Thursday, 17 March 2016

Time	Session	Purpose	Type
8.30 am 9:00 am	Session 5; Update on long-lasting insecticidal nets treated with a pyrethroid insecticide and piperonyl butoxide/Presentation *(A. Mnzava)* Changing WHO procurement criteria for malaria rapid diagnostic tests/Presentation *(A. Bosman / J. Cunningham)*	For information For discussion	open
10.00 am	**coffee**		
11.00 am	Session 6: Proposed Expert Review Group to review quality control methods for malaria rapid diagnostic tests *(J. Cunningham)*	For information	open
12.00 pm	**lunch**		
1.00 pm 2.00 pm	Session 7: WHO consultation to develop preferred product characteristics of ivermectin for malaria transmission control/Presentation *(P. Olumese)* Progress of elimination efforts in the Greater Mekong Subregion *(R. Abeyasinghe and E. Christophel)*	For information For information	open
3.00 pm	**coffee**		
3.30 pm	Session 8; Update of the Expert Review Group on Elimination *(K. Carter/H.Atta)*	For information	open
4.00 pm 5.00 pm	Session 9: Communicating MPAC meetings and resolutions Conclusions and closing of meeting	For information	closed
5.30 pm	**End of day**		

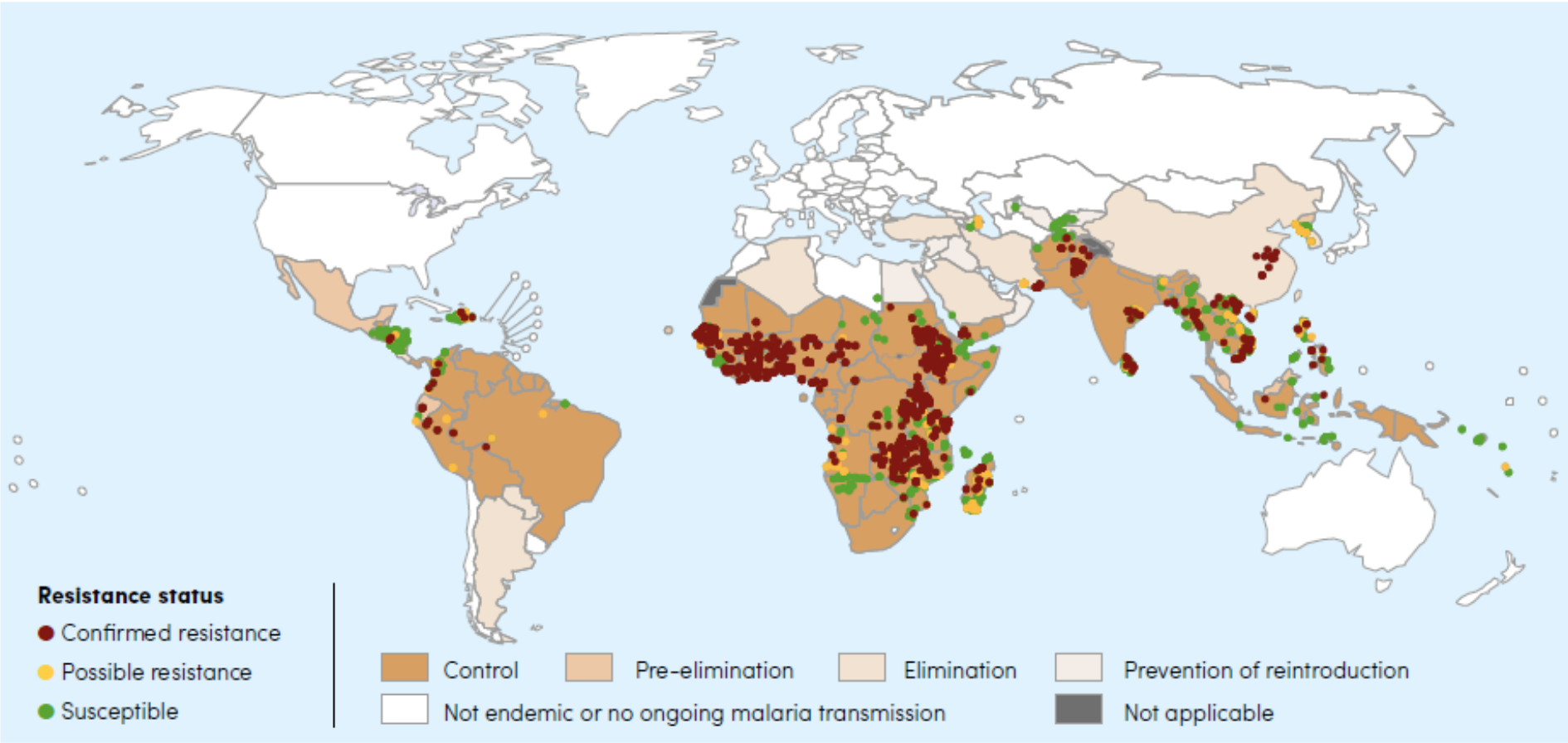
Recommendations on the use of LLINs treated with a pyrethroid and a synergist: An update

Malaria Policy Advisory Committee, Geneva, Switzerland, 16 March 2016

Global **Malaria** Programme

World Health Organization

Pyrethroid resistance increases in distribution and intensity



Data shown are for standard bioassays. Where multiple insecticide classes or types, mosquito species or time points were tested, the highest resistance status is shown.

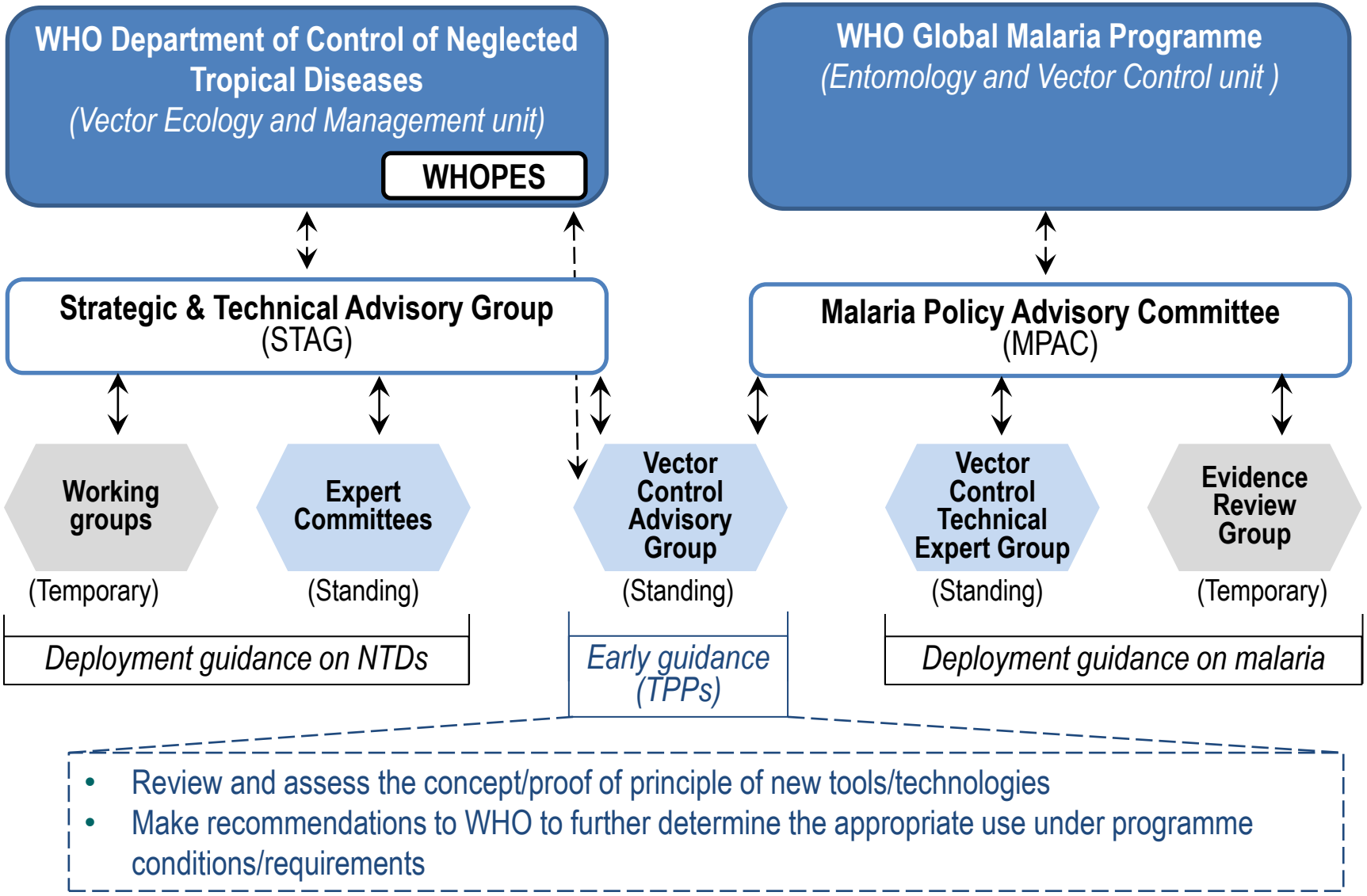
Source: *National malaria control programme reports, African Network for Vector Resistance, Malaria Atlas Project, President's Malaria Initiative (United States), scientific publications.*

