows discrimination in RDT performance.

Malaria endemic setting
Performance measure: sensitivity is the proportion of the population studied who have malaria for whom the test is positive.

- high, moderate, low transmission
- immune, non-immune
- vulnerable groups

Patients have varying parasite density. Most RDTs for *P. falciparum* and *P. vivax* perform well for a parasite density > 2000 parasites/µL, but clinically significant densities < 200 parasites/µL may be missed. The "overall" test performance will nevertheless be classified as very good in a field evaluation.

lower and the higher parasite density. The summary figures also show the false-positive rates against blood samples containing no malaria parasites or known markers of other diseases and the rate of invalid results.

The PDS is the percentage of malaria samples in the panel that give a positive result in two RDTs per lot at the lower parasite density or by a single RDT per lot at the higher parasite density. As each sample is tested with RDTs from two lots, for a sample to be positive at the lower parasite density, it must show a positive result in four tests (two RDTs per lot for two lots); at the higher parasite density, it must show a positive result in two tests (one RDT per lot for two lots). Thus, the PDS is a combined measure of positivity rate, incorporating inter-test and inter-lot consistency. As all tests performed on each sample must show a positive result for the sample to be considered positive, the PDS for a given RDT will usually be lower than a simple positivity rate per panel, measured by comparing the number of positive tests among all tests performed per panel. The PDS is also different from clinical sensitivity: the ability of the test to detect malaria infection in a given population of infected patients. Boxes 1 and 2 illustrate how the PDS is calculated and how it differs from a simple positivity rate for all samples tested and from clinical sensitivity in a population.

The PDS for a given RDT is different from the clinical sensitivity of that RDT (also called the true positive rate), which is a measure of the proportion of people known to have the disease who test positive for it. The sensitivity of malaria RDTs is highly dependent on local conditions, including the parasite density in the population; it therefore varies among populations with different levels of transmission, as their level of immunity affects the parasite density at which they exhibit symptoms that warrant a diagnostic test. Where transmission rates are low, the parasite densities in people with symptoms of malaria are likely to be low, and tests will be less sensitive. Test performance at 200 parasites/µL is therefore particularly important. The results in this report show the comparative performance of RDTs and indicate which products are likely to be more sensitive in the field, particularly in populations with low-density infections.

In general, as countries reduce the prevalence of malaria and even move towards malaria elimination, detection of low parasite densities becomes increasingly important in case management. As the high PDS at 2000 parasites/µL indicates, the sensitivity of many of these products is similar in populations with higher parasite densities and therefore it is not possible to discriminate RDTs with superior performance.

An important caveat to estimating field sensitivity from the PDS provided in this report is that the panels used include only parasites known to express the target antigens. While non-expression of the target antigens has not been recorded for aldolase or pLDH, it is known that parasites that infect people in some areas of South America and India do not express HRP2 (*10*, *11*). In areas where HRP2-deleted parasites exist, tests for HRP2 will have greatly reduced sensitivity or be incapable of detecting *P. falciparum*. In such populations, only tests for pLDH or aldolase in *P. falciparum* parasites will be effective for diagnosing falciparum malaria.

Heat stability (summarized in Table S3) is vital to maintaining the sensitivity of tests in the field. As a result, for procurement, careful consideration must be given to ensure that the products to be used in areas with high temperatures of transport and storage have demonstrated stability in the product testing programme. Requirements vary among countries; for example, if tests are to be deployed in areas where temperatures rarely rise above 30 °C, less emphasis is needed on stability at high temperatures than on other aspects of quality.

Ease-of-use requirements depend on the extent of training and the work environment of the users. Particularly in primary health care settings, the simpler the test, the easier it will be to avoid errors in preparation and interpretation.

Detailed results can be found in the report of each evaluation (*3*–*6*) and at http://www.who.int/malaria/publications/diagnostic_testing/en/.

1.4. Summary of outcomes

This laboratory-based evaluation provides a comparative, standardized measure of RDT performance for distinguishing between well and poorly performing tests to serve as a basis for procurement decisions by malaria control programmes and to guide United Nations procurement policy.

In round 5, the proportion of tests that achieved a PDS ≥ 75% at 200 parasites/µL is comparable to those in rounds 3 and 4 for *P. falciparum* (78.6%); that for *P. vivax*, 42.4%, is similar to that in round 4.

Several RDTs in the five rounds of testing consistently detected malaria at a low parasite density (200 parasites/µL), had low false-positive rates, are stable at tropical temperatures, are relatively easy to use and can detect *P. falciparum* or *P. vivax* infections or both.

Although the performance of the products varied widely at low parasite density (200 parasites/µL), all products had a high rate of detection of *P. falciparum* at 2000 or 5000 parasites/µL, as did the majority of products for *P. vivax* at 2000 parasites/µL.

P. falciparum tests that target the HRP2 antigen had the highest detection rates, and two previously evaluated tests that target pan-pLDH for detection of *Plasmodium spp.* infection also achieved a good PDS. In round 5, the two poorest performing tests for detection of *P. falciparum* were based on *P. falciparum*-specific pLDH detection. Thus, the choice of well-performing pLDH-based *P. falciparum* tests remains limited, as it does for pan-only-specific tests.

Test performance sometimes varied between lots and widely between similar products, confirming the advisability of testing lots after purchase and before use in the field. Furthermore, anomalies that interfered with test interpretation were regularly recorded during round 5 (Annex S2). All products had issues with red background and with incomplete clearing, and cases of samples failing to flow or migrate on the RDT were reported for 62% of products.

Ninety-eight percent of the RDTs evaluated in round 5 were in cassette format.

With regard to products retested under the compulsory resubmission requirement, one showed improved (4.8%) detection of *P. falciparum* and one improved (4.3%) detection of *P. vivax*, while six and two had diminished performance (> 5% decrease) for detection of *P. falciparum* (mean, 13.9%; median, 8.4%) and *P. vivax* (mean, 8.5%), respectively. All products except one had the same or lower false-positive rates (mean improvement, 3.7%).

1.5. How can product testing results inform RDT procurement and use?

Accurate diagnosis is vital to good malaria case management, whether based on microscopy or RDTs. The results of this report should be used to identify a short list of RDTs for procurement for use in settings where good microscopy is not available or appropriate. Box 3 lists WHO's minimum criteria for RDT selection, and Annex S3 provides a step-by-step approach to selecting an RDT, taking into consideration local malaria transmission and illness where the tests will be used (e.g. *Plasmodium* species, target antigen, parasite densities, climate) and other important considerations, including ease of use in the field (Annex S2), training or retraining requirements and lot testing.[1]

The tabular results in TableS2 are colour-coded to reflect achievement of WHO performance requirements for RDT procurement, and a web-based tool that allows filtering of product testing results by various parameters to assist in selecting products with the performance characteristics most suitable for a country's health programme is available and maintained by FIND (*12*). Comprehensive guidance on several aspects of procurement can be found in *Good practices for selecting and procuring rapid diagnostic tests for malaria* and guidance on implementation in *Universal access to malaria diagnosis* (*13*, *14*).

[1] The WHO-FIND malaria RDT evaluation programme provides lot-testing capacity in two regional laboratories free of charge; it can be accessed at *malaria_rdt@who.int* and *info@finddiagnostics.org.*

1.6. Product testing and WHO programme for prequalification of diagnostics and medical devices

The WHO prequalification of diagnostics and medical devices programme uses the results of product testing as the laboratory evaluation component of the prequalification process for malaria RDTs. These data are used to set priorities for dossier review and inspection. Although prequalification is not currently a requirement for WHO procurement, manufacturers are encouraged to apply for it. A list of prequalified diagnostics, including malaria RDTs, is available at *http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/*.

Box 3: WHO selection criteria for the procurement of RDTs

Products should be selected in line with the following set of criteria, based on the results of the assessment of the WHO Malaria RDT Product Testing Programme:

(A) For the detection of *Plasmodium falciparum* (Pf) in all transmission settings the panel detection score (PDS) against Pf samples should be at least 75% at 200 parasites/µL.

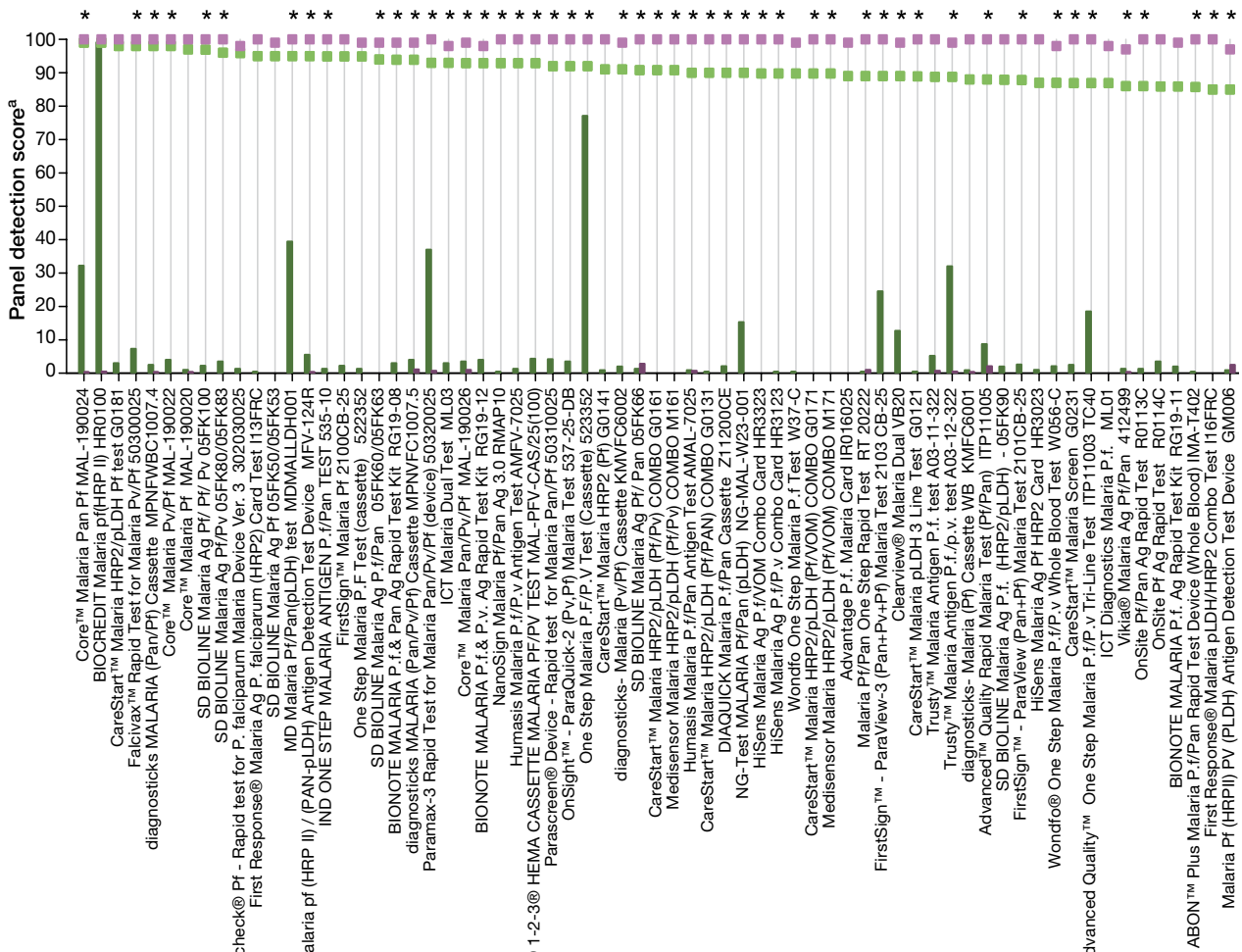
(B) For the detection of *Plasmodium vivax* (Pv) in all transmission settings the panel detection score (PDS) against Pv samples should be at least 75% at 200 parasites/µL.

(C) The false positive rate should be less than 10%.

(D) The invalid rate should be less than 5%.

Only products meeting performance criteria outlined in A,B,C and D are recommended for procurement

Figure S1: Malaria RDT performance in phase 2 of rounds 2–5 against wild-type (clinical) samples containing *P. falciparum* at low (200) and high (2000–5000) parasite density (parasites/µL) and clean-negative samples



[a] Panel detection score: A sample is considered detected only if all RDTs from both lots read by the first technician, at the minimum specified reading time, are positive.

[b] Clean-negative, blood samples from healthy volunteers with no known current illness or blood abnormality.