Use of PBO LLINs in pyrethroid resistant areas

- Three LLINs treated with a pyrethroid and a synergist (PBO) are now available and have a WHOPES recommendation
- PBO is a synergist that enhances effects of pyrethroids by inhibiting metabolic detoxification enzymes
- Nets treated with PBO are therefore expected to perform better than standard LLINs in areas of substantial pyrethroid resistance – due to presence of certain resistance mechanisms (e.g. mixed function-oxidase)
  - WHO reviewed the available evidence with the objective of identifying areas and conditions under which PBO nets could be deployed
  - Advise countries on their use accordingly

Current WHO policy setting process

Vector control tools and products



The process of reviewing the evidence

- Acknowledged by VCAG as a new tool/approach for potential use in areas of high resistance – Nov'14
- Presented to MPAC for a possible recommendation – March'15 following electronic input from VCTEG
- MPAC requested GMP to consolidate all available data and if possible commission the generation of new evidence to identify areas where PBO nets could be deployed
- GMP requested the consolidation of such evidence and constituted an independent Evidence Review Group (ERG) – Sept'15
- Report electronically reviewed by VCTEG and MPAC – October'15
- WHO issued recommendations – December 2015

Quality of the evidence (i)

- Laboratory data on the comparative efficacy of a pyrethroid-only LLIN versus a PBO LLIN against pyrethroid-resistant populations were available from **28 studies**, providing **137 data** points.
- These bioassay data showed that PBO LLINs can kill most resistant mosquito strains, except in those with very high resistance and with mechanisms unaffected by PBO.
- Semi-field data from **9 experimental hut trials** supported this finding, however:
  - Conducted in areas of documented high insecticide resistance
  - Data were available only for *An. gambiae* s.l.

Quality of the evidence (ii)

- There were some correlation between the data from the bioassays and the limited experimental hut data. However not adequate to rely on predictions of the entomological or epidemiological impact of PBO LLINs.
- Data were available from six village trials with entomological, but not epidemiological, outcomes.
- No data are available from high-quality cluster randomized trials on the epidemiological impact of PBO LLINs. One trial was under way and thought could help answer some of the outstanding questions.

NB: In one product, PBO component was shown not to be available after 10 laboratory washes compared to the required 20 washes for the pyrethroid

Recommendations for PBO nets implementation

- The evidence on the efficacy of PBO LLINs is still limited and does not justify at this point, a complete switch from pyrethroid-only LLINs to PBO LLINs **across all settings**.
- There is neither evidence to assume higher efficacy nor greater utility as a resistance management **strategy across all settings**.
- PBO LLINs should be used only where universal coverage with effective vector control (LLINs and / or IRS) of populations at risk of malaria will not be reduced.
- They should also not be used in areas programmed for IRS with pirimiphos methyl (actellic-cs) due to a potential negative interaction between PBO and pirimiphos methyl

Recommendations for PBO nets implementation

- Pilot implementation accompanied by **robust monitoring and evaluation** undertaken where prevalence of malaria in children aged 2–10 years is > 20% and mosquito bioassay mortality with pyrethroids is < 80%
- Guiding potential deployment, countries should be supported to:
  - collect data on the presence, level, intensity and mechanisms of pyrethroid resistance at representative sentinel sites;
  - design an evaluation with appropriate indicators based on detailed guidance
- To manage insecticide resistance, development and evaluation of non-pyrethroid LLINs and other innovative vector control tools for use **across all settings** is a priority

Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide

SEPTEMBER 2017 (REVISED DECEMBER 2017) RECOMMENDATIONS

BACKGROUND

Mosquito nets that include both a pyrethroid insecticide and the synergist piperonyl butoxide (PBO) have become available. PBO is a synergist that acts by inhibiting certain metabolic enzymes (e.g., mixed-function oxidases) within the mosquito that detoxify or sequester insecticides before they can have a toxic effect on the mosquito. Therefore, compared to a pyrethroid-only net, a pyrethroid-PBO net should, in theory, have an increased killing effect on malaria vectors that express such resistance mechanisms. However, the entomological and epidemiological impact of pyrethroid-PBO nets may vary depending on the bioavailability and retention of PBO in the net, and on the design of the net (i.e., whether only some or all panels are treated with PBO).

Five pyrethroid-PBO net products have been evaluated under the WHO Pesticide Evaluation Scheme (WHOPES) to determine whether they meet the criteria established for classification as a pyrethroid-treated long-lasting insecticidal net (LLIN).[1] WHOPES evaluation focused on assessing the physical durability of the net, and the biological activity and wash-resistance of the pyrethroid but not the PBO treatment. All five pyrethroid-PBO nets underwent experimental hut[2] evaluations, and two are currently undergoing long-term field evaluations.[3]

In accordance with the revised WHO evaluation process for vector control products, current WHOPES recommendations for the five products[4] are being converted into a WHO prequalification listing.[5] In line with the evaluations undertaken, the WHO recommendation for these products has been as pyrethroid-only LLINs. In 2014, the WHO Vector Control Advisory Group (VCAG) also reviewed one of the pyrethroid-PBO nets (PermaNet® 3.0)[6] for a claim of increased efficacy against malaria vectors with cytochrome P450-based metabolic pyrethroid resistance. The public health value[7] of PermaNet® 3.0 against vectors with cytochrome P450-based metabolic pyrethroid resistance, however, could not be established due to insufficient epidemiological data.

World Health Organization

WHO/HTM/GMP/2017.17

In 2015, WHO's Global Malaria Programme (GMP) convened an Evidence Review Group (ERG) to define the conditions for use of pyrethroid-PBO nets. WHO released an initial set of recommendations in December 2015. Since the 2015 ERG, a randomized controlled trial in the United Republic of Tanzania has generated new epidemiological evidence for pyrethroid-PBO nets. As a result, the WHO/GMP ERG re-convened in June 2017 to assess whether these new data demonstrate the public health value of pyrethroid-PBO nets in terms of the control of malaria where vectors are pyrethroid-resistant. Details of the review process, quality of the evidence, outstanding questions, and proposals to further strengthen the current evidence can be found in the ERG meeting report, which will be made available upon publication of the randomized control trial data.[8]

In the ongoing transition of the WHO evaluation process for vector control products from WHOPES to the Prequalification Team, WHO has developed an updated policy recommendation on pyrethroid-PBO nets that takes into account the epidemiological trial data from Tanzania. This update is an attempt to further clarify the available evidence base for these types of nets, their categorization under the revised evaluation system, and the additional data required to support WHO's policy-making process. This represents an exception to the standard review procedure, which requires a minimum of two epidemiological trials to assess the public health value of new vector control tools not covered by an existing WHO policy.

These recommendations replace the 2015 WHO recommendations on pyrethroid-PBO nets and will be further revised as new data become available.

CONCLUSIONS & RECOMMENDATIONS

On the basis of the current evidence, WHO concludes and recommends the following:

1. **Epidemiological data from one cluster randomized controlled trial indicated that a pyrethroid-PBO net product had additional public health value compared to a pyrethroid-only LLIN product in an area where the main malaria vector had confirmed pyrethroid resistance of moderate intensity conferred (at least in part) by monooxygenase-based resistance mechanism as determined by standard procedures.**[9, 10] This conclusion is based on a comparison of malaria infection rates in children in village clusters allocated pyrethroid-PBO nets (Olyset® Plus) and rates in village clusters allocated pyrethroid-only LLINs (Olyset® Net) over a period of 2 years in Muleba, United Republic of Tanzania. Entomological data from experimental hut studies on several similar pyrethroid-PBO products conducted in areas of pyrethroid resistance support the finding that pyrethroid-PBO nets are more effective at killing resistant mosquitoes. Mathematical modelling work drawing on relevant entomological data indicates that the added benefit of pyrethroid-PBO nets compared to pyrethroid-only LLINs is expected to be the greatest where pyrethroid resistance is at "intermediate levels", meaning where mosquito mortality after exposure to a pyrethroid insecticide in WHO test kits or CDC bottle assays ranges from 10% to 80%.[11] The benefit of pyrethroid-PBO nets is expected to diminish where bioassay mortality is outside of this range. Pyrethroid-PBO nets are not expected to have any added benefit in areas where the main malaria vectors are susceptible to pyrethroids and/or do not harbor resistance mechanism(s) that are affected by PBO, i.e., monooxygenase-based resistance mechanism.[10]

2. **Based on the epidemiological findings and the need to deploy products that are effective against pyrethroid-resistant mosquitoes, pyrethroid-PBO nets are being given a conditional endorsement as a new WHO class of vector control products.** As an exception, this establishment of a class is based on a single epidemiological study instead of two studies, as required by VCAG for the assessment of a new product class.[5] The endorsement is based on epidemiological evidence of the greater effectiveness of pyrethroid-PBO nets in areas of intermediate level resistance. Full confirmation of the class will require VCAG's assessment of data from a second epidemiological trial. Meanwhile, all pyrethroid-PBO nets that have a WHOPES recommendation or WHO prequalification listing will be considered to be at least as effective as pyrethroid-only LLINs at preventing malaria infections – and possibly more effective in areas with intermediate levels of pyrethroid resistance conferred by a monooxygenase-based resistance mechanism.

3. **National malaria control programmes and their partners should consider the deployment of pyrethroid-PBO nets in areas where the main malaria vector(s) have pyrethroid resistance that is: a) confirmed, b) of intermediate level (as defined above), and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures.**[10] Deployment of pyrethroid-PBO nets must only be considered in situations where coverage with effective vector control (primarily LLINs or indoor residual spraying [IRS]) will not be reduced; the primary goal must remain the achievement and maintenance of universal coverage for all people at risk of malaria.

4. **Further evidence on pyrethroid-PBO nets is required to support the refinement of WHO guidance regarding conditions for the deployment of products in this class:**

    a. VCAG will review data from the third intervention year of the ongoing randomized control trial in Tanzania once they become available. This will determine whether the higher effectiveness of the pyrethroid-PBO net (compared to a pyrethroid-only LLIN) has continued to be observed over the full period for which an LLIN is expected to retain its biological activity (i.e., a minimum of 3 years). These data will contribute to our understanding of whether the pyrethroid-PBO product under evaluation meets the former WHOPES requirements for an LLIN.

    b. VCAG will review further epidemiological trial data as soon as they become available, such as from a randomized controlled trial planned in Uganda using two pyrethroid-PBO nets (the same product as is being tested in Tanzania, treated with PBO on all panels, and another pyrethroid-PBO net with only the net roof treated with PBO). These data will provide additional evidence on how pyrethroid-PBO nets perform in another geographical setting and whether there are notable differences in effectiveness between products in this class. If VCAG is able to confirm additional public health value, it will allow the conditional endorsement of pyrethroid-PBO nets to be converted into the full establishment of the class.

    c. The effectiveness of other pyrethroid-PBO nets in comparison to the product for which data were generated in Tanzania needs to be determined. Evaluation procedures to determine whether other

products in a class perform at least as well as the product(s) for which epidemiological data were generated, and for which a product class has been established, are under development. Comparing the effectiveness of different pyrethroid-PBO nets will be aided by:

c.i. Identifying appropriate entomological indicators to assess the effectiveness of subsequent products entering an existing product class, given that these products will not be required to generate epidemiological data;

c.ii. Conducting comparative experimental hut trials on different pyrethroid-PBO nets to determine the relative effectiveness of different compositions of net (e.g., PBO applied to the roof panel of the net only versus all panels of the net), as well as different formulations including initial PBO treatment dosages and release properties;

c.iii. Conducting bioassays using characterized reference strains of insecticide-resistant *Anopheles* mosquito(es) on pyrethroid-PBO nets following a minimum of 2 to 3 years of routine use to determine the bioavailability and chemical retention of PBO over time. Current information suggests that PBO retention rates and wash resistance indices are much lower than for the pyrethroid component of the formulations. Studies should be conducted on the PBO-LLIN product assessed in Tanzania, with comparative studies performed on other products of the same class.

d. Further investigations (laboratory and field studies) are required to determine if there is an antagonistic effect between PBO and the organophosphate pirimiphos-methyl, which is one insecticide recommended for IRS. To date, limited evidence from laboratory studies and the randomized controlled trial in Tanzania suggests that this is not an operational concern; however, further studies are needed to determine the generalizability of current findings.

e. Further research will be required to investigate the relationship between entomological indices and epidemiological outcomes for vector control products in order to determine whether entomological surrogates may be sufficient for assessing the public health value of vector control products not currently covered by a WHO policy recommendation.

f. Synergist testing methods need to be validated, including identification of appropriate sub-lethal concentrations for pre-exposure to PBO in CDC bottle assays.

5. **Pyrethroid-PBO nets should not be considered a tool that can effectively manage insecticide resistance in malaria vectors.** It is an urgent task to develop and evaluate LLINs treated with non-pyrethroid insecticides and other innovative vector control tools for use across all settings in order to provide alternatives for use in a comprehensive insecticide-resistance management strategy.

Endnotes

The mention of specific companies or certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

1. Guidelines for laboratory and field testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf).

2. Phase II WHOPES evaluation

3. Phase III WHOPES evaluation

4. WHO recommended long-lasting insecticidal nets. Geneva: World Health Organization; 2017 (http://who.int/whopes/Long-lasting_insecticidal_nets_June_2017.pdf).

5. The evaluation process for vector control products. Geneva: World Health Organization; 2017 (http://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/).

6. Second meeting of the Vector Control Advisory Group. Summary report. Geneva: World Health Organization; 2014 (http://apps. who.int/iris/bitstream/10665/137318/1/9789241508025_eng.pdf).

7. Public health value is defined as: proven protective efficacy to reduce or prevent infection and/or disease in humans.

8. Report of the evidence review group to define the conditions of deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide, 26-27 June 2017. Geneva: World Health Organization; 2017. This will only be available when the data from Tanzania have been published.

9. Protopopoff N & Rowland M. Effectiveness of a long-lasting PBO treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid resistant mosquitoes: A community randomised factorial design trial.(Under final peer review)

10. Test procedures for insecticide resistance monitoring in malaria vector mosquitoes (2nd edition). Geneva: World Health Organization; 2016 (http://www.who.int/malaria/publications/atoz/9789241511575/).