* Indicates tests that also detect other non-*P. falciparum* parasites

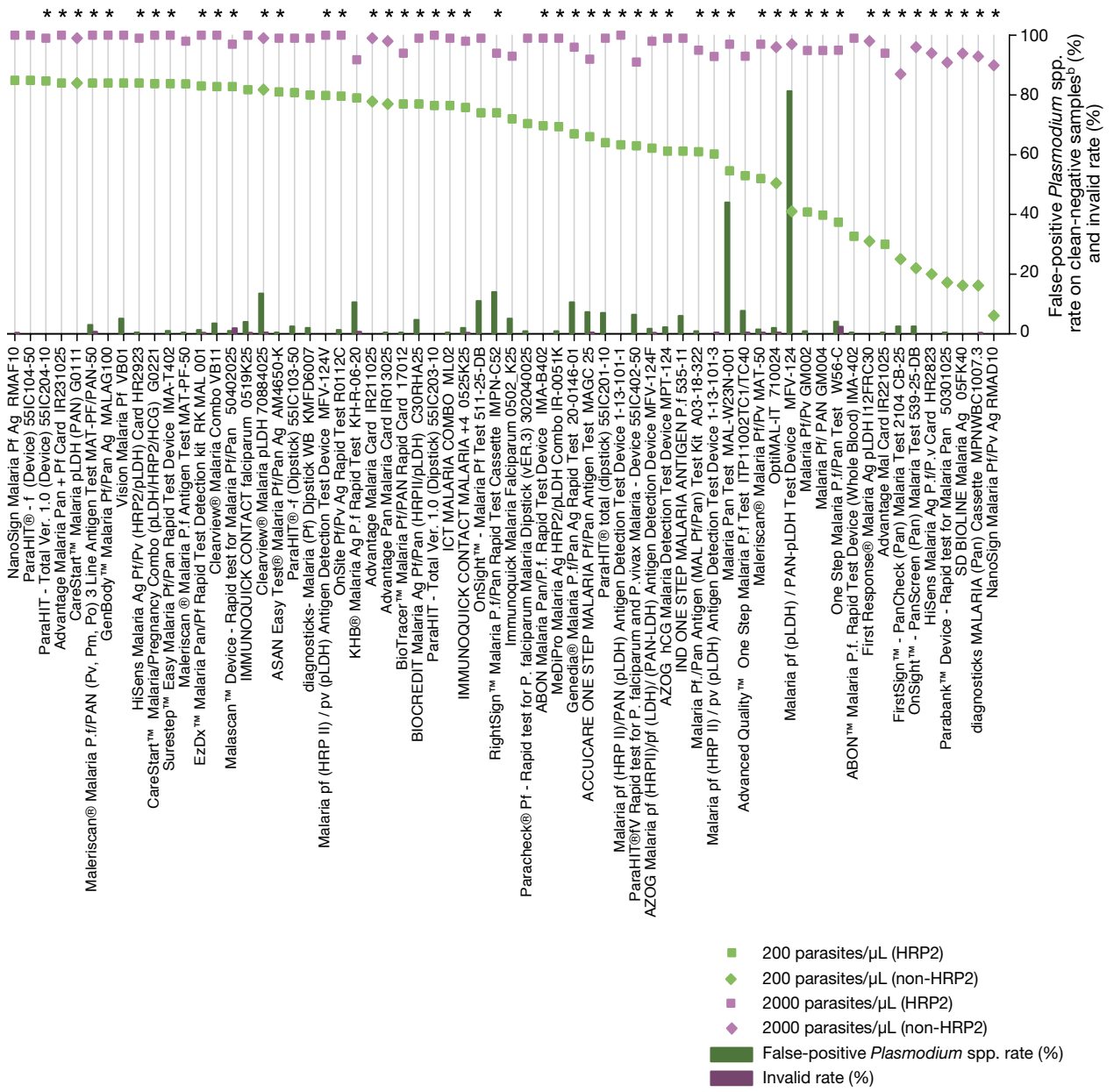
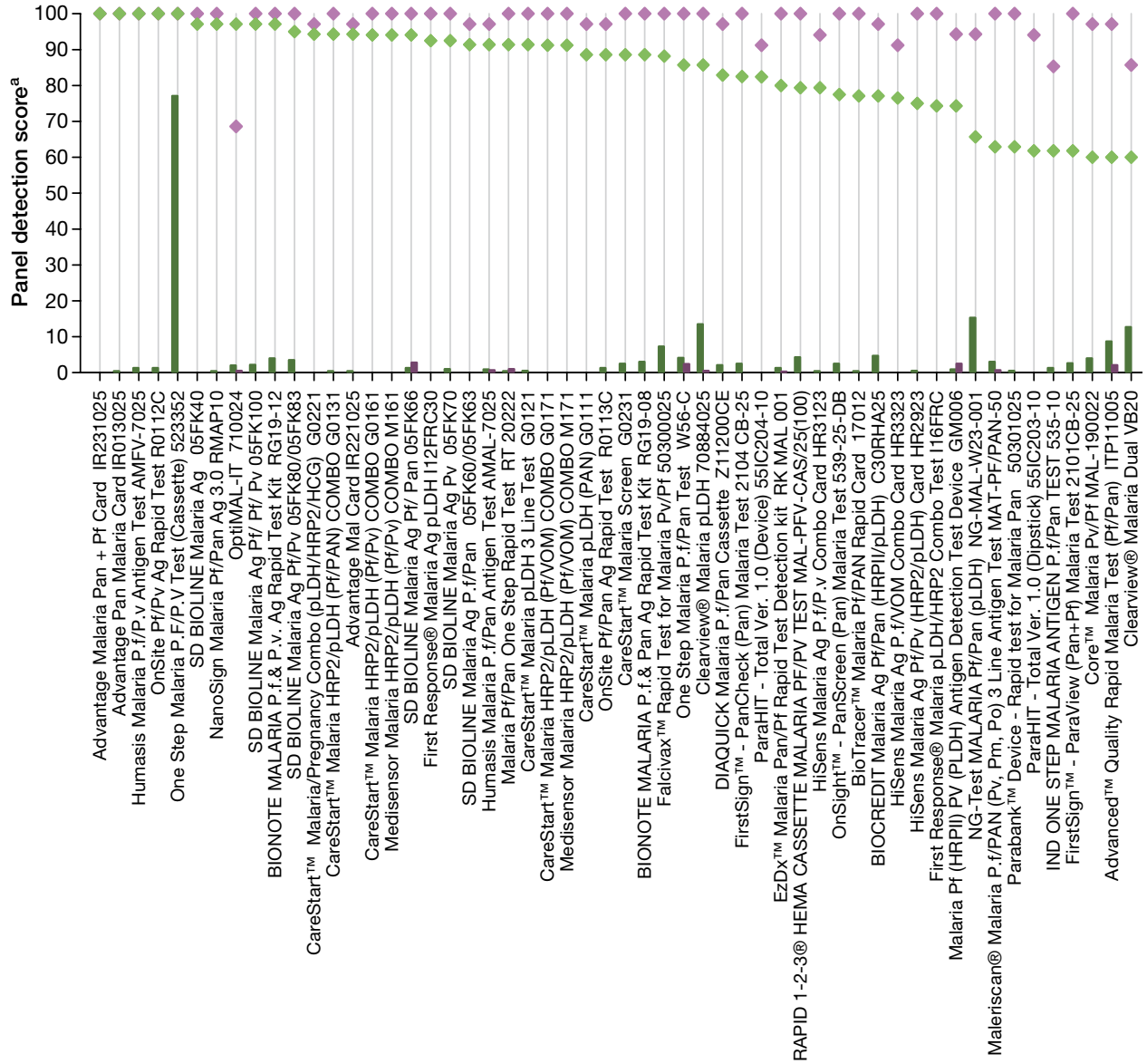

False-positive Plasmodium spp. rate on clean-negative samples[b] (%) and invalid rate (%)
0
20
40
60
80
100
NanoSign Malaria Pf Ag RMAF10
ParaHIT® -f (Device) 55IC104-50
ParaHIT - Total Ver. 1.0 (Device) 55IC204-10
Advantage Malaria Pan + Pf Card IR231025
CareStart™ Malaria pLDH (PAN) G0111
Maleriscan® Malaria P.f/PAN (Pv, Pm, Po) 3 Line Antigen Test MAT-PF/PAN-50
GenBody™ Malaria Pf/Pan Ag MALAG100
Vision Malaria Pf VB01
HiSens Malaria Ag Pf/Pv (HRP2/pLDH) Card HR2923
CareStart™ Malaria/Pregnancy Combo (pLDH/HRP2/HCG) G0221
Surestep™ Easy Malaria Pf/Pan Rapid Test Device IMA-T402
Maleriscan ® Malaria P.f Antigen Test MAT-PF-50
EzDx™ Malaria Pan/Pf Rapid Test Detection kit RK MAL 001
Clearview® Malaria Combo VB11
Malascan™ Device - Rapid test for Malaria Pf/Pan 50402025
IMMUNOQUICK CONTACT falciparum 0519K25
Clearview® Malaria pLDH 70884025
ASAN Easy Test® Malaria Pf/Pan Ag AM4650-K
ParaHIT®-f (Dipstick) 55IC103-50
diagnosticks- Malaria (Pf) Dipstick WB KMFD6007
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device MFV-124V
OnSite Pf/Pv Ag Rapid Test R0112C
KHB® Malaria Ag P.f Rapid Test KH-R-06-20
Advantage Malaria Card IR211025
Advantage Pan Malaria Card IR013025
BioTracer™ Malaria Pf/PAN Rapid Card 17012
BIOCREDIT Malaria Ag Pf/Pan (HRPII/pLDH) C30RHA25
ParaHIT - Total Ver. 1.0 (Dipstick) 55IC203-10
ICT MALARIA COMBO ML02
IMMUNOQUICK CONTACT MALARIA +4 0525K25
OnSight™ - Malaria Pf Test 511-25-DB
RightSign™ Malaria P.f/Pan Rapid Test Cassette IMPN-C52
Immunoquick Malaria Falciparum 0502_K25
Paracheck® Pf - Rapid test for P. falciparum Malaria Dipstick (vER.3) 302040025
ABON Malaria Pan/P.f. Rapid Test Device IMA-B402
MeDiPro Malaria Ag HRP2/pLDH Combo IR-0051K
Genedia® Malaria P.f/Pan Ag Rapid Test 20-0146-01
ACCUCARE ONE STEP MALARIA Pf/Pan Antigen Test MAGC 25
ParaHIT® total (dipstick) 55IC201-10
Malaria pf (HRP II)/PAN (pLDH) Antigen Detection Test Device 1-13-101-1
ParaHIT®fV Rapid test for P. falciparum and P.vivax Malaria - Device 55IC402-50
AZOG Malaria pf (HRPII)/pf (LDH)/ (PAN-LDH) Antigen Detection Device MFV-124F
AZOG hCG Malaria Detection Test Device MPT-124
IND ONE STEP MALARIA ANTIGEN P.f 535-11
Malaria Pf./Pan Antigen (MAL Pf/Pan) Test Kit A03-18-322
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device 1-13-101-3
Malaria Pan Test MAL-W23N-001
Advanced Quality™ One Step Malaria P.f Test ITP11002TC1/TC40
Maleriscan® Malaria Pf/Pv MAT-50
OptiMAL-IT 710024
Malaria pf (pLDH) / PAN-pLDH Test Device MFV-124
Malaria Pf/Pv GM002
Malaria Pf/ PAN GM004
One Step Malaria P.f/Pan Test W56-C
ABON™ Malaria P.f. Rapid Test Device (Whole Blood) IMA-402
First Response® Malaria Ag pLDH I12FRC30
Advantage Mal Card IR221025
FirstSign™ - PanCheck (Pan) Malaria Test 2104 CB-25
OnSight™ - PanScreen (Pan) Malaria Test 539-25-DB
HiSens Malaria Ag P.f/P.v Card HR2823
Parabank™ Device - Rapid test for Malaria Pan 50301025
SD BIOLINE Malaria Ag 05FK40
diagnosticks MALARIA (Pan) Cassette MPNWBC1007.3
NanoSign Malaria Pf/Pv Ag RMAD10
200 parasites/µL (HRP2)
200 parasites/µL (non-HRP2)
2000 parasites/µL (HRP2)
2000 parasites/µL (non-HRP2)
False-positive Plasmodium spp. rate (%)
Invalid rate (%)

Figure S2: Malaria RDT performance in phase 2 of rounds 2–5 against wild-type (clinical) samples containing *P. vivax* at low (200) and high (2000 or 5000) parasite density (parasites/µL) and clean-negative samples



[a] Panel detection score - A sample is considered detected only if all RDTs from both lots read by the first technician, at the minimum specified reading time, are positive.

[b] Clean-negative - blood samples from healthy volunteers with no known current illness or blood abnormality.

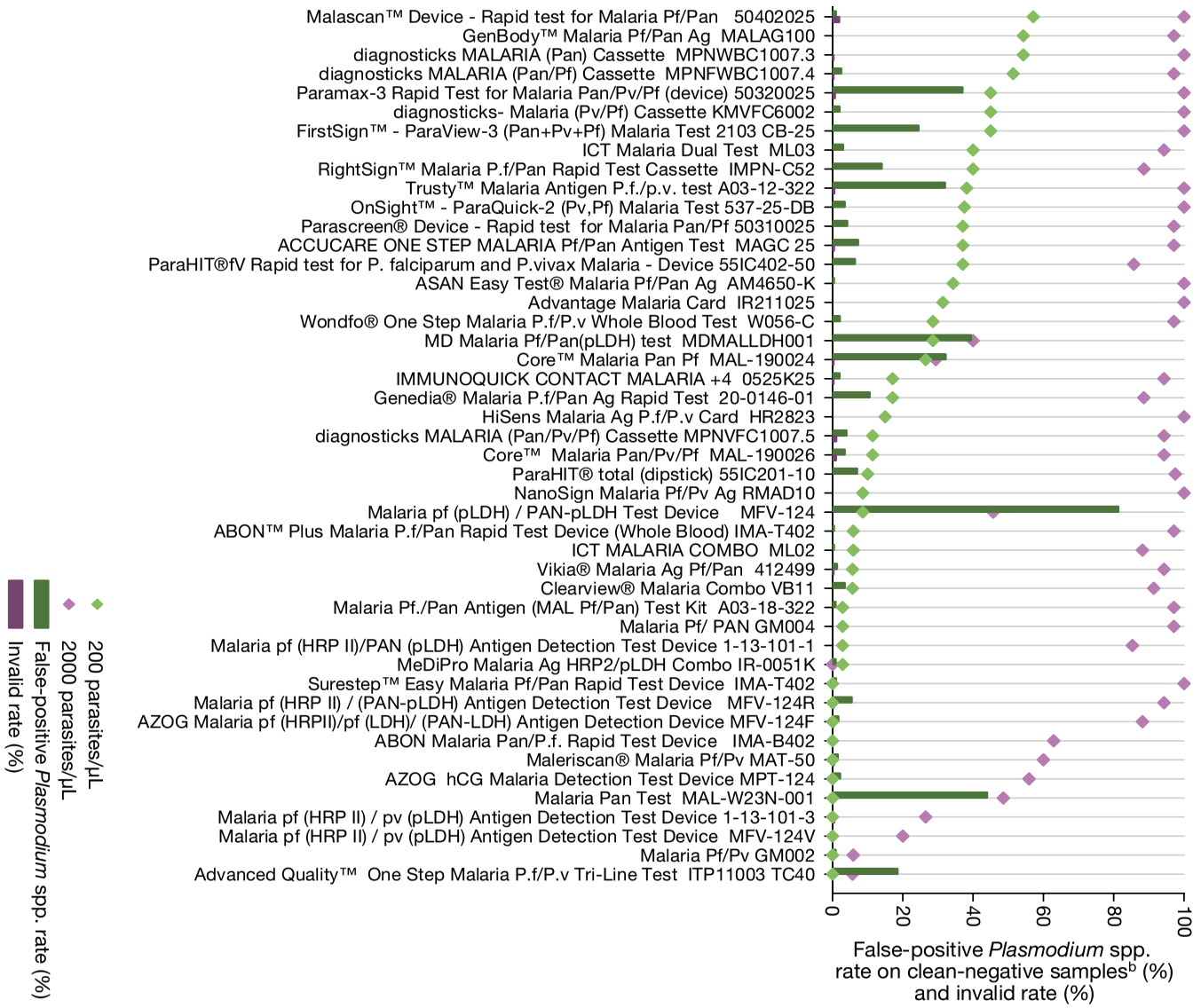
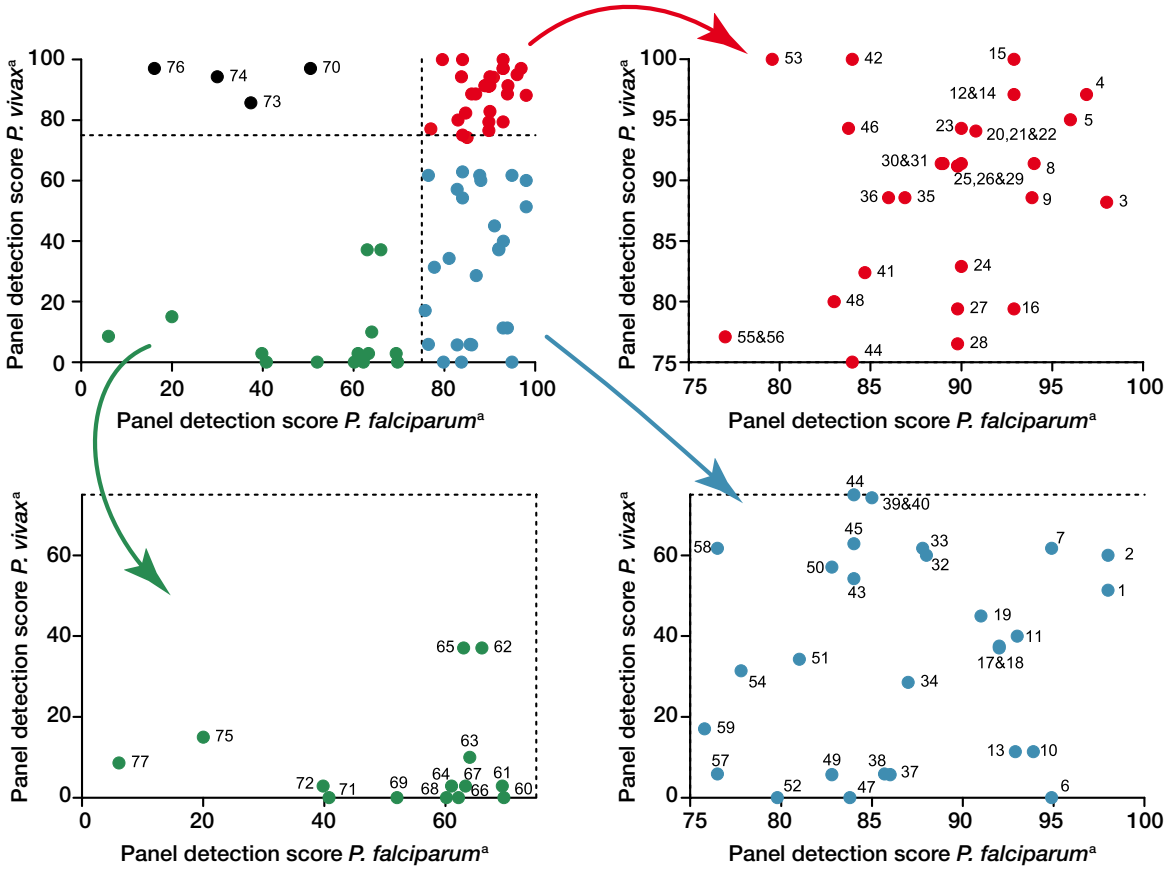

Malascan™ Device - Rapid test for Malaria Pf/Pan 50402025
GenBody™ Malaria Pf/Pan Ag MALAG100
diagnosticks MALARIA (Pan) Cassette MPNWBC1007.3
diagnosticks MALARIA (Pan/Pf) Cassette MPNFWBC1007.4
Paramax-3 Rapid Test for Malaria Pan/Pv/Pf (device) 50320025
diagnosticks- Malaria (Pv/Pf) Cassette KMVFC6002
FirstSign™ - ParaView-3 (Pan+Pv+Pf) Malaria Test 2103 CB-25
ICT Malaria Dual Test ML03
RightSign™ Malaria P.f/Pan Rapid Test Cassette IMPN-C52
Trusty™ Malaria Antigen P.f./p.v. test A03-12-322
OnSight™ - ParaQuick-2 (Pv,Pf) Malaria Test 537-25-DB
Parascreen® Device - Rapid test for Malaria Pan/Pf 50310025
ACCUCARE ONE STEP MALARIA Pf/Pan Antigen Test MAGC 25
ParaHIT®fV Rapid test for P. falciparum and P.vivax Malaria - Device 55IC402-50
ASAN Easy Test® Malaria Pf/Pan Ag AM4650-K
Advantage Malaria Card IR211025
Wondfo® One Step Malaria P.f/P.v Whole Blood Test W056-C
MD Malaria Pf/Pan(pLDH) test MDMALLDH001
Core™ Malaria Pan Pf MAL-190024
IMMUNOQUICK CONTACT MALARIA +4 0525K25
Genedia® Malaria P.f/Pan Ag Rapid Test 20-0146-01
HiSens Malaria Ag P.f/P.v Card HR2823
diagnosticks MALARIA (Pan/Pv/Pf) Cassette MPNVFC1007.5
Core™ Malaria Pan/Pv/Pf MAL-190026
ParaHIT® total (dipstick) 55IC201-10
NanoSign Malaria Pf/Pv Ag RMAD10
Malaria pf (pLDH) / PAN-pLDH Test Device MFV-124
ABON™ Plus Malaria P.f/Pan Rapid Test Device (Whole Blood) IMA-T402
ICT MALARIA COMBO ML02
Vikia® Malaria Ag Pf/Pan 412499
Clearview® Malaria Combo VB11
Malaria Pf./Pan Antigen (MAL Pf/Pan) Test Kit A03-18-322
Malaria Pf/ PAN GM004
Malaria pf (HRP II)/PAN (pLDH) Antigen Detection Test Device 1-13-101-1
MeDiPro Malaria Ag HRP2/pLDH Combo IR-0051K
Surestep™ Easy Malaria Pf/Pan Rapid Test Device IMA-T402
Malaria pf (HRP II) / (PAN-pLDH) Antigen Detection Test Device MFV-124R
AZOG Malaria pf (HRPII)/pf (LDH)/ (PAN-LDH) Antigen Detection Device MFV-124F
ABON Malaria Pan/P.f. Rapid Test Device IMA-B402
Maleriscan® Malaria Pf/Pv MAT-50
AZOG hCG Malaria Detection Test Device MPT-124
Malaria Pan Test MAL-W23N-001
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device 1-13-101-3
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device MFV-124V
Malaria Pf/Pv GM002
Advanced Quality™ One Step Malaria P.f/P.v Tri-Line Test ITP11003 TC40
0
20
40
60
80
100
False-positive Plasmodium spp. rate on clean-negative samples[b] (%) and invalid rate (%)
200 parasites/µL
2000 parasites/µL
False-positive Plasmodium spp. rate (%)
Invalid rate (%)

Figure S3: Panel detection score of malaria combination and pan-only RDTs, meeting WHO procurement criteria for false-positive and invalid rates, in phase 2 of rounds 2-5 against wild-type (clinical) samples containing *P. falciparum* and *P. vivax* at low (200) parasite density (parasites/µL)



1 diagnosticks MALARIA (Pan/Pf) Cassette- MPNFWBC1007.4
2 Core™ Malaria Pv/Pf - MAL-190022
3 FalciVax™ - Rapid test for Malaria Pv/Pf - 50300025
4 SD BIOLINE Malaria Ag Pf/ Pf/ Pv - 05FK100
5 SD BIOLINE Malaria Ag Pf/Pv - 05FK80/05FK83
6 Malaria pf (HRP II) / (PAN-pLDH) Antigen Detection Test Device - MFV-124R
7 IND ONE STEP MALARIA ANTIGEN P.f/Pan TEST - 535-10
8 SD BIOLINE Malaria Ag P.f/Pan - 05FK60/05FK63
9 BIONOTE MALARIA P.f.& Pan Ag Rapid Test Kit - RG19-08
10 diagnosticks MALARIA (Pan/Pv/Pf) Cassette - MPNVFC1007.5
11 ICT Malaria Dual Test - ML03
12 BIONOTE MALARIA P.f.& P.v. Ag Rapid Test Kit - RG19-12
13 Core™ Malaria Pan/Pv/Pf - MAL-190026
14 NanoSign Malaria pf/pan Ag 3.0 - RMAP10
15 Humasis Malaria P.f/P.v Antigen Test - AMFV-7025
16 RAPID 1-2-3® HEMA CASSETTE MALARIA PF/PV TEST - MAL-PFV-CAS/25(100)
17 Parascreen® - Rapid test for Malaria Pan/Pf - 50310025
18 OnSight™ - ParaQuick-2 (Pv,Pf) Malaria Test - 537-25-DB
19 diagnosticks- Malaria (Pv/Pf) Cassette - KMVFC6002
20 CareStart™ Malaria HRP2/pLDH (Pf/Pv) COMBO - G0161
21 Medisensor Malaria HRP2/pLDH (Pf/Pv) COMBO - M161
22 SD BIOLINE Malaria Ag Pf/ Pan - 05FK66
23 CareStart™ Malaria HRP2/pLDH (Pf/PAN) COMBO - G0131
24 DIAQUICK Malaria P.f/Pan Cassette - Z11200CE
25 Humasis Malaria P.f/Pan Antigen Test - AMAL-7025
26 CareStart™ Malaria HRP2/pLDH (Pf/VOM) COMBO - G0171
27 HiSens Malaria Ag P.f/P.v Combo Card - HR3123
28 HiSens Malaria Ag P.f/VOM Combo Card - HR3323
29 Medisensor Malaria HRP2/pLDH (Pf/VOM) COMBO - M171
30 Malaria Pf/Pan One Step Rapid Test - RT 20222
31 CareStart™ Malaria pLDH 3 Line Test - G0121
32 Advanced Quality™ Rapid Malaria Test (Pf/Pan) - ITP11005
33 FirstSign™ ParaView (Pan+Pf) - 2101CB-25
34 Wondfo® One Step Malaria P.f/P.v Whole Blood Test - W056-C
35 CareStart™ Malaria Screen - G0231
36 OnSite Pf/Pan Ag Rapid Test - R0113C
37 Vikia® Malaria Ag Pf/Pan - 412499
38 ABON™ Plus Malaria P.f/Pan Rapid Test Device (Whole Blood) - IMA-T402
39 First Response® Malaria Ag. pLDH/HRP2 Combo Card Test - I16FRC
40 Malaria Pf (HRPII)/ PV (PLDH) Antigen Detection Test Device - GM006
41 ParaHIT - Total Ver. 1.0 (Device) - 55IC204-10
42 Advantage Malaria Pan + Pf Card - IR231025
43 GenBody™Malaria Pf/Pan Ag - MALAG100
44 HiSens Malaria Ag Pf/Pv (HRP2/pLDH) Card - HR2923
45 Maleriscan® Malaria Pf/PAN (Pv, Pm, Po) 3 Line Antigen Test - MAT-PF/PAN-50
46 CareStart™ Malaria/Pregnancy Combo (pLDH/HRP2/HCG) - G0221
47 Surestep™ Easy Malaria Pf/Pan Rapid Test Device - IMA-T402
48 EzDx™ Malaria Pan/Pf Rapid Test Detection kit - RK MAL 001
49 Clearview® Malaria Combo - VB11
50 Malascan™ Device - Rapid test for Malaria Pf/Pan - 50402025
51 ASAN Easy Test® Malaria Pf/Pan Ag - AM4650-K
52 Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device - MFV-124V
53 OnSite Pf/Pv Ag Rapid Test - R0112C
54 Advantage Malaria Card - IR211025
55 BIOCREDIT Malaria Ag Pf/Pan (HRPII/pLDH) - C30RHA25
56 BioTracer™ Malaria Pf/PAN Rapid Card - 17012
57 ICT MALARIA COMBO - ML02
58 ParaHIT - Total Ver. 1.0 (Dipstick) - 55IC203-10
59 IMMUNOQUICK CONTACT MALARIA +4 - 0525K25
60 ABON Malaria Pan/P.f. Rapid Test Device - IMA-B402
61 MeDiPro Malaria Ag HRP2/pLDH Combo - IR-0051K
62 ACCUCARE ONE STEP MALARIA Pf/Pan Antigen Test - MAGC 25
63 ParaHIT® total (dipstick) - 55IC201-10
64 Malaria pf (HRP II)/PAN (pLDH) Antigen Detection Test Device - 1-13-101-1
65 ParaHIT®fV Rapid test for P. falciparum and P.vivax Malaria - Device - 55IC402-5
66 AZOG Malaria pf (HRPII)/pf (LDH)/ (PAN-LDH) Antigen Detection Device - MFV-124F
67 Malaria Pf./Pan Antigen (MAL Pf/Pan) Test Kit - A03-18-322
68 Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device - MFV-124V
69 Maleriscan® Malaria Pf/Pv - MAT-50
70 OptiMAL-IT - 710024
71 Malaria Pf/Pv - GM002
72 Malaria Pf/ PAN - GM004
73 One Step Malaria P.f/Pan Test - W56-C
74 Advantage Mal Card - IR221025
75 HiSens Malaria Ag P.f/P.v Card - HR2823
76 SD BIOLINE Malaria Ag - 05FK40
77 NanoSign Malaria Pf/Pv Ag - RMAD10

[a] Panel detection score - A sample is considered detected only if all RDTs from both lots read by the first technician, at the minimum specified reading time, are positive.

Table S1: Product resubmissions: WHO malaria RDT product testing rounds 1–5

Manufacturer	Product name	Catalogue No.	Product re-submission Round	
			Voluntary	Compulsory
Access Bio, Inc.	CareStart™ Malaria HRP2/PLDH (Pf/Pv) COMBO	G0161	2, 4	
	CareStart™ Malaria HRP2/PLDH (Pf/VOM) COMBO	G0171	2, 4	
	CareStart™Malaria HRP2 (Pf)	G0141	1	5
	CareStart™ Malaria HRP2/pLDH (Pf/PAN) Combo	G0131	1	5
	CareStart™Malaria pLDH (PAN)	G0111	1	5
Advy Chemical Pvt. Ltd. (Affiliate of Bharat Serums & Vaccines Ltd.)	EzDx™ Malaria Pan/Pf Rapid Test Detection Kit	RK MAL 001	4, 5	
Biosynex	IMMUNOQUICK® MALARIA *falciparum*	0502_K25	1	5
AZOG	Malaria pf (HRP II) / (PAN-LDH) Antigen Detection Test Device[a]	MFV-124R	1, 3	
	Malaria pf (pLDH) / PAN-pLDH Test Device	MFV-124	3, 5	
Bhat Bio-Tech India (P) Ltd.	Maleriscan® Malaria Pf/PAN (Pv, Pm, Po) 3 Line Antigen Test	MAT-PF/PAN-50	4, 5	
Bioland	NanoSign Malaria Pf/Pan Ag	RMAP10	3, 4	
Blue Cross Bio-Medical (Beijing) Co., Ltd.	One Step Malaria Pf Test (cassette)	522352	2, 3, 4	
	One Step Malaria P.F/P.V Test (Cassette)	523352	4, 5	
CTK Biotech, Inc.	Onsite Pf Ag Rapid Test	R0114C	2, 3	
	Onsite Malaria Pf/Pan Malaria Ag Rapid Test	R0113C	2, 3, 4, 5	
	Onsite Malaria Pf/Pv Ag Rapid Test	R0112C	2, 3, 4	
DiaMed - A Division of Bio-Rad	OptiMAL-IT	710024	1, 3	
Guangzhou Wondfo Biotech Co. Ltd.	Wondfo One Step Malaria Pf/Pan Whole Blood Test	W56-C	1, 3	
	One Step Malaria P.f Test[b]	W37-C	2, 3, 4	
ICT INTERNATIONAL	ICT Malaria Combo Cassette Test	ML02	1, 3, 4	
	ICT Malaria Pf Cassette Test	ML01	1, 3	
	ICT Malaria Dual Test	ML03	3, 5	
InTec Products, Inc.	Advanced Quality™ One Step Malaria Pf Test	ITP11002TC1/TC40	1, 3	5
Humasis Co., Ltd.	Humasis Malaria Pf/Pan Antigen Test	AMAL-7025	4, 5	
J.Mitra & Co. Pvt. Ltd.	Advantage Pan Malaria Card	IR013025	1	5
	Advantage Mal Card	IR221025	1	5
	Advantage P.f Malaria Card	IR016025	1	5
Orchid Biomedical Systems	Paracheck® Pf Device - Rapid test for *P. falciparum* Malaria (Ver. 3)[c]	30301025	1, 3, 4	
	Paracheck® Pf Dipstick - Rapid test for *P. falciparum* Malaria (Ver.3)[c]	30302025	1, 3, 4	
Premier Medical Corporation Ltd.	First Response® Malaria Ag Combo (pLDH/HRP2)[d]	I16FRC	1, 2, 5	
	First Response Malaria Ag *P. falciparum* (HRP2) Card Test	I13FRC	1	5
SSA Diagnostics & Biotech Systems	diagnosticks- Malaria (Pf)Cassette WB	KMFC6001	2, 5	
Standard Diagnostics Inc.	SD BIOLINE Malaria Ag	05FK40	1, 3	
	SD BIOLINE Malaria Ag Pf/Pan	05FK60/05FK63	1, 3, 5	
	SD BIOLINE Malaria Antigen	05FK50/05FK53	1	5
Unimed International Inc.	FirstSign™ - ParaView (Pan+Pf) Malaria Test	2101 CB-25	2, 4	
Vision Biotech (Pty) Ltd / Orgenics (Alere Healthcare (Pty) Ltd subsidaries)	Malaria Rapid Combo/Clearview® Malaria Combo	VB11[e]	1, 3	
	Malaria Rapid Pf /Clearview ®Malaria Pf	VB01	1, 3, 5	
	Malaria Rapid Dual/Clearview® Malaria Dual Test Device	VB20[e]	1, 3, 5	
Zephyr Biomedical Systems	Malascan™ Device - Rapid test for Malaria Pf/Pan	50402025	1, 3	
	Parabank™ Device - Rapid test for Malaria Pan	50301025	1, 3	
	Parascreen™ Device -Rapid test for Malaria Pan/Pf	50310025	1, 3, 4, 5	
	Falcivax Rapid Test for Malaria Pv/Pf (device)	50300025	2, 4	

[a] Round 1 product name error: published - Malaria Pf (HRPII)/pv-LDH) Antigen Detection Test Device Code; corrected product name: Malaria Pf (HRPII/PAN-LDH) Antigen Detection Test Device Code. No change in product code.

[b] In round 2, product did not pass phase-1, therefore results do not feature in summary tables.

[c] Ver.3 was introduced after round 1

[d] Error in WHO malaria RDT product testing: round 1 report: product code (II6FRC30) should have been (I16FRC), as in round 2

[e] New company acquisition (Alere™), therefore change in product branding and catalogue numbers; VB011 to VB11 and VB020 to VB20. Manufacturer confirmed compliance with product definition.