11. Intermediate level of resistance classified by epidemiological predictions of pyrethroid-PBO nets on average averting >0.1 clinical cases per person per year over pyrethroid-only LLINs (Churcher TS, Lissenden N, Griffin JT, Worrall E, Ranson H. The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in Africa. Elife. 2016;5:e16090 [https://elifesciences.org/articles/16090]).

Malaria Policy Advisory Committee Meeting
16–17 March 2016, Geneva, Switzerland
Background document for Session 5

Transitioning to WHO prequalification as a requirement for malaria rapid diagnostic tests procurement: caveats and timelines

March 2016, Geneva, Switzerland

Background

Since 2010, WHO's guidance for malaria rapid diagnostic tests (RDT) procurement has been based on the performance results of the WHO Product Testing Programme. By evaluating RDTs and sharing results with buyers, the programme has shifted the malaria RDT market share to well-performing products and dramatically expanded access to diagnostic testing. WHO is now considering prequalification as a requirement for procurement. WHO prequalification involves a review of a product dossier and inspection of the manufacturing site(s), in addition to an independent performance evaluation by Product Testing. The goal of universal access to diagnosis requires quality-assured products, as well as a healthy market. Therefore, before adopting the new criteria for WHO prequalification, the WHO Global Malaria Programme commissioned an independent assessment of the potential impact of this policy change on RDT quality, supply security and affordability.

Rationale for the policy change

Given the extent of lot-to-lot variation seen in RDTs, issues with heat stability (e.g., the failure of products containing single-use buffer vials), and market factors that put pressure on quality (e.g., cost-reduction efforts, rapid production scale-up), introducing a quality assessment system would provide consumers with insight into quality at the manufacturing level, which in turn would create an additional incentive for manufacturers to invest in their quality management system (QMS). The WHO prequalification of in vitro diagnostics programme (WHO PQ) has prequalified eight products over the past year, totalling twelve malaria RDTs prequalified across four main test type categories (Table 1). As a result, the number of prequalified products could now potentially begin to support a competitive market.

WHO/HTM/GMP/MPAC/2016.3

Table 1. Prequalified products as of February 2016 by product type

Test name	Manfacturer	2014 MS (w/in category)	2014 MS (overall)	Prequalified date
Pf Only				
1 CareStartTM Malaria HRP2 (Pf)	Access Bio	34%	21%	28-May-15
2 First Response® Malaria Ag P. falciparum (HRP2) Card Test	PMC	15%	9%	25-Feb-15
3 ParaHIT f Ver. 1.0 Rapid Test for P.falciparum Malaria Dipstick	Span/Arkray	0%		7-Oct-14
4 ParaHIT f Ver. 1.0 Rapid Test for P.falciparum Malaria Device	Span/Arkray	3%	2%	7-Oct-14
5 SD BIOLINE Malaria Ag P.f	Alere/SD	41%	26%	6-Dec-10
		93%	58%	
Pf/pan				
1 Carestart pf/pan Combo	Access Bio	12%	4%	28-May-15
2 SD BIOLINE Malaria Ag P.f/Pan	Alere/SD	72%	21%	8-Jul-13
		84%	24%	
Pf/pv				
1 CareStartTM Malaria HRP2/pLDH (Pf/Pv) COMBO	Access Bio	6%	0%	28-May-15
2 SD BIOLINE Malaria Ag P.f/P.v	Alere/SD	94%	5%	16-Oct-15
		100%	6%	
Other				
1 CareStartTM Malaria HRP2/pLDH (Pf)	Access Bio		2%	28-May-15
2 CareStartTM Malaria pLDH (PAN)	Access Bio		0%	28-May-15
3 SD BIOLINE Malaria Ag P.f (HRP2/pLDH)	Alere/SD		1%	16-Oct-15
12			3%	

Recommendations

The report considers how requiring WHO prequalification for malaria RDTs, as of the end of 2017,1 would impact the market. The assessment also evaluates potential risks and risk-mitigating strategies. Analyses of the market and the WHO prequalification pipeline suggest that WHO prequalification for malaria RDTs is beneficial, as it provides an incentive for manufacturers to invest in quality and enables consumers to identify products produced by manufacturers that have invested in strong QMS. However, given some of the market risks identified, a phased implementation of WHO PQ as a WHO procurement requirement for malaria RDTs is recommended. The recommended timelines for different categories of RDTs are as follows:

- For *P.falciparum*-only RDTs,2 there are already four prequalified products (including 1 dipstick) from four different manufacturers, and additional RDTs are likely to be prequalified in the next two years. Therefore, the shift to the new policy of WHO prequalification as a prerequisite for WHO procurement could be implemented as per the proposed timeline.
- For both the Pf-pan and Pf/pv combination RDTs, there are currently only two prequalified products per test type, and slightly fewer tests are likely to be prequalified. Therefore, an extended timeline and/or additional incentives should be considered. Extending the timeline until four to six products (from different manufacturers) per test type are prequalified would mitigate the risks associated with overreliance on a limited number of suppliers.
- For pan-only RDTs, there is a small but potentially growing need/market, but only one prequalified product; only one other product that meets the current procurement criteria has been evaluated by Product Testing. Therefore, an extended timeline would also be required.

This recommendation assumes that major donors and procurers generally support WHO prequalification and the broadening of the supply base. At the same time, WHO and its partners should consider several risk-mitigating strategies. First, because the buy side of the malaria RDT market is highly concentrated, it is possible for WHO and the major procurers to discuss how current procurement practices contribute to market concentration and what measures could be taken to reduce the risk of supply disruption and to ensure competition. In particular, it is important to consider options for encouraging new RDT manufacturers to engage in the public sector market and to build out their production capacity. Second, there are several areas of work, led by WHO, that could contribute to a larger number of prequalified malaria RDTs in 2017, for example: i) requiring that products submitted to Product Testing also apply for WHO prequalification; ii) ensuring that malaria RDT manufacturers are knowledgeable about the WHO prequalification process and expectations; and iii) closely monitoring the progress of malaria RDTs through the WHO prequalification process, and responding to major delays if warranted. Lastly, clear communication is needed to inform both the buy side and supply side of the changes, especially because a phased implementation introduces an additional element of complexity.

Notes

1. This deadline is set to allow manufacturers not currently in the PQ pipeline, but with well-performing tests, to realistically complete the PQ process (including both PQ and manufacturing time). It also ensures that procurers have time to revise their policies to align with new requirements, and countries have time to plan tenders and programmatic activities if they need to change products.
2. In this report "*Pf*-only RDTs" refers to RDTs that detect only the HRP2 antigen. These are traditionally the most commonly used RDTs on the market.

Transition from WHO Product Testing to WHO Prequalification as basis for procurement of malaria RDTs

Malaria Policy Advisory Committee, Geneva, Switzerland, 16 March 2016

Global **Malaria** Programme

World Health Organization

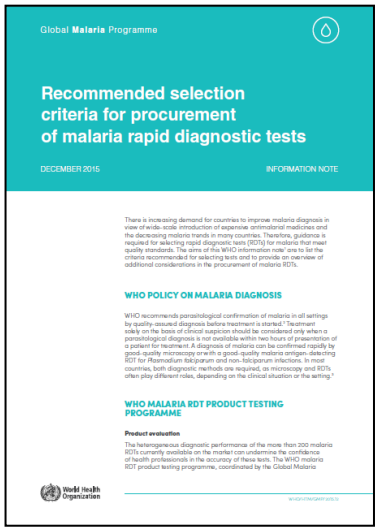
Presentation outline

- WHO Product Testing and Lot Testing Programme
- Current WHO procurement criteria for malaria RDTs
- Relations between Product Testing and Prequalification of malaria RDTs
- Recent progress in prequalification of malaria RDTs
- Specificity of mRDT market and PQ pipeline
- Phased transition to WHO PQ as procurement requirement
- Other mitigating strategies to ensure healthy market of quality RDTs

Product Testing of malaria RDTs

- Evaluates malaria RDTs to produce comparative performance data to guide procurement and use
- Data relevant to performance in all endemic countries
- Forms basis of WHO RDT procurement recommendations
- Starting point for choosing a product: assurance that product can perform sufficiently well
- Since 2008, 251 products have been evaluated in six rounds of product testing, comprising 171 unique products and 58 product resubmissions

WHO recommended procurement criteria



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%.