Table S2: Malaria RDT phase-2 performance in rounds 2–5 against wild-type (clinical) samples containing *P. falciparum* (Pf) and *P. vivax* (Pv) at low (200) and high (2000–5000) parasite density (parasites/µL) and clean-negative samples

Product	Catalogue number	Manufacturer	Panel detection score[a]				False-positive rates (%)				Total false-positive rates[b] (%)	Invalid rate (%)[l]	Round
			200 parasites/µL		2000 or 5000 parasites/µL		200 parasites/µL		2000 or 5000 parasites/µL		Clean-negative samples		
							Pf samples	Pv samples	Pf samples	Pv samples			
			Pf samples[c]	Pv samples[d]	Pf samples[c]	Pv samples[d]	False-positive non-Pf infection[e]	False-positive Pf infection[f]	False-positive non-Pf infection[g]	False-positive Pf infection[h]	False-positive *Plasmodium* spp. Infection[i]		
Pf only													
ABON™ Malaria P.f. Rapid Test Device (Whole Blood)	IMA-402	ABON Biopharm (Hangzhou) Co. Ltd	32.7	NA	99.0	NA	NA	0.0	NA	0.0	0.4	0.0	4
Advanced Quality™ One Step Malaria Pf Test[j]	ITP11002TC1/ TC40	InTec Products, Inc.	53.0	NA	93.0	NA	NA	3.6	NA	5.7	7.7 (233)	0.4	5
Advantage P.f. Malaria Card[j]	IR016025	J. Mitra & Co. Pvt. Ltd.	89.0	NA	99.0	NA	NA	0.7	NA	0.0	0.0	0.0	5
BIOCREDIT Malaria pf(HRP II)	HR0100	RapiGen Inc.	99.0	NA	100.0	NA	NA	97.1	NA	95.59	99.1 (231)	0.5	4
BIONOTE MALARIA P.f. Ag Rapid Test Kit	RG19-11	Bionote,Inc.	85.9	NA	99.0	NA	NA	0.0	NA	1.4	2.0	0.1	3
CareStart™ Malaria HRP2 (Pf)[j]	G0141	Access Bio, Inc.	91.0	NA	100.0	NA	NA	0.0	NA	0.0	0.9	0.0	5
CareStart™ Malaria HRP2/pLDH Pf test	G0181	Access Bio, Inc.	98.0	NA	100.0	NA	NA	0.6	NA	1.3	3.0	0.0	2
Clearview® Malaria P.f.[j]	VB01	Vision Biotech (Pty) Ltd	83.8	NA	100.0	NA	NA	0.0	NA	0.0	0.0	0.0	3
Core™ Malaria Pf	MAL-190020	Core Diagnostics	97.0	NA	100.0	NA	NA	0.0	NA	0.0	1.0 (198)	0.3	3
diagnosticks- Malaria (Pf) Cassette WB	KMFC6001	SSA Diagnostics & Biotech Systems	88.0	NA	100.0	NA	NA	2.1	NA	1.4	0.9 (235)	0.3	5
diagnosticks- Malaria (Pf) Dipstick WB	KMFD6007	SSA Diagnostics & Biotech Systems	80.0	NA	99.0	NA	NA	2.5	NA	3.8	2.0	0.0	2
First Response® Malaria Ag *P. falciparum* (HRP2) Card Test[j]	I13FRC	Premier Medical Corporation Ltd.	95.0	NA	100.0	NA	NA	0.7	NA	0.0	0.4	0.0	5
FirstSign™ Malaria Pf	2100CB-25	Unimed International Inc.	94.9	NA	100.0	NA	NA	0.7	NA	1.47	2.2 (231)	0.2	4
HiSens Malaria Ag Pf HRP2 Card	HR3023	HBI Co., Ltd.	87.0	NA	100.0	NA	NA	0.0	NA	0.0	1.0	0.1	2
ICT Diagnostics Malaria P.f.[j]	ML01	ICT INTERNATIONAL	86.9	NA	98.0	NA	NA	0.0	NA	0.0	0.0	0.0	3
IMMUNOQUICK CONTACT *falciparum*	0519K25	Biosynex	81.8	NA	100.0	NA	NA	3.6 (139)	NA	1.4	4.0 (199)	0.3	3
IMMUNOQUICK® MALARIA *falciparum*[j]	0502_K25	Biosynex	72.0	NA	93.0	NA	NA	3.6	NA	4.3	5.1 (234)	0.2	5
IND ONE STEP MALARIA ANTIGEN P.f	535-11	IND Diagnostics Inc.	61.2	NA	99.0	NA	NA	2.2	NA	14.71	6.0	0.1	4
KHB® Malaria Ag P.f Rapid Test	KH-R-06-20	Shanghai Kehua Bio-engineering Co.,Ltd.	79.0	NA	91.8(98)	NA	NA	11.4	NA	12.9	10.6 (235)	0.7	5
Maleriscan ® Malaria P.f Antigen Test	MAT-PF-50	Bhat Bio-Tech India (Pte.) Ltd.	83.7	NA	98.0	NA	NA	1.5	NA	0.0	0.4	0.2	4
NanoSign Malaria Pf Ag	RMAF10	Bioland, Ltd	84.9	NA	100.0	NA	NA	0.0	NA	0.0	0.0	0.3	3
One Step Malaria P.F Test (Cassette)[j]	522352	Blue Cross Bio-Medical (Beijing) Co., Ltd.	94.9	NA	99.0	NA	NA	0.0	NA	1.47	1.3	0.0	4
OnSight™ - Malaria Pf Test	511-25-DB	Amgenix International, Inc.	74.0	NA	99.0	NA	NA	8.1	NA	2.5	11.0	0.0	2
OnSite Pf Ag Rapid Test[j]	R0114C	CTK Biotech, Inc.	85.9	NA	100.0	NA	NA	0.7	NA	0.0	3.5	0.0	3
Paracheck® Pf-Rapid Test for *P. falciparum* Malaria Device (Ver.3)[j]	302030025	Orchid Biomedical Systems	95.9	NA	98.0	NA	NA	0.0	NA	0.0	1.3	0.0	4
Paracheck® Pf-Rapid Test for *P. falciparum* Malaria Dipstick (Ver.3)[j]	302040025	Orchid Biomedical Systems	70.4	NA	99.0	NA	NA	0.0	NA	0.0	0.9	0.0	4
ParaHIT® - f (Device)	55IC104-50	Span Diagnostics Ltd.	84.9	NA	100.0	NA	NA	0.0	NA	0.0	0.0	0.0	3
ParaHIT® -f (Dipstick)	55IC103-50	Span Diagnostics Ltd.	80.8	NA	99.0	NA	NA	0.0	NA	1.4	2.5	0.0	3
SD BIOLINE Malaria Ag P.f. (HRP2/pLDH)[k]	05FK90	Standard Diagnostics Inc.	87.9	NA	100.0	NA	NA	0.0	NA	0.0	2.0	0.0	3
SD BIOLINE Malaria Ag Pf[j]	05FK50/05FK53	Standard Diagnostics, Inc.	95.0	NA	99.0	NA	NA	0.0	NA	2.9	0.0	0.0	5
Trusty™ Malaria Antigen P.f. test	A03-01-322	Artron Laboratories Inc.	88.8	NA	100.0	NA	NA	4.4 (135)	NA	2.94	5.2 (230)	0.7	4
Vision Malaria Pf[j]	VB01	Vision Biotech (Pty) Ltd	84.0	NA	100.0	NA	NA	2.1	NA	1.4	5.1 (235)	0.1	5
Wondfo One Step Malaria P.f Test[j]	W 37-C	Guangzhou Wondfo Biotech Co. Ltd.	89.8	NA	99.0	NA	NA	0.0	NA	0.0	0.4 (231)	0.2	4
Pf and pan													
ABON Malaria Pan/P.f. Rapid Test Device	IMA-B402	ABON Biopharm (Hangzhou) Co. Ltd.	69.7	0.0	99.0	62.9	0.0	0.0	0.0	0.0	0.0	0.0	3
ABON™ Plus Malaria *P.f/Pan* Rapid Test Device (Whole Blood)	IMA-T402	ABON Biopharm (Hangzhou) Co. Ltd	85.7	5.9	100.0	97.1	0.0	0.0	0.0	0.0	0.4	0.0	4
ACCUCARE ONE STEP MALARIA Pf/Pan Antigen Test	MAGC 25	LAB-CARE Diagnostics (India) PVT. LTD.	66.0	37.1	92.0	97.1	0.3	0.0 (139)	0.0 (199)	0.0	7.3 (234)	0.4	5
Advanced Quality™ Rapid Malaria Test (Pf/Pan)	ITP11005	InTec Products, Inc.	88.0	60.0	100.0	97.1	0.3 (389)	6.7 (134)	0.0 (197)	1.4	8.7 (231)	2.1	5
Advantage Mal Card[j]	IR221025	J. Mitra & Co. Pvt. Ltd.	30.0	94.3	94.0	97.1	1.5	0.7	0.5	0.0	0.4	0.0	5

Table S2 *(continued)*

Product	Catalogue number	Manufacturer	Panel detection score[a]				False-positive rates (%)				Total false-positive rates[b] (%)	Invalid rate (%)[l]	Round
			200 parasites/µL		2000 or 5000 parasites/µL		200 parasites/µL		2000 or 5000 parasites/µL		Clean-negative samples		
							Pf samples	Pv samples	Pf samples	Pv samples			
			Pf samples[c]	Pv samples[d]	Pf samples[c]	Pv samples[d]	False-positive non-Pf infection[e]	False-positive Pf infection[f]	False-positive non-Pf infection[g]	False-positive Pf infection[h]	False-positive *Plasmodium* spp. Infection[i]		
Advantage Malaria Pan + Pf Card	IR231025	J. Mitra & Co. Pvt. Ltd.	84.0	100.0	100.0	100.0	3.5	0.0	0.0	0.0 (69)	0.0	0.2	5
AZOG Malaria pf (HRPII)/pf (LDH)/ (PAN-LDH) Antigen Detection Device[k]	MFV-124F	AZOG, INC.	62.2	0.0	98.0	88.2	0.0 (390)	5.2	0.0	0.0	1.7 (231)	0.3	4
BIOCREDIT Malaria Ag Pf/Pan (HRPII/pLDH)	C30RHA25	RapiGEN INC.	77.0	77.1	99.0	97.1	0.8	0.7	0.5 (198)	0.0	4.7	0.2	5
BIONOTE MALARIA P.f.& Pan Ag Rapid Test Kit	RG19-08	Bionote,Inc.	93.9	88.6	99.0	100.0	0.0	0.0	0.0	0.0	3.0 (199)	0.1	3
BioTracer™ Malaria Pf/PAN Rapid Card	17012	Bio Focus Co., Ltd.	77.0	77.1	94.0	100.0	0.5	0.7	2.0	0.0	0.4	0.0	5
CareStart™ Malaria/Pregnancy Combo (pLDH/HRP2/HCG)	G0221	Access Bio, Inc.	83.8	94.3	100.0	97.1	2.3	1.4 (139)	0.0 (194)	1.4	0.0	0.2	3
CareStart™ Malaria HRP2/pLDH (Pf/PAN) COMBO[j]	G0131	Access Bio, Inc.	90.0	94.3	100.0	100.0	1.5	0.7	0.0	0.0	0.4	0.0	5
CareStart™ Malaria pLDH 3 Line Test	G0121	Access Bio, Inc.	88.9	91.4	100.0	100.0	1.3	0.7	6.1	0.0	0.5	0.0	3
CareStart™ Malaria Screen	G0231	Access Bio, Inc.	86.9	88.6	100.0	100.0	1.8	2.1	0.0	0.0	2.5 (199)	0.1	3
Clearview® Malaria Combo[j]	VB11	Vision Biotech (Pty) Ltd	82.8	5.7	100.0	91.4	0.0	5.7	0.5	5.7	3.5	0.0	3
Clearview® Malaria Dual[j]	VB20	Orgenics Ltd.(IS)	89.0	60.0	99.0	85.7	0.3	12.1	0.5	7.1	12.7	0.0	5
Core™ Malaria Pan Pf	MAL-190024	Core Diagnostics Ltd.	99.0	26.5	100.0	29.4	0.0	33.8	0.0	42.7	32.2 (230)	0.3	4
diagnosticks MALARIA (Pan/Pf) Cassette	MPNFWBC 1007.4	SSA Diagnostics & Biotech Systems	98.0	51.4	100.0	97.1	0.0 (394)	0.0	0.0	0.0 (69)	2.5	0.3	3
DIAQUICK Malaria *P.f/Pan* Cassette	Z11200CE	DIALAB GmbH	90.0	82.9	100.0	97.1	0.3	2.9	0.0	1.5 (67)	2.1	0.2	5
EzDx™ Malaria Pan/Pf Rapid Test Detection kit[j]	RK MAL 001	Advy Chemical (Affiliate of Bharat Serums & Vaccines Ltd.)	83.0	80.0	100.0	100.0	0.3	0.7 (139)	0.0	0.0	1.3 (235)	0.3	5
First Response® Malaria Ag. pLDH/HRP2 Combo Card Test[j]	I16FRC	Premier Medical Corporation Ltd.	85.0	74.3	100.0	100.0	0.3	0.0	0.0	0.0	0.0	0.0	5
FirstSign™ ParaView (Pan+Pf)[j]	2101CB-25	Unimed International Inc.	87.8	61.8	100.0	100.0	0.3	1.5	0.0	0.0	2.6	0.0	4
GenBody™Malaria Pf/Pan Ag	MALAG100	GenBody Inc.	84.0	54.3	100.0	97.1	0.0	0.0	0.0	0.0	0.0 (235)	0.2	5
Genedia® Malaria *P.f/Pan* Ag Rapid Test	20-0146-01	Green Cross Medical Science Corp. (Korea)	67.0	17.1	96.0	88.6	0.0	13.6	0.0	7.1	10.6	0.1	5
HiSens Malaria Ag P.f/P.v Card	HR2823	HBI Co., Ltd.	20.0	15.0	94.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	2
HiSens Malaria Ag Pf/Pv (HRP2/pLDH) Card	HR2923	HBI Co., Ltd.	84.0	75.0	99.0	100.0	0.0	0.0	0.0	0.0	0.5	0.0	2
Humasis Malaria *P.f/Pan* Antigen Test[j]	AMAL-7025	Humasis, Co., Ltd.	90.0	91.4	100.0	97.1	0.5 (396)	0.0 (138)	0.0 (199)	1.4	0.9 (235)	0.7	5
ICT Malaria Dual Test [j]	ML03	ICT INTERNATIONAL	93.0	40.0	98.0	94.3	0.3	4.3	0.5	2.9	3.0	0.0	5
ICT MALARIA COMBO[j]	ML02	ICT INTERNATIONAL	76.5	5.9	99.0	88.2	0.5	0.7	0.0 (195)	1.5	0.4	0.1	4
IMMUNOQUICK CONTACT MALARIA +4	0525K25	Biosynex	75.8	17.1	98.0	94.3	1.8 (395)	5.1 (138)	0.0	0.0	2.0	0.3	3
IND ONE STEP MALARIA ANTIGEN *P.f/Pan* TEST	535-10	IND Diagnostics Inc.	94.9	61.8	100.0	85.3	0.0	2.2	0.0	5.9	1.3	0.0	4
Malaria Pan Test	MAL-W23N-001	Dima • Gesellschaft für Diagnostika mbH	54.6	0.0	97.0	48.6	2.8	15.7	0.0	17.1	44.0	0.0	3
Malaria Pf./Pan Antigen (MAL Pf/Pan) Test Kit	A03-18-322	Artron Laboratories Inc.	61.0	2.9	95.0	97.1	0.0 (398)	4.3	0.0 (199)	0.0	0.9	0.2	5
Malaria pf (HRP II) / (PAN-pLDH) Antigen Detection Test Device[j]	MFV-124R	AZOG, Inc.	95.0	0.0	100.0	94.3	0.0 (395)	7.9	8.1	0.0	5.5 (199)	0.3	3
Malaria pf (HRP II)/PAN (pLDH) Antigen Detection Test Device	1-13-101-1	United Biotech, Inc.	63.3	2.9	100.0	85.3	0.0	0.0 (135)	0.0	0.0	0.0	0.1	4
Malaria pf (pLDH) / PAN-pLDH Test Device [j]	MFV-124	AZOG, Inc.	41.0	8.6	97.0	45.7	22.5	47.9	1.5	35.7	81.3 (235)	0.1	5
Malaria Pf/ PAN	GM004	Genomix Molecular Diagnostics *Pvt.Ltd.*	39.8	2.9	94.9	97.1	0.3	0.7	0.0	0.0	0.0	0.0	4
Malaria Pf/Pan One Step Rapid Test	RT 20222	Zhejiang Orient Gene Biotech Co., Ltd.	89.0	91.4	100.0	100.0	0.0 (398)	0.7 (138)	0.0 (199)	0.0 (69)	0.4 (232)	1.0	5
Malascan™ Device - Rapid test for Malaria Pf/Pan[j]	50402025	Zephyr Biomedical Systems	82.8	57.1	97.0	100.0	1.0 (392)	0.7 (136)	1.0 (194)	0.0 (68)	1.0 (195)	1.9	3
MD Malaria Pf/Pan(pLDH) test	MDMALLDH001	Medical Diagnostech (Pty) Ltd	95.0	28.6	100.0	40.0	0.0	38.6	0.0	40.0	39.4	0.0	5
MeDiPro Malaria Ag HRP2/pLDH Combo	IR-0051K	Formosa Biomedical Technology Corp.	69.4	2.9	99.0	0.0	0.0 (391)	0.0	0.0	1.5	0.9	0.1	4
NanoSign Malaria pf/pan Ag 3.0[j]	RMAP10	Bioland Ltd.	92.9	97.1	100.0	100.0	0.8	0.0	0.0	0.0	0.4	0.0	4
NanoSign Malaria Pf/Pv Ag -	RMAD10	Bioland, Ltd	6.1	8.6	89.9	100.0	0.5	0.0 (139)	0.0	0.0	0.0	0.1	3
NG-Test MALARIA Pf/Pan (pLDH)	NG-MAL-W23-001	SARL NG Biotech, Z.A.	90.0	65.7	100.0	94.3	0.5 (399)	9.3	0.0	4.3	15.3	0.1	5

(continued)

Table S2: Malaria RDT phase-2 performance in rounds 2–5 against wild-type (clinical) samples containing *P. falciparum* (Pf) and *P. vivax* (Pv) at low (200) and high (2000–5000) parasite density (parasites/µL) and clean-negative samples *(continued)*

Product	Catalogue number	Manufacturer	Panel detection score[a]				False-positive rates (%)				Total false-positive rates[b] (%)	Invalid rate (%)[l]	Round
			200 parasites/µL		2000 or 5000 parasites/µL		200 parasites/µL		2000 or 5000 parasites/µL		Clean-negative samples		
			Pf samples[c]	Pv samples[d]	Pf samples[c]	Pv samples[d]	Pf samples	Pv samples	Pf samples	Pv samples			
							False-positive non-Pf infection[e]	False-positive Pf infection[f]	False-positive non-Pf infection[g]	False-positive Pf infection[h]	False-positive *Plasmodium* spp. Infection[i]		
One Step Malaria *P.f/Pan* Test[j]	W56-C	Guangzhou Wondfo Biotech Co. Ltd.	37.4	85.7	95.0	100.0	8.4 (383)	0.0 (137)	0.0 (194)	0.0 (68)	4.1 (195)	2.4	3
OnSite Pf/Pan Ag Rapid Test[j]	R0113C	CTK Biotech, Inc.	86.0	88.6	100.0	97.1	0.0 (399)	0.0	0.0	1.4	1.3	0.1	5
OptiMAL-IT	710024	Diamed - A Division of Bio-Rad	50.5	97.1	96.0	68.6	1.5	0.0	0.5	20.3 (69)	2.0 (198)	0.5	3
ParaHIT - Total Ver. 1.0 (Device)	55IC204-10	Span Diagnostics Ltd.	84.7	82.4	99.0	91.2	0.3	0.0	0.5	3.0 (67)	0.0	0.1	4
ParaHIT - Total Ver. 1.0 (Dipstick)	55IC203-10	Span Diagnostics Ltd.	76.5	61.8	100.0	94.1	0.8	0.0	0.0	1.5	0.0	0.0	4
ParaHIT® total (dipstick)	55IC201-10	Span Diagnostics Ltd	64.0	10.0	99.0	97.5	0.0	0.0	0.0	0.0	7.0	0.0	2
Parascreen® - Rapid test for Malaria Pan/Pf[j]	50310025	Zephyr Biomedicals	92.0	37.1	100.0	97.1	0.5	0.7	0.0 (199)	1.4	4.2	0.1	5
RightSign™ Malaria P.f./Pan Rapid Test Cassette	IMPN-C52	Hangzhou Biotest Biotech Co. Ltd.	74.0	40.0	94.0	88.6	2.0	2.9	0.5	5.7	14.0	0.0	5
SD BIOLINE Malaria Ag *P.f/Panj*	05FK60/05FK63	Standard Diagnostics Inc.	94.0	91.4	99.0	97.1	0.8	0.7	0.5	1.4	0.0	0.0	5
SD BIOLINE Malaria Ag Pf/ Pan	05FK66	Standard Diagnostics Inc.	90.8	94.1	100.0	100.0	1.0 (385)	0.0 (130)	0.0 (195)	0.0 (67)	1.3 (226)	2.8	4
SD BIOLINE Malaria Ag[j]	05FK40	Standard Diagnostics Inc.	16.2	97.1	93.9	100.0	0.8	0.0	0.0	0.0	0.0	0.0	3
Surestep™ Easy Malaria Pf/Pan Rapid Test Device	IMA-T402	ACON Biotech (Hangzhou) Co. Ltd.	83.8	0.0	100.0	100.0	0.0	0.0	0.0	0.0	1.0	0.0	3
Vikia® Malaria Ag Pf/Pan	412499	IMACCESS S.A.S	86.0	5.7	97.0	94.3	0.0	0.7 (139)	0.5 (199)	0.0 (69)	1.3 (235)	0.3	5
Pf and Pv/Pvom													
Advanced Quality™ One Step Malaria P.f/P.v Tri-Line Test	ITP11003 TC40	InTec Products, Inc.	86.9	0.0	100.0	5.7	15.7 (395)	5.7	8.1 (197)	4.3	18.5	0.2	3
Advantage Malaria Card	IR211025	J. Mitra & Co. Pvt. Ltd.	77.8	31.4	99.0	100.0	0.5	0.7	0.0	0.0	0.0	0.0	3
ASAN Easy Test® Malaria Pf/Pan Ag	AM4650-K	ASAN Pharmaceutical Co., Ltd	81.0	34.3	99.0	100.0	16.5	0.0	85.5	0.0	0.4 (235)	0.2	5
BIONOTE MALARIA P.f.& P.v. Ag Rapid Test Kit	RG19-12	Bionote,Inc.	92.9	97.1	98.0	100.0	0.3	0.7	1.5 (197)	0.0	4.0	0.0	3
CareStart™ Malaria HRP2/pLDH (Pf/Pv) COMBO[j]	G0161	Access Bio, Inc.	90.8	94.1	100.0	100.0	0.3	0.0	1.0	1.5	0.0	0.0	4
CareStart™ Malaria HRP2/pLDH (Pf/VOM) COMBO[j]	G0171	Access Bio, Inc.	89.8	91.2	100.0	100.0	0.3	0.7	0.5	2.9	0.0	0.0	4
Core™ Malaria Pv/Pf	MAL-190022	Core Diagnostics	98.0	60.0	100.0	97.1	0.3	0.0	0.0	0.0	4.0	0.1	3
diagnosticks- Malaria (Pv/Pf) Cassette	KMVFC6002	SSA Diagnostics & Biotech Systems	91.0	45.0	99.0	100.0	0.3 (399)	0.6	0.0	0.0	2.0	0.1	2
FalciVax™ - Rapid test for Malaria Pv/Pf[j]	50300025	Zephyr Biomedicals	98.0	88.2	100.0	100.0	0.8	2.9	0.0	2.9	7.3	0.0	4
HiSens Malaria Ag P.f/P.v Combo Card	HR3123	HBI Co., Ltd.	89.8	79.4	100.0	94.1	0.3 (391)	0.0	0.5	0.0	0.4	0.1	4
HiSens Malaria Ag *P.f/VOM* Combo Card	HR3323	HBI Co., Ltd.	89.8	76.5	100.0	91.2	0.0	0.0	0.5	0.0	0.0	0.0	4
Humasis Malaria P.f/P.v Antigen Test	AMFV-7025	Humasis, Co., Ltd.	92.9	100.0	100.0	100.0	0.5	0.7	0.5	1.5	1.3	0.0	4
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device	1-13-101-3	United Biotech, Inc.	60.2	0.0	92.9	26.5	0.5	0.0 (135)	3.1 (195)	1.5	0.0 (230)	0.5	4
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device	MFV-124V	AZOG, Inc.	79.8	0.0	100.0	20.0	0.0	1.4	0.0	0.0	0.0 (199)	0.1	3
Malaria Pf (HRPII)/ PV (PLDH) Antigen Detection Test Device	GM006	Genomix Molecular Diagnostics Pvt. Ltd.	85.0	74.3	97.0	94.3	1.5 (391)	6.5 (138)	3.6 (195)	2.9	0.9 (232)	2.5	5
Malaria Pf/Pv	GM002	Genomix Molecular Diagnostics *Pvt.Ltd.*	40.8	0.0	94.9	5.9	0.8	0.7	0.5	0.0	0.9	0.0	4
Maleriscan® Malaria Pf/PAN (Pv, Pm, Po) 3 Line Antigen Test[j]	MAT-PF/PAN-50	Bhat Bio-Tech India (P) Ltd.	84.0	62.9	100.0	100.0	27.3 (399)	5.8 (139)	87.4 (199)	4.3 (69)	3.0 (232)	0.7	5
Maleriscan® Malaria Pf/Pv	MAT-50	Bhat Bio-Tech India (P) Ltd	52.0	0.0	97.0	60.0	1.8 (399)	2.5	32.5	2.5 (79)	1.5 (199)	0.4	2
Medisensor Malaria HRP2/pLDH (Pf/Pv) COMBO	M161	Medisensor, Inc.	90.8	94.1	100.0	100.0	0.3	0.0	1.0	1.5	0.0	0.0	4
Medisensor Malaria HRP2/pLDH (Pf/VOM) COMBO	M171	Medisensor, Inc.	89.8	91.2	100.0	100.0	0.3	0.7	0.5	2.9	0.0	0.0	4
One Step Malaria P.F/P.V Test (Cassette)[j]	523352	Blue Cross Bio-Medical (Beijing) Co., Ltd.	92.0	100.0	100.0	100.0	21.5	53.6	9.0	34.3	77.1	0.0	5
OnSight™ - ParaQuick-2 (Pv,Pf) Malaria Test	537-25-DB	Amgenix International, Inc.	92.0	37.5	100.0	100.0	0.5	1.9	0.0	0.0	3.5	0.1	2
OnSite Pf/Pv Ag Rapid Test[j]	R0112C	CTK Biotech, Inc.	79.6	100.0	100.0	100.0	1.5	0.0	2.0	0.0	1.3	0.0	4
ParaHIT®fV Rapid test for *P. falciparum* and *P. vivax* Malaria - Device	55IC402-50	Span Diagnostics Ltd.	63.0	37.1	91.0	85.7	2.0 (399)	5.7	0.5	2.9	6.4	0.1	5
RAPID 1-2-3® HEMA CASSETTE MALARIA PF/PV TEST	MAL-PFV-CAS/25(100)	Hema Diagnostic Systems, LLC	92.9	79.4	100.0	100.0	0.0	0.7	0.0	1.5	4.3	0.0	4

Table S2 *(continued)*

Product	Catalogue number	Manufacturer	Panel detection score[a]				False-positive rates (%)				Total false-positive rates[b] (%)	Invalid rate (%)[l]	Round
			200 parasites/µL		2000 or 5000 parasites/µL		200 parasites/µL		2000 or 5000 parasites/µL		Clean-negative samples		
							Pf samples	Pv samples	Pf samples	Pv samples			
			Pf samples[c]	Pv samples[d]	Pf samples[c]	Pv samples[d]	False-positive non-Pf infection[e]	False-positive Pf infection[f]	False-positive non-Pf infection[g]	False-positive Pf infection[h]	False-positive *Plasmodium* spp. Infection[i]		
SD BIOLINE Malaria Ag Pf/ Pf/ Pv[k]	05FK100	Standard Diagnostics Inc.	96.9	97.1	100.0	100.0	0.3	0.0	0.5	0.0	2.2	0.0	4
SD BIOLINE Malaria Ag Pf/Pv	05FK80/05FK83	Standard Diagnostics, Inc.	96.0	95.0	100.0	100.0	0.0	0.0 (159)	0.0 (199)	0.0	3.5	0.2	2
Trusty™ Malaria Antigen P.f./p.v. test	A03-12-322	Artron Laboratories Inc.	88.8	38.2	99.0	100.0	13.3	27.4 (135)	16.0 (194)	19.4 (67)	32.0 (231)	0.5	4
Wondfo® One Step Malaria P.f/P.v Whole Blood Test	W056-C	Guangzhou Wondfo Biotech Co. Ltd.	87.0	28.6	98.0	97.1	1.5 (399)	2.9	1.5	2.9	2.1	0.1	5
Pf, Pv and pan													
Core™ Malaria Pan/Pv/Pf	MAL-190026	Core Diagnostics	92.9	11.4	99.0	94.3	0.3 (391)	0.0 (137)	0.0 (197)	1.4	3.5 (198)	1.0	3
diagnosticks MALARIA (Pan/Pv/Pf) Cassette	MPNVFC1007.5	SSA Diagnostics & Biotech Systems	93.9	11.4	99.0	94.3	0.0 (389)	0.0 (139)	0.0 (196)	2.9 (69)	4.0 (199)	1.1	3
FirstSign™ - ParaView-3 (Pan+Pv+Pf) Malaria Test	2103 CB-25	Unimed International Inc.	89.0	45.0	100.0	100.0	0.0 (399)	2.5	0.0	0.0	24.5	0.1	2
Paramax-3 Rapid Test for Malaria Pan/Pv/Pf (device)	50320025	Zephyr Biomedicals	93.0	45.0	100.0	100.0	0.0 (396)	0.0 (159)	0.0 (199)	0.0	37.0 (198)	0.7	2
Pan only													
Advantage Pan Malaria Card[j]	IR013025	J. Mitra & Co. Pvt. Ltd.	77.0	100.0	98.0	100.0	NA	NA	NA	NA	0.4	0.0	5
AZOG hCG Malaria Detection Test Device	MPT-124	AZOG, INC.	61.2	0	99	55.9	NA	NA	NA	NA	2.2	0.2	4
CareStart™ Malaria pLDH (PAN)[j]	G0111	Access Bio, Inc.	84.0	88.6	99.0	97.1	NA	NA	NA	NA	0.0	0.0	5
Clearview® Malaria pLDH[j]	70884025	Orgenics Ltd. (Inverness Medical Innovations)	81.8	85.7	99.0	100.0	NA	NA	NA	NA	13.5	0.5	3
diagnosticks MALARIA (Pan) Cassette	MPNWBC1007.3	SSA Diagnostics & Biotech Systems	16.2	54.3	92.9	100.0	NA	NA	NA	NA	0.0	0.3	3
First Response® Malaria Ag pLDH	I12FRC30	Premier Medical Corporation Ltd.	31.0	92.5	98.0	100.0	NA	NA	NA	NA	0.0	0.0	2
FirstSign™ - PanCheck (Pan) Malaria Test	2104 CB-25	Unimed International Inc.	25.0	82.5	87.0	100.0	NA	NA	NA	NA	2.5	0.2	2
OnSight™ - PanScreen (Pan) Malaria Test	539-25-DB	Amgenix International, Inc.	22.0	77.5	96.0	100.0	NA	NA	NA	NA	2.5	0.2	2
Parabank™ Device - Rapid test for Malaria Pan[j]	50301025	Zephyr Biomedical Systems	17.2	62.9	90.9	100.0	NA	NA	NA	NA	0.5	0.2	3
Pv only													
SD BIOLINE Malaria Ag Pv	05FK70	Standard Diagnostics, Inc.	NA	92.5	NA	100.0	0.3	NA	1.0	NA	1.0	0.0	2

NA, not applicable

Pf, *Plasmodium falciparum* Pv, *Plasmodium vivax* pan, *Plasmodium* species
Pvom, *Plasmodium vivax, ovale* and *malariae*

[a] A sample is considered detected only if all RDTs from both lots read by the first technician, at minimum specified reading time, are positive

[b] The total number of times a positive result for malaria was generated when it should not have been

[c] Round 1, n=79; round 2, n=100; round 3, n=99; round 4, n=98; round 5, n=100

[d] Round 1, n=20; round 2, n=40; round 3, n=35; round 4, n=34; round 5, n=35

[e] For combination tests, pan or Pv line, only, positive indicates a false-positive non *P. falciparum* infection (round 1 n=316; round 2, n=400; round 3, n=396; round 4, n=392; round 5, n=400)

[f] Pf line positive indicates a false-positive *P. falciparum* infection (round 1, n=80; round 2, n=160; round 3, n=140; round 4, n=136; round 5, n=140)

[g] For combination tests, pan or Pv line, only, positive indicates a false-positive non-*P. falciparum* infection (round 1, n=158; round 2, n=200; round 3, n=198; round 4, n=196; round 5, n=200)

[h] Pf line positive indicates a false-positive *P. falciparum* infection (round 1, n=40; round 2, n=80, round 3, n=70; round 4, n=68; round 5, n=70)

[i] Round 1, n=168; round 2, n=200; round 3, n=200; round 4, n=232 round 5, n=236

[j] Product resubmission, results from most recent round of testing replace previous results. Refer to Table S1.