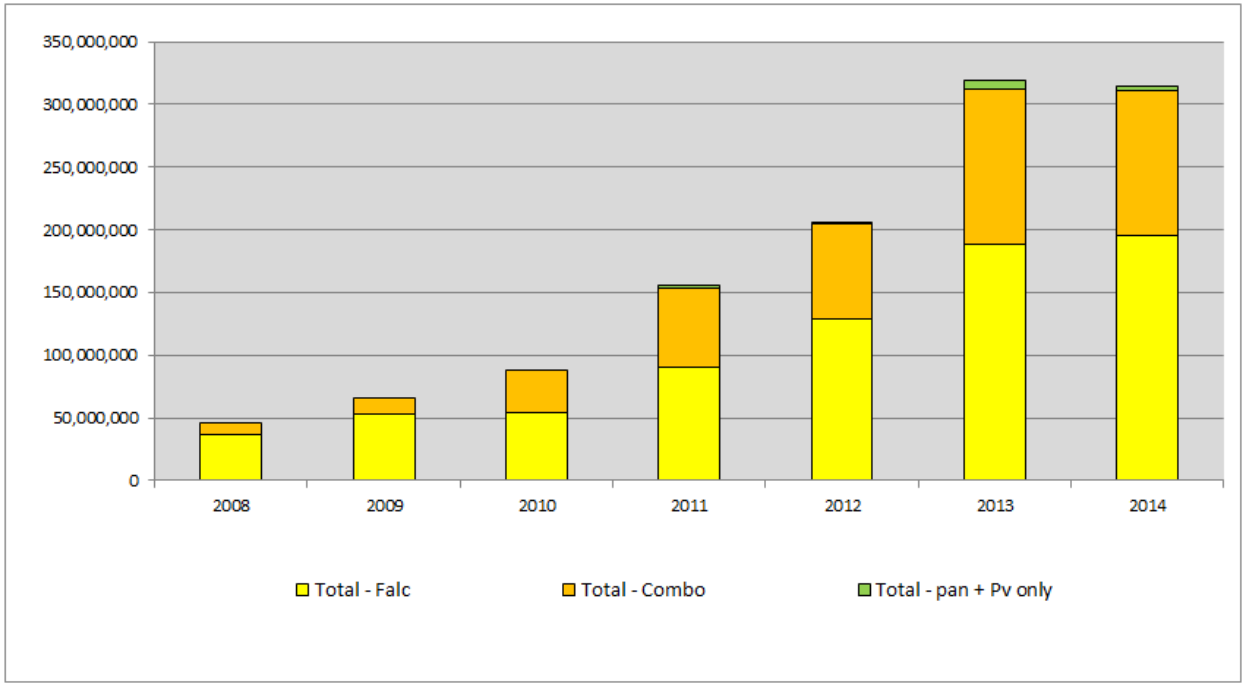
D. The invalid rate should be less than 5%.

Approved by MPAC in January 2012

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

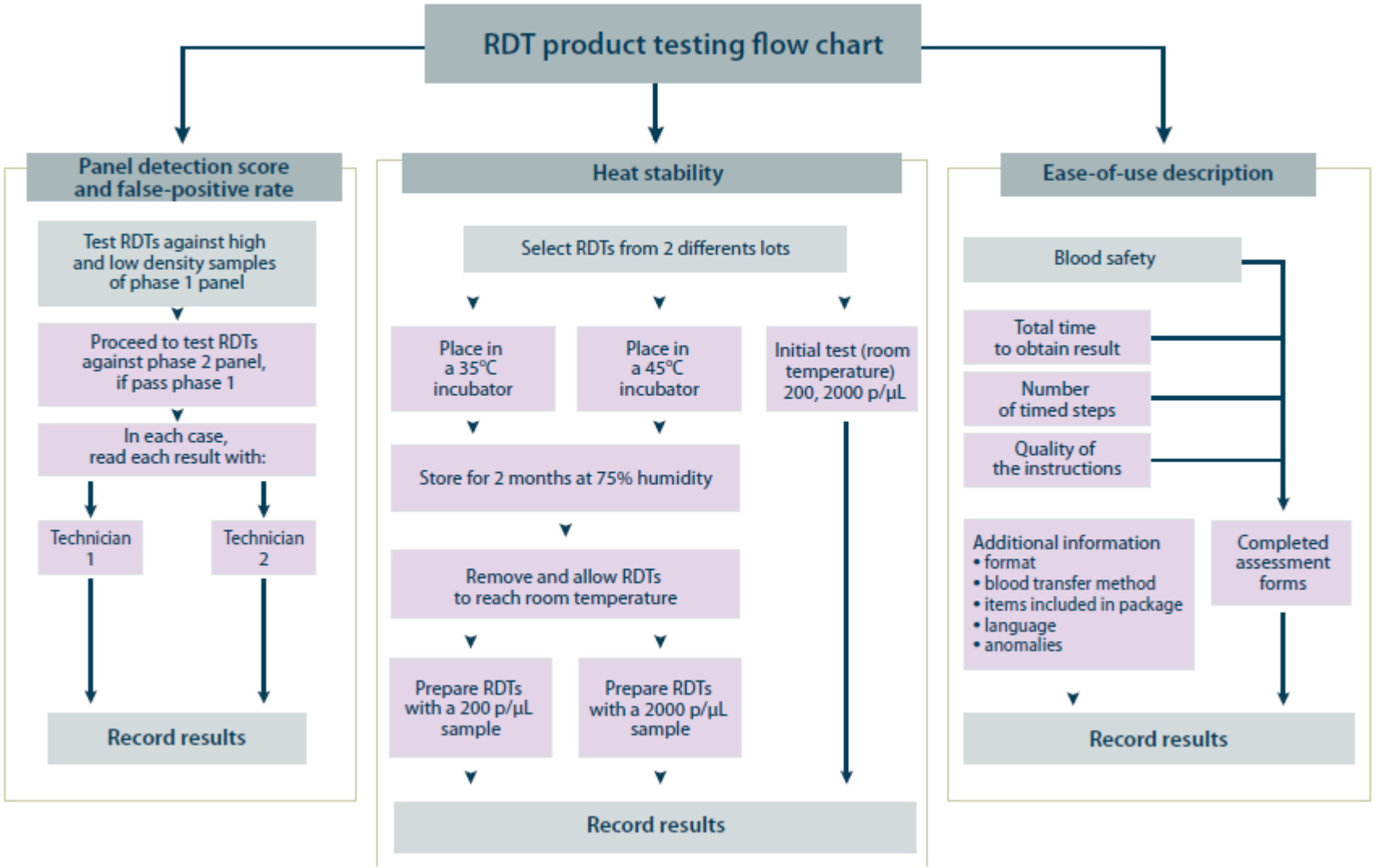
RDTs deliveries compliant with WHO criteria