[k] PDS presented in the table is based on a positive pf test line (either pf-HRP2 or pf-pLDH). For test line-specific results refer to the tables and annexes in the full reports.

[l] Round 1, n=954; round 2, n=1240; round 3, n=1204; round 4, n=1192; Round 5, n=1214

Performance measure	Recommended WHO procurement criteria
Panel detection score for Pf and Pv 200/µL samples	≥ 75%
False-positive rates against clean-negatives	< 10%
Invalid rate	< 5% of tests conducted

Table S3: Malaria RDT rounds 2—5 heat stability results on a cultured *P. falciparum* sample at low (200) and high (2000) parasite density (parasites/µL). Positivity rate at baseline and after 60 days' incubation at 35 °C and 45 °C

Product	Catalogue number	Manufacturer	Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (pan line)			Percentage positive test results for *P. falciparum* (pan line)			Round
			200 parasites/µL			2000 parasites/µL			200 parasites/µL			2000 parasites/µL			
			Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	
			Number of tests positive			Number of tests positive			Number of tests positive			Number of tests positive			
			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			
Pf only															
ABON™ Malaria P.f. Rapid Test Device (Whole Blood)	IMA-402	ABON Biopharm (Hangzhou) Co. Ltd	15.0	15.0	17.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Advanced Quality™ One Step Malaria Pf Test[a]	ITP11002TC1/ TC40	InTec Products, Inc.	93.3	96.7	90.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
Advantage P.f. Malaria Card[a]	IR016025	J. Mitra & Co. Pvt. Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
BIOCREDIT Malaria pf(HRP II)	HR0100	RapiGen Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
BIONOTE MALARIA P.f. Ag Rapid Test Kit	RG19-11	Bionote,Inc.	100.0	100.0	86.7	100.0	90.0	80.0	NA	NA	NA	NA	NA	NA	3
CareStart™ Malaria HRP2 (Pf)[a]	G0141	Access Bio, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
CareStart™ Malaria HRP2/pLDH Pf test	G0181	Access Bio, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	2
Clearview® Malaria P.f.[a]	VB01	Vision Biotech (Pty) Ltd	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
Core™ Malaria Pf	MAL-190020	Core Diagnostics	100.0	100.0	96.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
diagnosticks- Malaria (Pf) Cassette WB[a]	KMFC6001	SSA Diagnostics & Biotech Systems	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
diagnosticks- Malaria (Pf) Dipstick WB	KMFD6007	SSA Diagnostics & Biotech Systems	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	2
First Response® Malaria Ag *P. falciparum* (HRP2) Card Test[a]	I13FRC	Premier Medical Corporation Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
FirstSign™ Malaria Pf	2100CB-25	Unimed International Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
HiSens Malaria Ag Pf HRP2 Card	HR3023	HBI Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	2
ICT Diagnostics Malaria P.f.[a]	ML01	ICT International	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
IMMUNOQUICK CONTACT *falciparum*	0519K25	Biosynex	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
IMMUNOQUICK® MALARIA *falciparum*[a]	0502_K25	Biosynex	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
IND ONE STEP MALARIA ANTIGEN P.f	535-11	IND Diagnostics Inc.	100.0	100.0	86.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
KHB® Malaria Ag P.f Rapid Test	KH-R-06-20	Shanghai Kehua Bio-engineering Co.,Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
Maleriscan ® Malaria P.f Antigen Test	MAT-PF-50	Bhat Bio-Tech India (Pte.) Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
NanoSign Malaria Pf Ag	RMAF10	Bioland, Ltd	96.7	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
One Step Malaria P.F Test (Cassette)[a]	522352	Blue Cross Bio-Medical (Beijing) Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
OnSight™ - Malaria Pf Test	511-25-DB	Amgenix International, Inc.	100.0	95.0	90.0	100.0	100.0	65.0	NA	NA	NA	NA	NA	NA	2
OnSite Pf Ag Rapid Test[a]	R0114C	CTK Biotech, Inc.	96.7	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
Paracheck® Pf-Rapid Test for *P. falciparum* Malaria Device (Ver.3)[j]	302030025	Orchid Biomedical Systems	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Paracheck® Pf-Rapid Test for *P. falciparum* Malaria Dipstick (Ver.3)[j]	302040025	Orchid Biomedical Systems	100.0	96.7	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
ParaHIT® - f (Device)	55IC104-50	Span Diagnostics Ltd.	100.0	96.7	100.0	100.0	100.0	90.0	NA	NA	NA	NA	NA	NA	3
ParaHIT® -f (Dipstick)	55IC103-50	Span Diagnostics Ltd.	100.0	100.0	56.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
SD BIOLINE Malaria Ag P.f. (HRP2/pLDH)[b]	05FK90	Standard Diagnostics Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
SD BIOLINE Malaria Ag Pf[a]	05FK50/05FK53	Standard Diagnostics, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
Trusty™ Malaria Antigen P.f. test	A03-01-322	Artron Laboratories Inc.	100.0	100.0	56.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Vision Malaria Pf	VB01	Vision Biotech (Pty) Ltd	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
Wondfo One Step Malaria P.f Test[a]	W 37-C	Guangzhou Wondfo Biotech Co. Ltd.	100.0	96.7	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Pf and pan															
ABON Malaria Pan/P.f. Rapid Test Device	IMA-B402	ABON Biopharm (Hangzhou) Co. Ltd.	100.0	80.0	90.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	3
ABON™ Plus Malaria *P.f/Pan* Rapid Test Device (Whole Blood)	IMA-T402	ABON Biopharm (Hangzhou) Co. Ltd	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	
ACCUCARE ONE STEP MALARIA Pf/Pan Antigen Test	MAGC 25	LAB-CARE Diagnostics (India) PVT. LTD.	83.3	73.3	10.0	100.0	100.0	100.0	3.3	10.0	0.0	70.0	90.0	30.0	5
Advanced Quality™ Rapid Malaria Test (Pf/Pan)	ITP11005	InTec Products, Inc.	86.7	96.7	100.0	100.0	100.0	100.0	0.0	0.0	0.0	70.0	100.0	80.0	5
Advantage Mal Card[a]	IR221025	J. Mitra & Co. Pvt. Ltd.	0.0	0.0	0.0	100.0	100.0	100.0	0.0	0.0	0.0	70.0	100.0	80.0	5

Table S3 *(continued)*

Product	Catalogue number	Manufacturer	Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (pan line)			Percentage positive test results for *P. falciparum* (pan line)			Round
			200 parasites/µL			2000 parasites/µL			200 parasites/µL			2000 parasites/µL			
			Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	
			Number of tests positive			Number of tests positive			Number of tests positive			Number of tests positive			
			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			
Advantage Malaria Pan + Pf Card	IR231025	J. Mitra & Co. Pvt. Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	80.0	93.3	26.7	100.0	100.0	100.0	5
AZOG Malaria pf (HRPII)/pf (LDH)/ (PAN-LDH) Antigen Detection Device[b]	MFV-124F	AZOG, INC.	96.7	96.7	100.0	100.0	100.0	100.0	3.3	0.0	0.0	20.0	0.0	0.0	4
BIOCREDIT Malaria Ag Pf/Pan (HRPII/pLDH)	C30RHA25	RapiGEN INC.	100.0	100.0	96.7	90.0	100.0	100.0	0.0	53.3	0.0	90.0	100.0	100.0	5
BIONOTE MALARIA P.f.& Pan Ag Rapid Test Kit	RG19-08	Bionote,Inc.	100.0	100.0	96.7	100.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	90.0	3
BioTracer™ Malaria Pf/PAN Rapid Card	17012	Bio Focus Co., Ltd.	100.0	96.7	90.0	100.0	100.0	100.0	0.0	0.0	66.7	100.0	100.0	100.0	5
CareStart™ Malaria/Pregnancy Combo (pLDH/HRP2/HCG)	G0221	Access Bio Inc	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	3
CareStart™ Malaria HRP2/pLDH (Pf/PAN) COMBO[a]	G0131	Access Bio, Inc.	100.0	100.0	96.7	100.0	100.0	100.0	93.3	86.7	53.3	100.0	100.0	100.0	5
CareStart™ Malaria pLDH 3 Line Test	G0121	Access Bio, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	3
CareStart™ Malaria Screen	G0231	Access Bio, Inc.	100.0	100.0	93.3	100.0	100.0	100.0	100.0	100.0	93.3	100.0	100.0	100.0	3
Clearview® Malaria Comboa	VB11	Vision Biotech (Pty) Ltd	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	90.0	20.0	0.0	3
Clearview® Malaria Dual	VB20	Orgenics Ltd.(IS)	100.0	100.0	100.0	100.0	100.0	100.0	0.0	10.0	3.3	90.0	90.0	100.0	5
Core™ Malaria Pan Pf	MAL-190024	Core Diagnostics Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	26.7	80.0	83.3	100.0	100.0	100.0	4
diagnosticks MALARIA (Pan/Pf) Cassette	MPNFWBC 1007.4	SSA Diagnostics & Biotech Systems	100.0	100.0	96.7	100.0	100.0	100.0	0.0	0.0	0.0	100.0	90.0	90.0	3
DIAQUICK Malaria *P.f/Pan* Cassette	Z11200CE	DIALAB GmbH	100.0	100.0	96.7	100.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	80.0	5
EzDx™ Malaria Pan/Pf Rapid Test Detection kit[a]	RK MAL 001	Advy Chemical (Affiliate of Bharat Serums & Vaccines Ltd.)	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	3.3	100.0	100.0	100.0	5
First Response® Malaria Ag. pLDH/HRP2 Combo Card Test[a]	I16FRC	Premier Medical Corporation Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	10.0	0.0	100.0	100.0	100.0	5
FirstSign™ ParaView (Pan+Pf)[a]	2101CB-25	Unimed International Inc.	96.7	100.0	100.0	100.0	100.0	100.0	0.0	0.0	13.3	100.0	100.0	100.0	4
GenBody™Malaria Pf/Pan Ag	MALAG100	GenBody Inc.	100.0	100.0	93.3	100.0	100.0	100.0	0.0	0.0	0.0	50.0	100.0	10.0	5
Genedia® Malaria *P.f/Pan* Ag Rapid Test	20-0146-01	Green Cross Medical Science Corp. (Korea)	100.0	100.0	43.3	100.0	100.0	100.0	3.3	0.0	13.3	0.0	0.0	0.0	5
HiSens Malaria Ag P.f/P.v Card	HR2823	HBI Co., Ltd.	35.0	0.0	5.0	100.0	100.0	100.0	0.0	0.0	0.0	35.0	0.0	0.0	2
HiSens Malaria Ag Pf/Pv (HRP2/pLDH) Card	HR2923	HBI Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	95.0	100.0	100.0	100.0	2
Humasis Malaria *P.f/Pan* Antigen Test[j]	AMAL-7025	Humasis, Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	100.0	5
ICT Malaria Dual Test[a]	ML03	ICT International	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	90.0	90.0	90.0	5
ICT MALARIA COMBO[a]	ML02	ICT International	96.7	96.7	93.3	100.0	100.0	100.0	3.3	20.0	13.3	100.0	50.0	70.0	4
IMMUNOQUICK CONTACT MALARIA +4	0525K25	Biosynex	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	50.0	50.0	100.0	3
IND ONE STEP MALARIA ANTIGEN *P.f/Pan* TEST	535-10	IND Diagnostics Inc.	100.0	100.0	100.0	100.0	100.0	100.0	20.0	3.3	33.3	100.0	100.0	100.0	4
Malaria Pan Test	MAL-W23N-001	Dima • Gesellschaft für Diagnostika mbH	60.0	33.3	23.3	100.0	100.0	90.0	13.3	53.3	40.0	10.0	60.0	40.0	3
Malaria Pf./Pan Antigen (MAL Pf/Pan) Test Kit	A03-18-322	Artron Laboratories Inc.	10.0	6.7	0.0	100.0	100.0	100.0	10.0	3.3	0.0	100.0	100.0	90.0	5
Malaria pf (HRP II) / (PAN-pLDH) Antigen Detection Test Device[a]	MFV-124R	AZOG, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	3
Malaria pf (HRP II)/PAN (pLDH) Antigen Detection Test Device	1-13-101-1	United Biotech, Inc.	100.0	96.7	96.7	100.0	100.0	100.0	16.6	0.0	0.0	90.0	40.0	50.0	4
Malaria pf (pLDH) / PAN-pLDH Test Device a	MFV-124	AZOG, Inc.	46.7	56.7	66.7	100.0	100.0	100.0	13.3	93.3	100.0	60.0	100.0	100.0	5
Malaria Pf/ PAN	GM004	Genomix Molecular Diagnostics *Pvt.Ltd.*	56.7	23.3	26.7	100.0	100.0	100.0	0.0	0.0	0.0	60.0	90.0	50.0	4
Malaria Pf/Pan One Step Rapid Test	RT 20222	Zhejiang Orient Gene Biotech Co., Ltd.	100.0	100.0	96.7	100.0	90.0	100.0	0.0	0.0	0.0	100.0	90.0	100.0	5
Malascan™ Device - Rapid test for Malaria Pf/Pan[a]	50402025	Zephyr Biomedical Systems	96.7	100.0	96.7	100.0	100.0	100.0	0.0	0.0	6.7	100.0	100.0	100.0	3
MD Malaria Pf/Pan(pLDH) test	MDMALLDH001	Medical Diagnostech (Pty) Ltd	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	100.0	5
MeDiPro Malaria Ag HRP2/pLDH Combo	IR-0051K	Formosa Biomedical Technology Corp.	100.0	96.7	96.7	100.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	4
NanoSign Malaria pf/pan Ag 3.0[a]	RMAP10	Bioland Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	100.0	4
NanoSign Malaria Pf/Pv Ag	RMAD10	Bioland, Ltd	0.0	0.0	0.0	20.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3
NG-Test MALARIA Pf/Pan (pLDH)	NG-MAL-W23-001	SARL NG Biotech, Z.A.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	6.7	0.0	100.0	100.0	100.0	5
One Step Malaria *P.f/Pan* Test[a]	W56-C	Guangzhou Wondfo Biotech Co. Ltd.	46.7	13.3	26.7	100.0	100.0	100.0	0.0	36.7	73.3	70.0	80.0	100.0	3

(continued)

Table S3: Malaria RDT rounds 2—5 heat stability results on a cultured *P. falciparum* sample at low (200) and high (2000) parasite density (parasites/µL). Positivity rate at baseline and after 60 days' incubation at 35 °C and 45 °C *(continued)*