1,193,774,230 malaria RDTs delivered from 2008 to 2014

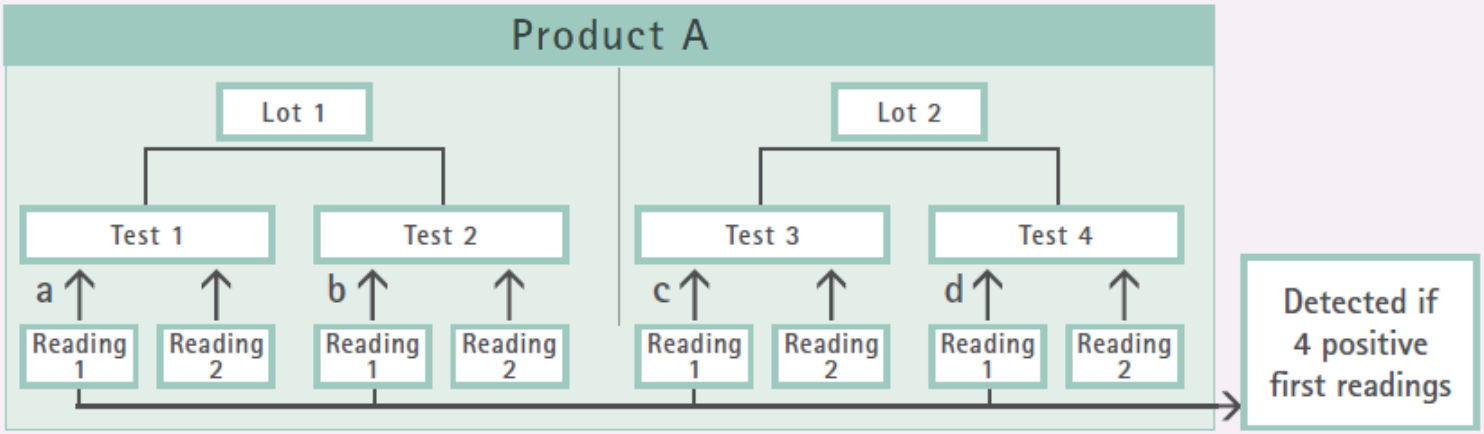


Data provided by 31 (2008-2010), 24 (2011), 24 (2012), 29 (2013) and 27 (2014) manufacturers who have participated in the WHO RDT Product Testing conducted at CDC, Atlanta.

Overview of malaria RDTs Product Testing



Calculation of Panel Detection Score (PDS)



[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.

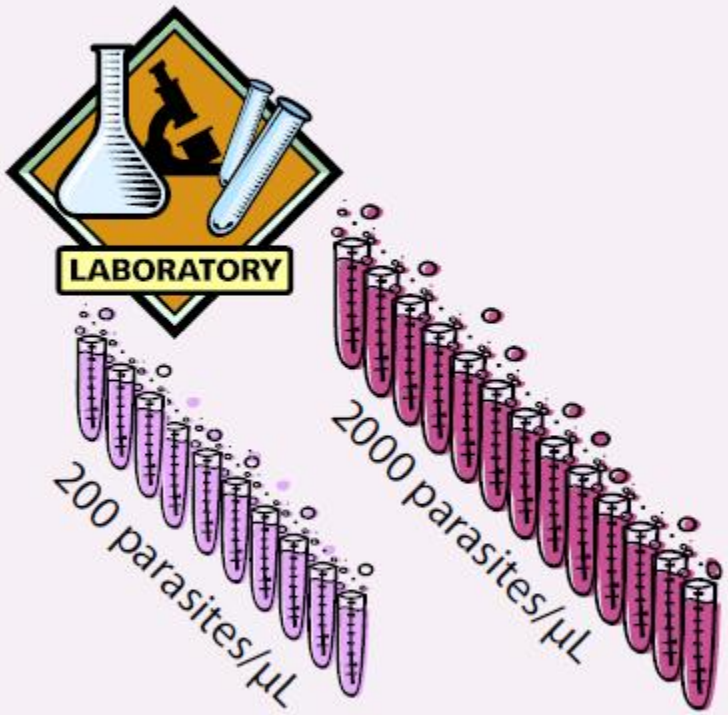
In the above example, the positivity rate is: 9/12 = 75%.

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

PDS versus 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.

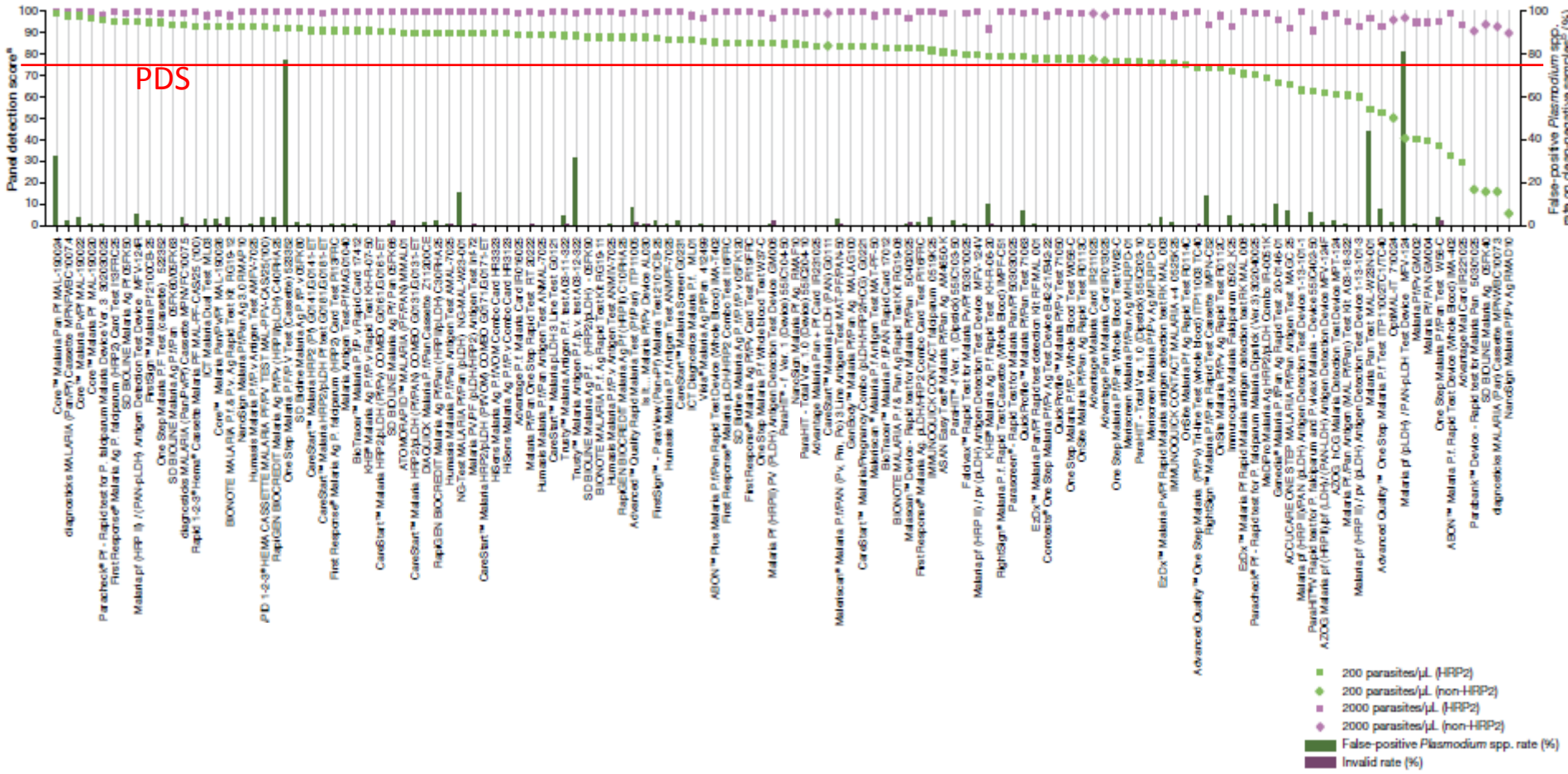
Malaria endemic setting

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.

R3-6 performance against Pf clinical samples



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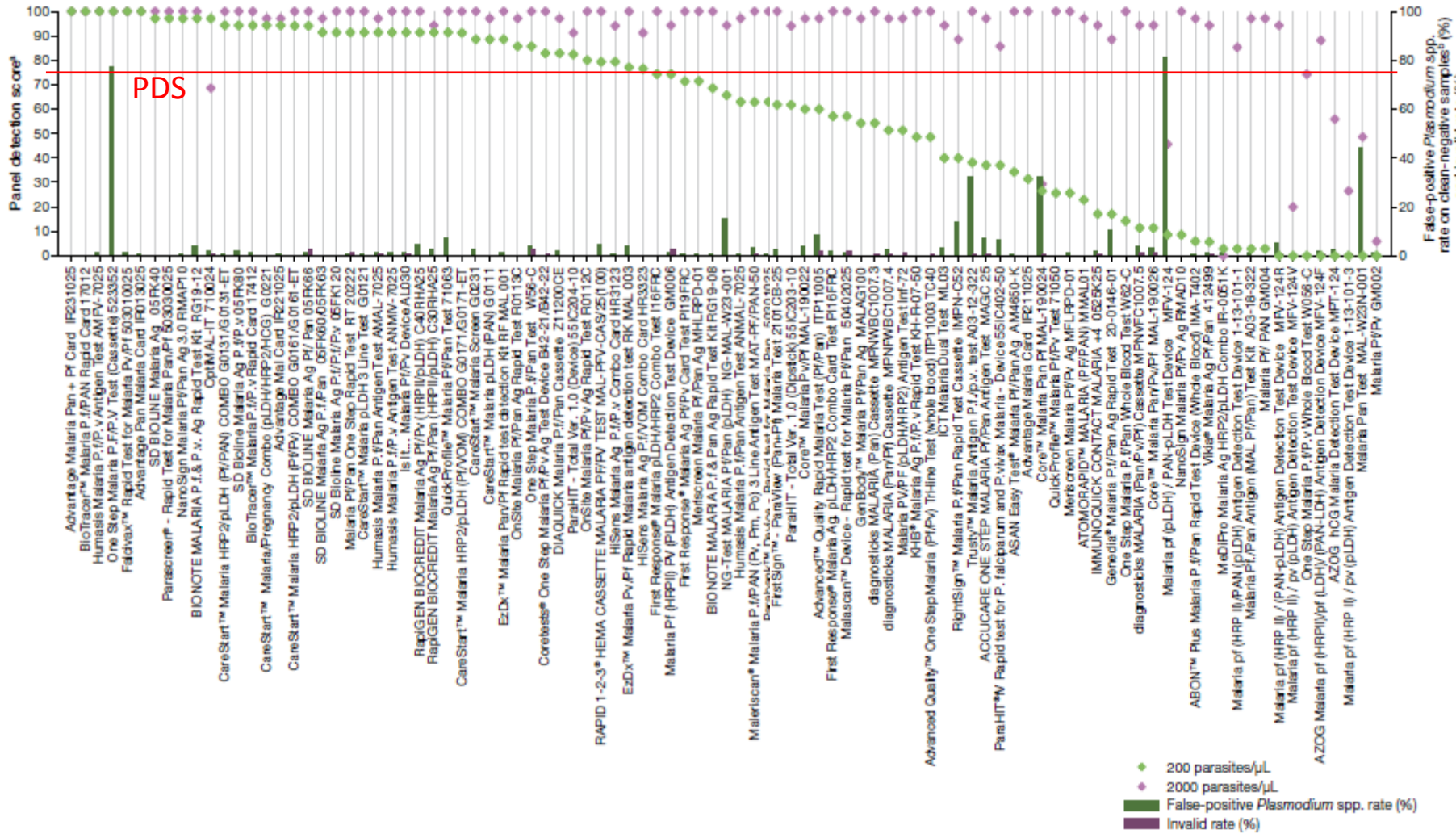
World Health Organization

R3-6 performance against Pv clinical samples

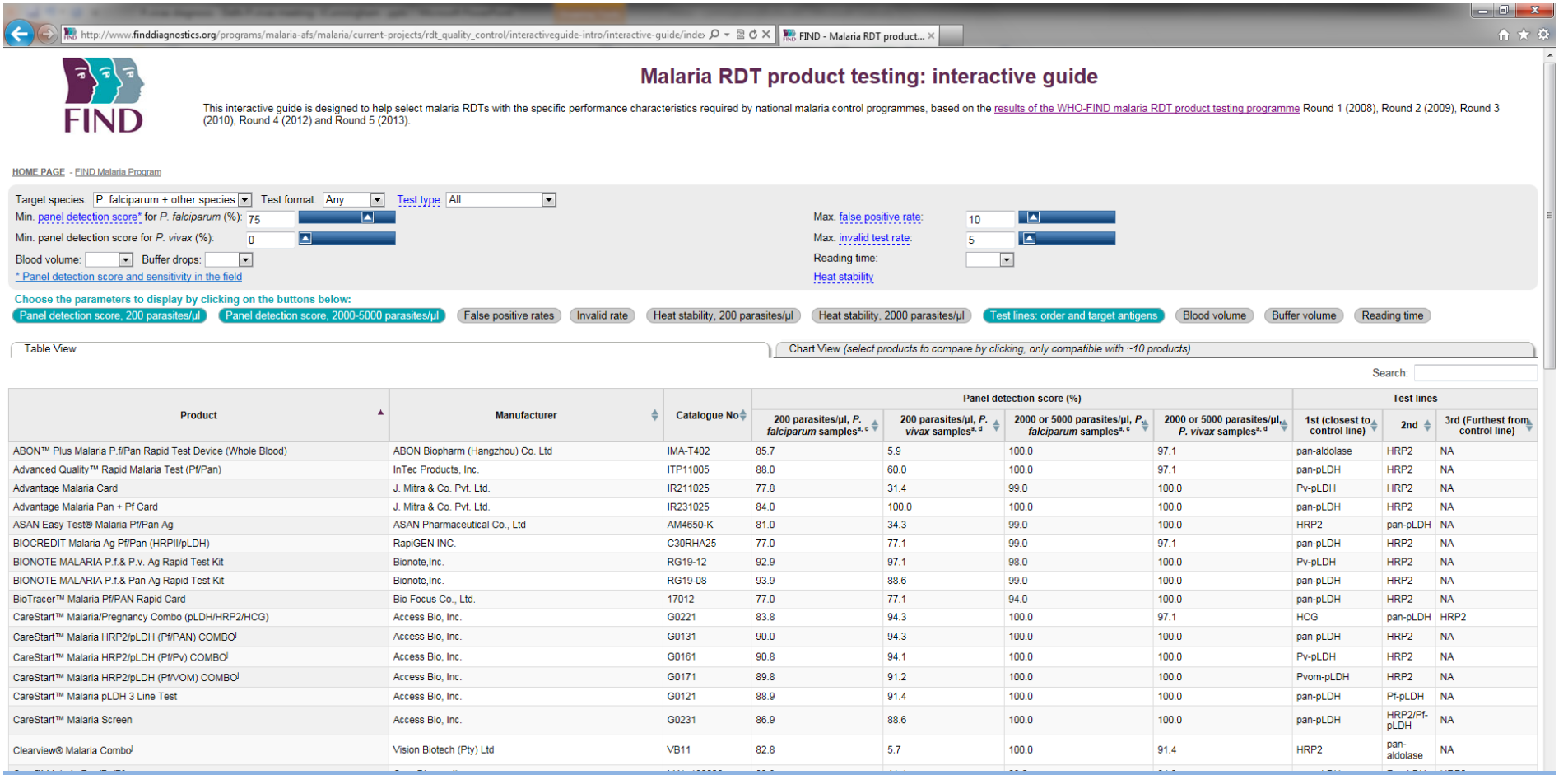


Global **Malaria** Programme

World Health Organization

FIND Interactive Guide for malaria RDTs

- Web based database of product testing results (Rounds 1-6)



http://www.finddiagnostics.org/programs/malaria-afs/malaria/current-projects/rdt_quality_control/interactiveguide-intro/interactive-guide/index.jsp

Malaria RDT product testing: interactive guide

This interactive guide is designed to help select malaria RDTs with the specific performance characteristics required by national malaria control programmes, based on the results of the WHO-FIND malaria RDT product testing programme Round 1 (2008), Round 2 (2009), Round 3 (2010), Round 4 (2012) and Round 5 (2013).