Product	Catalogue number	Manufacturer	Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (pan line)			Percentage positive test results for *P. falciparum* (pan line)			Round
			200 parasites/µL			2000 parasites/µL			200 parasites/µL			2000 parasites/µL			
			Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	
			Number of tests positive			Number of tests positive			Number of tests positive			Number of tests positive			
			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			
OnSite Pf/Pan Ag Rapid Test[a]	R0113C	CTK Biotech, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	3.3	90.0	100.0	100.0	5
OptiMAL-IT	710024	Diamed - A Division of Bio-Rad	0.0	0.0	0.0	100.0	90.0	0.0	0.0	0.0	0.0	100.0	90.0	0.0	3
ParaHIT - Total Ver. 1.0 (Device)	55IC204-10	Span Diagnostics Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	100.0	4
ParaHIT - Total Ver. 1.0 (Dipstick)	55IC203-10	Span Diagnostics Ltd.	100.0	93.3	46.7	100.0	100.0	60.0	50.0	0.0	0.0	100.0	90.0	0.0	4
ParaHIT® total (dipstick)	55IC201-10	Span Diagnostics Ltd	55.0	85.0	55.0	100.0	100.0	95.0	10.0	0.0	0.0	50.0	45.0	70.0	2
Parascreen® - Rapid test for Malaria Pan/Pf[a]	50310025	Zephyr Biomedicals	100.0	100.0	100.0	100.0	100.0	100.0	10.0	3.3	13.3	100.0	100.0	100.0	5
RightSign™ Malaria P.f./Pan Rapid Test Cassette	IMPN-C52	Hangzhou Biotest Biotech Co. Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	20.0	100.0	100.0	60.0	100.0	5
SD BIOLINE Malaria Ag *P.f/Pana*	05FK60/05FK63	Standard Diagnostics Inc.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	100.0	5
SD BIOLINE Malaria Ag Pf/ Pan	05FK66	Standard Diagnostics Inc.	96.7	96.7	100.0	90.0	100.0	100.0	16.6	10.0	0.0	90.0	100.0	100.0	4
SD BIOLINE Malaria Ag[a]	05FK40	Standard Diagnostics Inc.	0.0	0.0	0.0	100.0	80.0	90.0	0.0	0.0	0.0	80.0	20.0	90.0	3
Surestep™ Easy Malaria Pf/Pan Rapid Test Device	IMA-T402	ACON Biotech (Hangzhou) Co. Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	3
Vikia® Malaria Ag Pf/Pan	412499	IMACCESS S.A.S	100.0	96.7	96.7	100.0	100.0	100.0	0.0	0.0	0.0	60.0	60.0	0.0	5
Pf and Pv/Pvom															
Advanced Quality™ One Step Malaria P.f/P.v Tri-Line Test	ITP11003 TC40	InTec Products, Inc.	96.7	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
Advantage Malaria Card	IR211025	J. Mitra & Co. Pvt. Ltd.	100.0	96.7	96.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
ASAN Easy Test® Malaria Pf/Pan Ag	AM4650-K	ASAN Pharmaceutical Co., Ltd	100.0	96.7	63.3	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
BIONOTE MALARIA P.f.& P.v. Ag Rapid Test Kit	RG19-12	Bionote,Inc.	100.0	96.7	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
CareStart™ Malaria HRP2/pLDH (Pf/Pv) COMBO[a]	G0161	Access Bio, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
CareStart™ Malaria HRP2/pLDH (Pf/VOM) COMBO[a]	G0171	Access Bio, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Core™ Malaria Pv/Pf	MAL-190022	Core Diagnostics	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
diagnosticks- Malaria (Pv/Pf) Cassette	KMVFC6002	SSA Diagnostics & Biotech Systems	100.0	95.0	95.0	100.0	100.0	95.0	NA	NA	NA	NA	NA	NA	2
FalciVax™ - Rapid test for Malaria Pv/Pf[a]	50300025	Zephyr Biomedicals	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
HiSens Malaria Ag P.f/P.v Combo Card	HR3123	HBI Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
HiSens Malaria Ag *P.f/VOM* Combo Card	HR3323	HBI Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Humasis Malaria P.f/P.v Antigen Test	AMFV-7025	Humasis, Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device	1-13-101-3	United Biotech, Inc.	100.0	100.0	100.0	90.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Malaria pf (HRP II) / pv (pLDH) Antigen Detection Test Device	MFV-124V	AZOG, Inc.	100.0	100.0	96.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	3
Malaria Pf (HRPII)/ PV (PLDH) Antigen Detection Test Device	GM006	Genomix Molecular Diagnostics Pvt. Ltd.	83.3	90.0	83.3	100.0	90.0	70.0	NA	NA	NA	NA	NA	NA	5
Malaria Pf/Pv	GM002	Genomix Molecular Diagnostics *Pvt.Ltd.*	40.0	33.3	40.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Maleriscan® Malaria Pf/PAN (Pv, Pm, Po) 3 Line Antigen Test	MAT-PF/PAN-50	Bhat Bio-Tech India (P) Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
Maleriscan® Malaria Pf/Pv	MAT-50	Bhat Bio-Tech India (P) Ltd	100.0	60.0	30.0	100.0	90.0	95.0	NA	NA	NA	NA	NA	NA	2
Medisensor Malaria HRP2/pLDH (Pf/Pv) COMBO	M161	Medisensor, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Medisensor Malaria HRP2/pLDH (Pf/VOM) COMBO	M171	Medisensor, Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
One Step Malaria P.F/P.V Test (Cassette)[a]	523352	Blue Cross Bio-Medical (Beijing) Co., Ltd.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5
OnSight™ - ParaQuick-2 (Pv,Pf) Malaria Test	537-25-DB	Amgenix International, Inc.	100.0	100.0	100.0	100.0	100.0	85.0	NA	NA	NA	NA	NA	NA	2
OnSite Pf/Pv Ag Rapid Test[a]	R0112C	CTK Biotech, Inc.	100.0	100.0	90.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
ParaHIT®fV Rapid test for *P. falciparum* and *P. vivax* Malaria - Device	55IC402-50	Span Diagnostics Ltd.	100.0	96.7	96.7	100.0	100.0	90.0	NA	NA	NA	NA	NA	NA	5
RAPID 1-2-3® HEMA CASSETTE MALARIA PF/PV TEST	MAL-PFV-CAS/25(100)	Hema Diagnostic Systems, LLC	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
SD BIOLINE Malaria Ag Pf/ Pf/ Pv[b]	05FK100	Standard Diagnostics Inc.	100.0	100.0	96.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
SD BIOLINE Malaria Ag Pf/Pv	05FK80/05FK83	Standard Diagnostics, Inc.	100.0	100.0	100.0	100.0	100.0	95.0	NA	NA	NA	NA	NA	NA	2
Trusty™ Malaria Antigen P.f./p.v. test	A03-12-322	Artron Laboratories Inc.	100.0	100.0	36.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
Wondfo® One Step Malaria P.f/P.v Whole Blood Test	W056-C	Guangzhou Wondfo Biotech Co. Ltd.	100.0	96.7	93.3	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	5

Table S3 *(continued)*

Product	Catalogue number	Manufacturer	Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (pan line)			Percentage positive test results for *P. falciparum* (pan line)			Round
			200 parasites/µL			2000 parasites/µL			200 parasites/µL			2000 parasites/µL			
			Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	
			Number of tests positive			Number of tests positive			Number of tests positive			Number of tests positive			
			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			
Pf, Pv and pan															
Core™ Malaria Pan/Pv/Pf	MAL-190026	Core Diagnostics	100.0	100.0	100.0	100.0	90.0	100.0	0.0	0.0	0.0	80.0	50.0	70.0	3
diagnosticks MALARIA (Pan/Pv/Pf) Cassette	MPNVFC1007.5	SSA Diagnostics & Biotech Systems	96.7	100.0	93.3	100.0	100.0	100.0	0.0	0.0	0.0	70.0	0.0	50.0	3
FirstSign™ - ParaView-3 (Pan+Pv+Pf) Malaria Test	2103 CB-25	Unimed International Inc.	100.0	100.0	100.0	100.0	100.0	100.0	60.0	50.0	15.0	100.0	90.0	100.0	2
Paramax-3 Rapid Test for Malaria Pan/Pv/Pf (device)	50320025	Zephyr Biomedicals	100.0	100.0	100.0	100.0	100.0	100.0	100.0	25.0	30.0	100.0	95.0	100.0	2
Pan only															
Advantage Pan Malaria Card[a]	IR013025	J. Mitra & Co. Pvt. Ltd.	NA	NA	NA	NA	NA	NA	36.7	66.7	60.0	100.0	100.0	90.0	5
AZOG hCG Malaria Detection Test Device	MPT-124	AZOG, INC.	NA	NA	NA	NA	NA	NA	100.0	100.0	100.0	100.0	100.0	100.0	4
CareStart™ Malaria pLDH (PAN)[a]	G0111	Access Bio, Inc.	NA	NA	NA	NA	NA	NA	100.0	100.0	100.0	100.0	100.0	100.0	5
Clearview® Malaria pLDH[a]	70884025	Orgenics Ltd. (Inverness Medical Innovations)	NA	NA	NA	NA	NA	NA	96.7	93.3	100.0	100.0	100.0	100.0	3
diagnosticks MALARIA (Pan) Cassette	MPNWBC1007.3	SSA Diagnostics & Biotech Systems	NA	NA	NA	NA	NA	NA	0.0	0.0	0.0	80.0	100.0	80.0	3
First Response® Malaria Ag pLDH	I12FRC30	Premier Medical Corporation Ltd.	NA	NA	NA	NA	NA	NA	50.0	80.0	55.0	100.0	100.0	100.0	2
FirstSign™ - PanCheck (Pan) Malaria Test	2104 CB-25	Unimed International Inc.	NA	NA	NA	NA	NA	NA	25.0	5.0	10.0	100.0	100.0	100.0	2
OnSight™ - PanScreen (Pan) Malaria Test	539-25-DB	Amgenix International, Inc.	NA	NA	NA	NA	NA	NA	5.0	35.0	15.0	100.0	100.0	100.0	2
Parabank™ Device - Rapid test for Malaria Pan[a]	50301025	Zephyr Biomedical Systems	NA	NA	NA	NA	NA	NA	0.0	0.0	0.0	90.0	100.0	100.0	3
Pv only															
SD BIOLINE Malaria Ag Pv	05FK70	Standard Diagnostics, Inc.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2

NA, not applicable

Pf, *Plasmodium falciparum* Pv, *Plasmodium vivax* pan, *Plasmodium* species Pvom, *Plasmodium vivax, ovale* and *malariae*

Indicates results for those products that meet all WHO recommended procurement criteria

[a] Product resubmission, results from most recent round of testing replace previous results. Refer to Table S1.

[b] Results presented in the table are based on stability of a Pf test line (either Pf-HRP2 or Pf-pLDH). Results based on stability of individual test lines is presented in the following table:

Product	Catalogue number	Manufacturer	Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (Pf line)			Percentage positive test results for *P. falciparum* (pan line)			Percentage positive test results for *P. falciparum* (pan line)			Round
			200 parasites/µL			2000 parasites/µL			200 parasites/µL			2000 parasites/µL			
			Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	Baseline	35 °C	45 °C	
			Number of tests positive			Number of tests positive			Number of tests positive			Number of tests positive			
			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			Lots 1 and 2 combined			
SD BIOLINE Malaria Ag P.f. (HRP2/pLDH) - (PF(HRP2) line)	05FK90	Standard Diagnostics Inc.	100.0	100.0	100.0	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	NA
SD BIOLINE Malaria Ag P.f. (HRP2/pLDH)- (PF(pLDH) line)	05FK90	Standard Diagnostics Inc.	0.0	0.0	0.0	33.3	33.3	33.3	NA	NA	NA	NA	NA	NA	NA
AZOG Malaria pf (HRPII)/pf (LDH)/ (PAN-LDH) Antigen Detection Device - (PF(HRP2) line)	MFV-124F	AZOG, INC.	96.7	96.7	100.0	100.0	100.0	100.0	3.3	0.0	0.0	20.0	0.0	0.0	4
AZOG Malaria pf (HRPII)/pf (LDH)/ (PAN-LDH) Antigen Detection Device - (PF(pLDH) line)	MFV-124F	AZOG, INC.	13.3	3.3	6.7	50.0	10.0	50.0	3.3	0.0	0.0	20.0	0.0	0.0	4
SD BIOLINE Malaria Ag Pf/ Pf/ Pv - (PF(HRP2) line)	05FK100	Standard Diagnostics Inc.	100.0	100.0	96.7	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4
SD BIOLINE Malaria Ag Pf/ Pf/ Pv - (PF(pLDH) line)	05FK100	Standard Diagnostics Inc.	26.7	3.3	3.3	100.0	100.0	100.0	NA	NA	NA	NA	NA	NA	4

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ANNEXES

Annex S1: Characteristics of evaluation panels used in rounds 1–5 of WHO malaria RDT product testing, 2008–2013

Currently, the basis for diagnosing malaria with antigen-detecting RDTs is the detection in a patient's blood of one or more target malaria antigens, including HRP2 (*P. falciparum* only), pLDH (*Plasmodium* spp.(pan-pLDH), *P. falciparum* (Pf-pLDH), non-*falciparum* (Pv-pLDH, Pvom-pLDH) and aldolase (all *Plasmodium* spp). The antigen concentration in samples with the same parasite density varies. Therefore, the concentrations of malaria antigens in the samples that comprise evaluation panels must be consistent in successive rounds of WHO malaria RDT product testing to ensure that the results of each round are highly comparable (statistically equivalent).

Therefore, antigen concentrations were quantified in triplicate in all panel samples, including dilution pairs of 200 and 2000 parasites/µL, by quantitative ELISA. Only results that were consistent in the triplicate runs and showed a value factor between the 200 and the 2000 parasites/µL dilutions close to 10 were considered acceptable and eligible for the performance evaluation panel. In some instances, the antigen concentration was below the detection limit of the ELISA, particularly for aldolase, which is present in malaria parasite samples at much lower concentrations than the other two antigens. Samples that gave inconsistent results for more than one of the three antigens were excluded from the panel.

Despite careful standardization of procedures, the tables and figures below show a wide variation in antigen concentrations for the same parasite density. There are a number of possible explanations, including differences in the level of antigen expression by isolates; different durations of infection (accumulating antigens); different parasite growth stages at the time of collection (expressing different levels of antigen); the presence of circulating HRP2 from previous growth cycles; and HRP2 produced by parasites sequestered in the host's vascular tissues that cannot be accounted for in the estimate of parasite density on the blood slide.

Before each round of WHO malaria RDT product testing, the distribution of HRP2, pLDH and aldolase concentrations at 200 parasites/µL dilution of the wild-type *P. falciparum* and wild-type *P. vivax* samples selected for the phase-2 panels were systematically compared with those in the previous round to ensure there was no statistically significant difference. The figures and tables below show the distribution of antigen concentrations in all five performance evaluation panels. No statistically significant differences were seen (Kruskal-Wallis test; $p > 0.15$), confirming that the results of each new round are additive (and comparable) to the previous ones. In the following box and whisker plots, the end of whiskers represent minimum and maximum values; the box represents middle 50% of data and the line through box represents median values; the crosses represent the mean values.

Figure AS1.1: Box-and-whisker plot of distribution of *P. falciparum* HRP2 concentration (ng/mL) in product testing phase 2 (wildtype) panels.

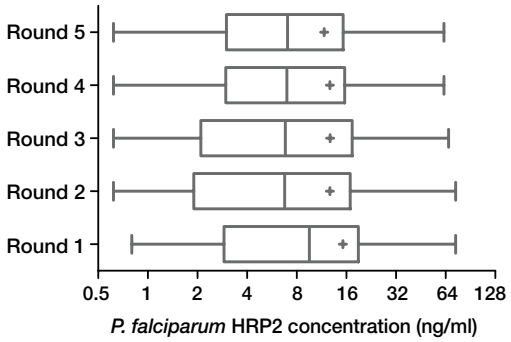


Figure AS1.2: Box-and-whisker plot of distribution of *P. falciparum* pLDH concentration (ng/mL) in product testing phase 2 (wildtype) panels.

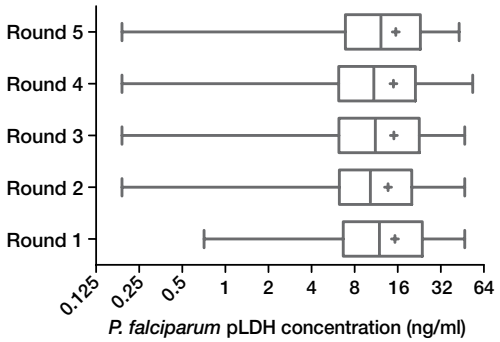


Figure AS1.3: Box-and-whisker plot of distribution of *P. vivax* pLDH concentration (ng/mL) in product testing phase 2 (wild-type) panels.

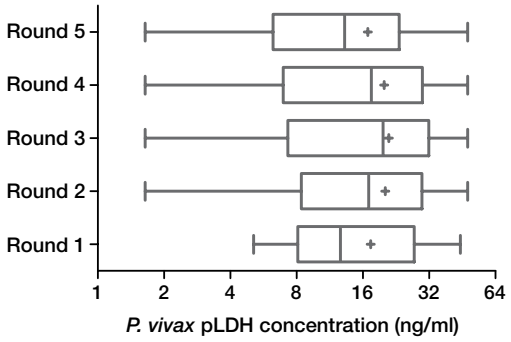


Figure AS1.4: Box-and-whisker plot of distribution of *P. falciparum* aldolase concentration (ng/mL) in product testing phase 2 (wild-type) panels.

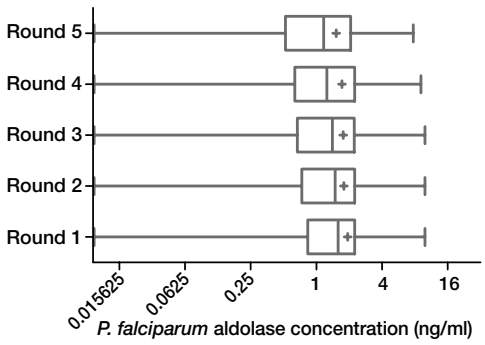


Figure AS1.5: Box-and-whisker plot of distribution of *P. vivax* aldolase concentration (ng/mL) in product testing phase 2 (wild-type) panels.

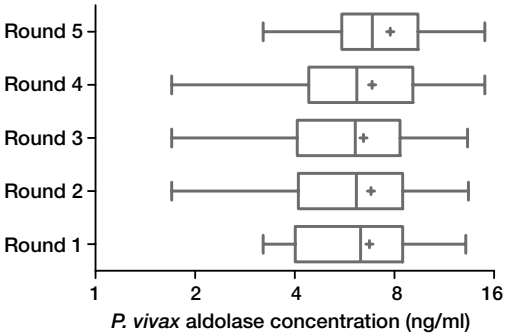


Table AS1.1: Statistics for *P. falciparum* HRP2 concentration (ng/mL) in product testing phase 2 (wild-type) panels.

	Round 1	Round 2	Round 3	Round 4	Round 5
Number of values[a]	78	99	99	98	99
Minimum	0.80	0.62	0.62	0.62	0.62
25% percentile	2.90	1.90	2.10	2.97	3.00
Median	9.57	6.76	6.83	6.98	7.05
75% percentile	18.94	16.91	17.37	15.65	15.31
Maximum	73.70	73.70	66.70	62.48	62.48
Mean	15.28	12.70	12.77	12.72	11.74
Std. Deviation	16.98	15.75	15.19	14.72	13.20

[a] The number of values is the number of samples for which consistent ELISA results were obtained.

Table AS1.2: Statistics for *P. falciparum* pLDH concentration (ng/mL) in product testing phase 2 (wild-type) panels.

	Round 1	Round 2	Round 3	Round 4	Round 5
Number of values[a]	74	93	92	92	94
Minimum	0.71	0.19	0.19	0.19	0.19
25% percentile	6.68	6.27	6.23	6.20	6.90
Median	11.95	10.31	11.18	10.92	12.24
75% percentile	23.75	20.10	22.70	21.28	23.05
Maximum	47.15	47.15	47.15	53.53	43.02
Mean	15.31	13.71	15.08	14.97	15.53
Std. Deviation	11.47	10.90	11.72	11.98	11.43

[a] The number of values is the number of samples for which consistent ELISA results were obtained.

Table AS1.3: Statistics for *P. vivax* pLDH concentration (ng/mL) in wildtype product testing phase 2 (wild-type) panels.

	Round 1	Round 2	Round 3	Round 4	Round 5
Number of values[a]	20	37	33	32	34
Minimum	5.10	1.64	1.64	1.64	1.64
25% percentile	8.10	8.40	7.30	6.96	6.26
Median	12.65	17.00	19.78	17.50	13.22
75% percentile	27.40	29.69	31.89	29.84	23.42
Maximum	44.40	47.90	47.90	47.90	47.90
Mean	17.38	20.24	20.99	20.00	16.84
Std. Deviation	11.57	13.27	13.55	13.00	12.59

[a] The number of values is the number of samples for which consistent ELISA results were obtained.

Table AS1.4: Statistics for *P. falciparum* aldolase concentration (ng/mL) in product testing phase 2 (wild-type) panels.

	Round 1	Round 2	Round 3	Round 4	Round 5
Number of values[a]	77	98	99	98	99
Minimum	0.00	0.00	0.00	0.00	0.00
25% percentile	0.84	0.74	0.67	0.63	0.52
Median	1.61	1.49	1.40	1.25	1.17
75% percentile	2.25	2.25	2.23	2.25	2.07
Maximum	9.90	9.90	9.90	9.08	7.74
Mean	1.93	1.79	1.76	1.72	1.52
Std. Deviation	1.73	1.66	1.69	1.68	1.52

[a] The number of values is the number of samples for which consistent ELISA results were obtained.

Table AS1.5: Statistics for *P. vivax* aldolase concentration (ng/mL) in product testing phase 2 (wild-type) panels.

	Round 1	Round 2	Round 3	Round 4	Round 5
Number of values[a]	20	40	34	33	35
Minimum	3.21	1.70	1.70	1.70	3.21
25% Percentile	4.02	4.11	4.07	4.41	5.55
Median	6.33	6.15	6.10	6.16	6.86
75% Percentile	8.47	8.47	8.32	9.10	9.43
Maximum	13.15	13.40	13.30	15.00	15.00
Mean	6.73	6.81	6.45	6.86	7.78
Std. Deviation	2.89	3.15	2.90	3.23	3.30

[a] The number of values is the number of samples for which consistent ELISA results were obtained.

Annex S2: Malaria RDT field assessment and anomalies

The purpose of this assessment, on a limited number of RDTs, is to assess aspects of packaging, safety and ease-of-use and not to evaluate diagnostic accuracy.

Obtain samples of each malaria RDT under consideration (at least one box packaged as intended for delivery to end users).

Obtain malaria parasite-negative blood samples, and where readily accessible, parasite-positive blood samples for testing against RDTs.

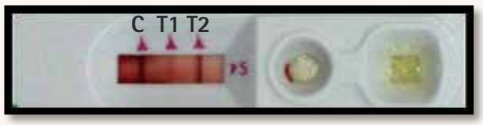
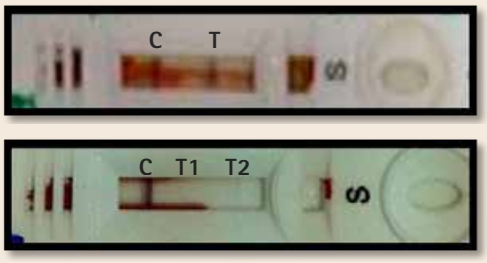
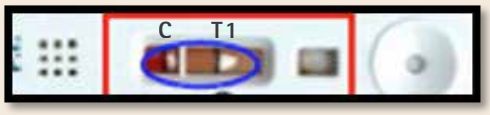
Table AS2.1: Field assessment of RDT packaging, safety and ease-of-use to guide product selection

Date of assessment				
Commercial name				
Catalogue number				
Lot number(s)				
	Yes	**No**	**NA**	**Problems /Comments**
Packaging and accessories				
The RDT box is in good condition				
RDTs are in individual sealed pouches				
The correctly indicated number of RDTs are in the box				
A desiccant is included in each individual RDT pouch				
An expiry date is visible on each RDT pouch				
All required accessories are included in the correct quantities (RDT, buffer, blood transfer device, alcohol swab, lancet, gloves, test tubes (for dipsticks, only)				If no, what is not included:
Instructions				
Instructions are included				
Instructions are in the national language(s)				
The instructions are for the correct product				
The instructions include figures displaying all possible interpretations of the RDT results				
The text and figures are accurate and consistent (specifically order of test lines and results interpretation)				
Preparation and procedure				
The test pouch is easy to open				
It is easy to write on the test device				
The test lines on the device are clearly labelled				
It is easy to use the device for blood collection				
It is easy to open the buffer bottle or ampoule				
The buffer bottle or ampoules have sufficient volume for testing all RDTs in the box				
The buffer bottle or ampoule dispenses even drops				
It is easy to fill the sample well correctly with the provided blood transfer device				
It is easy to fill the buffer well correctly (no overflow)				
The buffer and sample flow well along the test strip				
Result interpretation				
Control and test lines				
Control line is clear				
Test line(s) are clear				
Good clearance of blood by time of reading				If no, number of tests in the box affected:
Steps and reading time				
Reading time <30 min				
Two or fewer timed steps				
Was one or more of the last 10 tests you performed invalid (no control line)?				
If YES, how many?				
Safety				
Are there mixing wells (risk of blood splash)?				
Retractable needle for finger prick?				
Is the RDT in a cassette format (unexposed strip)?				
Have waste disposal safety concerns been addressed? (If no, please describe)				

Figure AS2.1 illustrates examples of RDT observations/anomalies encountered and routinely recorded during Round 5 of WHO Malaria RDT Product Testing at the CDC. In most cases, these anomalies do not invalidate the results, as reactivity in the control and test line areas are still visible, but they may pose challenges to health workers interpreting the results. Furthermore, they should be reported to manufacturers.

An expanded list of notable observations concerning RDT packaging, kit accessories (buffer vials, desiccants) and instructions for use, is under development for use in both product testing and lot testing activities of the WHO-FIND Malaria RDT Evaluation Programme.

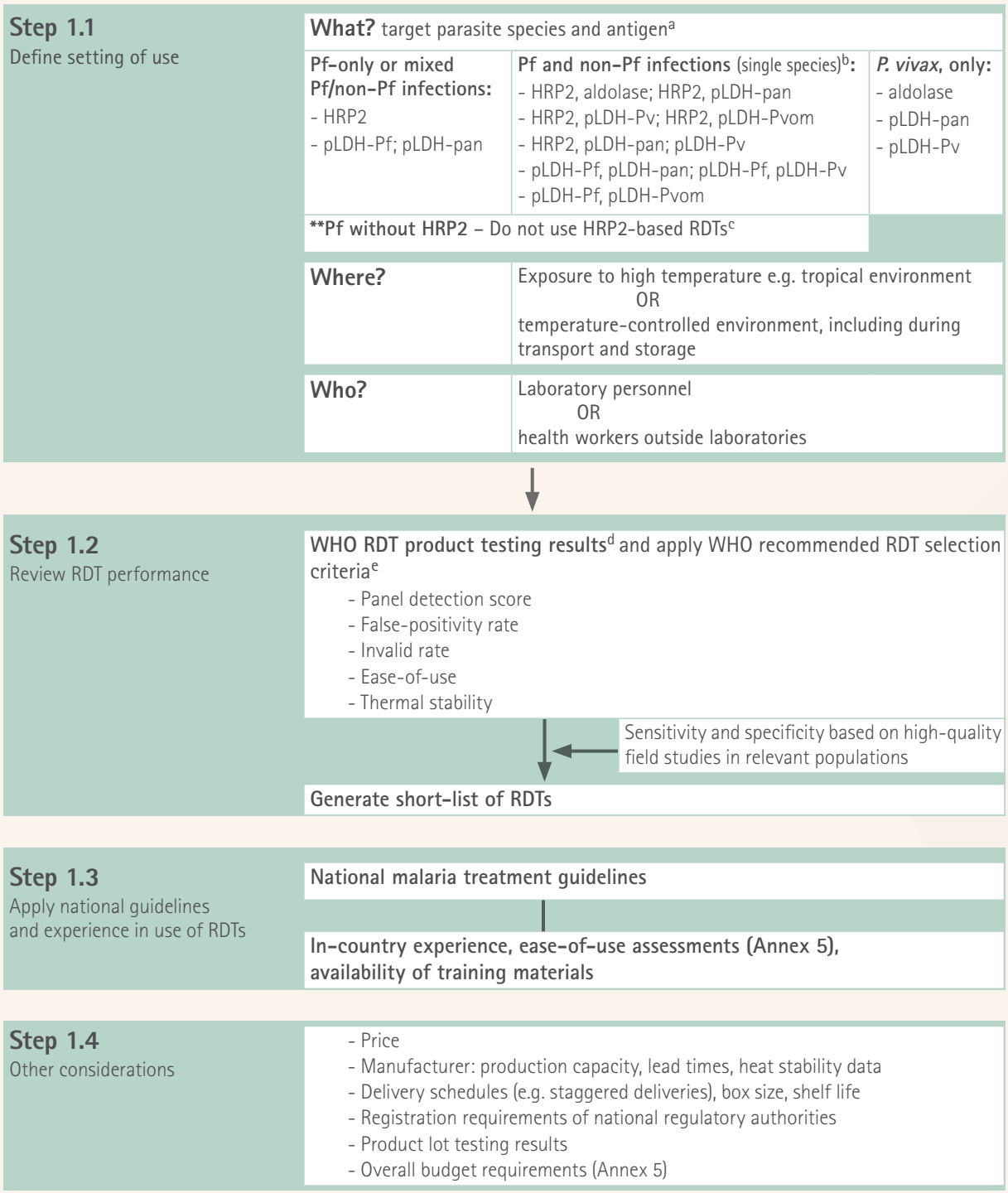
Figure AS2.1: Malaria RDT anomalies encountered in production lots

a) Observations on the test strip		
Red background		Background staining is relatively common. In this example, the result is positive as test lines are positive; however, a more intense red background may obscure weak positive test lines, giving false-negative results
Incomplete clearing		Poor clearing of blood may obscure weak positive test lines, giving false-negative results. In this example, the result is positive as the test line is visible
b) Observations of flow problems		
Failure to flow		Blood and buffer did not run the length of the strip
Irregular migration that obscures test line(s)		One portion of the nitrocellulose near the test band was not absorptive and remained dry during wicking, creating irregular migration of blood/buffer with red background that may obscure test line.
Irregular migration		One portion of the nitrocellulose near the test band was not absorptive and remained dry during wicking, creating irregular migration of blood/buffer with red background. In this example, the result is positive, as the test line is clearly visible.

c) Observations on test lines		
Ghost test lines		*White lines on a stained background. In this example, the result is negative, as the test line is not dark and is thus not visible.*
Patchy broken test line(s)		*The test line is visible but interrupted (broken).*
Diffuse test line(s)		*Test line wider than control, without clearly defined edge.*
d) RDT structural problems		
Strip misplaced in the cassette		*Strip can be seen only partially in the results window.*
Specimen pad not seen in sample window		*Normally, the colour of the conjugated antibody can be seen in the sample window (commonly purple, pink or blue).*

Annex S3: Selection of an appropriate RDT

Figure AS3.1: How to select of an appropriate RDT



[a] Pf-only or mixed Pf/non-Pf infections: Most areas of sub-Saharan Africa and lowland Papua New Guinea; Pf and non-Pf infections (single species): Most endemic areas of Asia and the Americas and isolated areas of the Horn of Africa; Mainly *P. vivax*-only: areas of East Asia, central Asia, South America, and some highland areas elsewhere

[b] Tests with a *P. falciparum*-specific line and pan-specific line will not distinguish *P. falciparum*-only infections from mixed *P. falciparum* infections. Distinguishing *P. falciparum* from mixed *P. falciparum-vivax* infections is important only if a full course of primaquine is routinely given for infections due to *P. vivax*. This must be weighed against the loss of ability to detect *P. malariae* and *P. ovale* if a test has only *P. falciparum*- and *P. vivax*-specific lines. Inclusion of further test lines (e.g. Pf-Pv-pan-pLDH) to detect these increases the complexity of test interpretation. A programme should prioritize these various advantages and disadvantages according to local conditions in the initial stage of making procurement decisions.

[c] *P. falciparum* parasites lacking HRP2 +/- HRP3 genes have been identified with high frequency in parts of South America *(10)*.

[d] See references *(3–6)*.

[e] WHO RDT procurement criteria : http://www.who.int/malaria/publications/atoz/rdt_selection_criteria/en/ (accessed 26 June 2014).

For a comprehensive guide to procurement of malaria RDTs extending beyond selection to quantification, budgeting, technical specifications, management of tenders, contracts, supply management and monitoring of supplier performance and managing product variations, see reference *(13)*.

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