HOME PAGE - FIND Malaria Program

Target species: P. falciparum + other species | Test format: Any | Test type: All

Min. panel detection score* for *P. falciparum* (%): 75

Min. panel detection score for *P. vivax* (%): 0

Blood volume: | Buffer drops:

* Panel detection score and sensitivity in the field

Max. false positive rate: 10

Max. invalid test rate: 5

Reading time:

Heat stability

Choose the parameters to display by clicking on the buttons below:

Panel detection score, 200 parasites/µl | Panel detection score, 2000-5000 parasites/µl | False positive rates | Invalid rate | Heat stability, 200 parasites/µl | Heat stability, 2000 parasites/µl | Test lines: order and target antigens | Blood volume | Buffer volume | Reading time

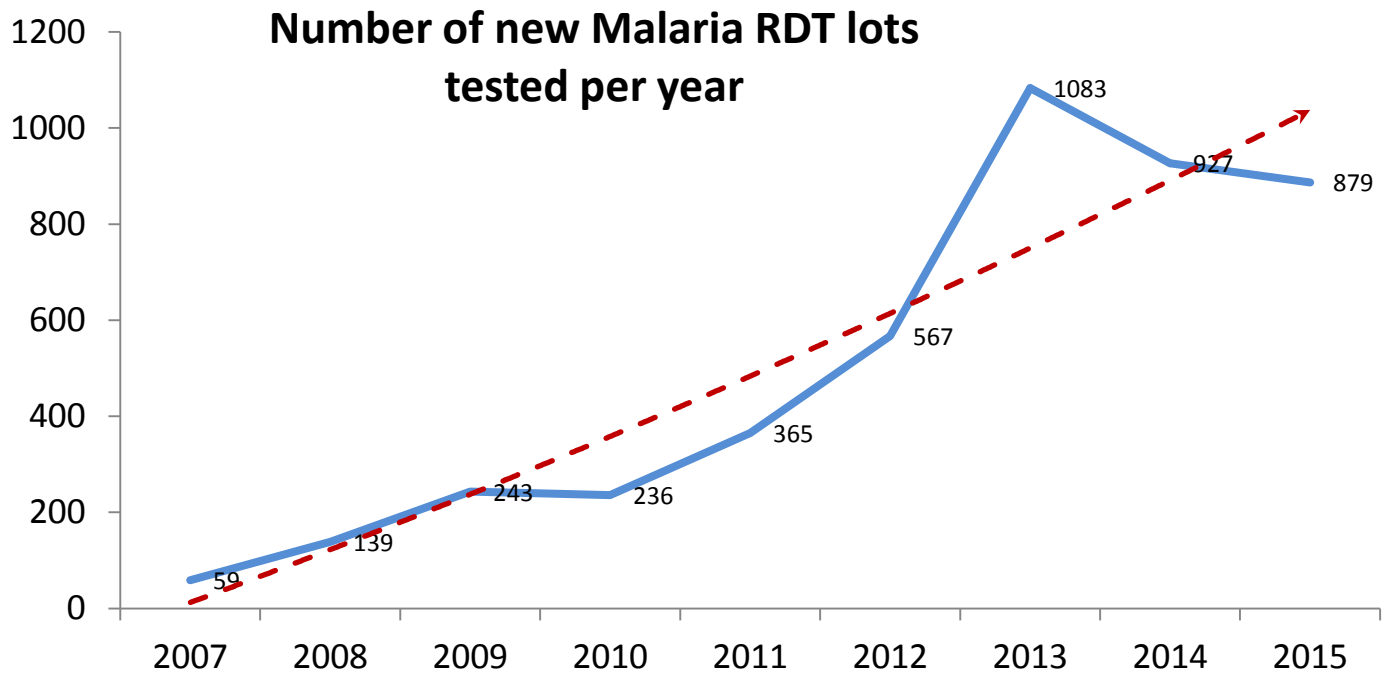
Table View | Chart View (select products to compare by clicking, only compatible with ~10 products)

Search:

Product	Manufacturer	Catalogue No	Panel detection score (%)				Test lines		
			200 parasites/µl, *P. falciparum* samples[a, c]	200 parasites/µl, *P. vivax* samples[a, d]	2000 or 5000 parasites/µl, *P. falciparum* samples[a, c]	2000 or 5000 parasites/µl, *P. vivax* samples[a, d]	1st (closest to control line)	2nd	3rd (Furthest from control line)
ABON™ Plus Malaria P.f/Pan Rapid Test Device (Whole Blood)	ABON Biopharm (Hangzhou) Co. Ltd	IMA-T402	85.7	5.9	100.0	97.1	pan-aldolase	HRP2	NA
Advanced Quality™ Rapid Malaria Test (Pf/Pan)	InTec Products, Inc.	ITP11005	88.0	60.0	100.0	97.1	pan-pLDH	HRP2	NA
Advantage Malaria Card	J. Mitra & Co. Pvt. Ltd.	IR211025	77.8	31.4	99.0	100.0	Pv-pLDH	HRP2	NA
Advantage Malaria Pan + Pf Card	J. Mitra & Co. Pvt. Ltd.	IR231025	84.0	100.0	100.0	100.0	pan-pLDH	HRP2	NA
ASAN Easy Test® Malaria Pf/Pan Ag	ASAN Pharmaceutical Co., Ltd	AM4650-K	81.0	34.3	99.0	100.0	HRP2	pan-pLDH	NA
BIOCREDIT Malaria Ag Pf/Pan (HRPII/pLDH)	RapiGEN INC.	C30RHA25	77.0	77.1	99.0	97.1	pan-pLDH	HRP2	NA
BIONOTE MALARIA P.f.& P.v. Ag Rapid Test Kit	Bionote,Inc.	RG19-12	92.9	97.1	98.0	100.0	Pv-pLDH	HRP2	NA
BIONOTE MALARIA P.f.& Pan Ag Rapid Test Kit	Bionote,Inc.	RG19-08	93.9	88.6	99.0	100.0	pan-pLDH	HRP2	NA
BioTracer™ Malaria Pf/PAN Rapid Card	Bio Focus Co., Ltd.	17012	77.0	77.1	94.0	100.0	pan-pLDH	HRP2	NA
CareStart™ Malaria/Pregnancy Combo (pLDH/HRP2/HCG)	Access Bio, Inc.	G0221	83.8	94.3	100.0	97.1	HCG	pan-pLDH	HRP2
CareStart™ Malaria HRP2/pLDH (Pf/PAN) COMBO[j]	Access Bio, Inc.	G0131	90.0	94.3	100.0	100.0	pan-pLDH	HRP2	NA
CareStart™ Malaria HRP2/pLDH (Pf/Pv) COMBO[j]	Access Bio, Inc.	G0161	90.8	94.1	100.0	100.0	Pv-pLDH	HRP2	NA
CareStart™ Malaria HRP2/pLDH (Pf/VOM) COMBO[j]	Access Bio, Inc.	G0171	89.8	91.2	100.0	100.0	Pvom-pLDH	HRP2	NA
CareStart™ Malaria pLDH 3 Line Test	Access Bio, Inc.	G0121	88.9	91.4	100.0	100.0	pan-pLDH	Pf-pLDH	NA
CareStart™ Malaria Screen	Access Bio, Inc.	G0231	86.9	88.6	100.0	100.0	pan-pLDH	HRP2/Pf-pLDH	NA
Clearview® Malaria Combo[j]	Vision Biotech (Pty) Ltd	VB11	82.8	5.7	100.0	91.4	HRP2	pan-aldolase	NA

Lot testing programme of mRDTs

- An important component of product testing is the WHO-FIND lot testing programme, which screens approximately 83% lots on the market. Through this system several product defects have been identified and information shared with WHO/PQ team, supporting investigations which led to 'delisting' of some prequalified products.

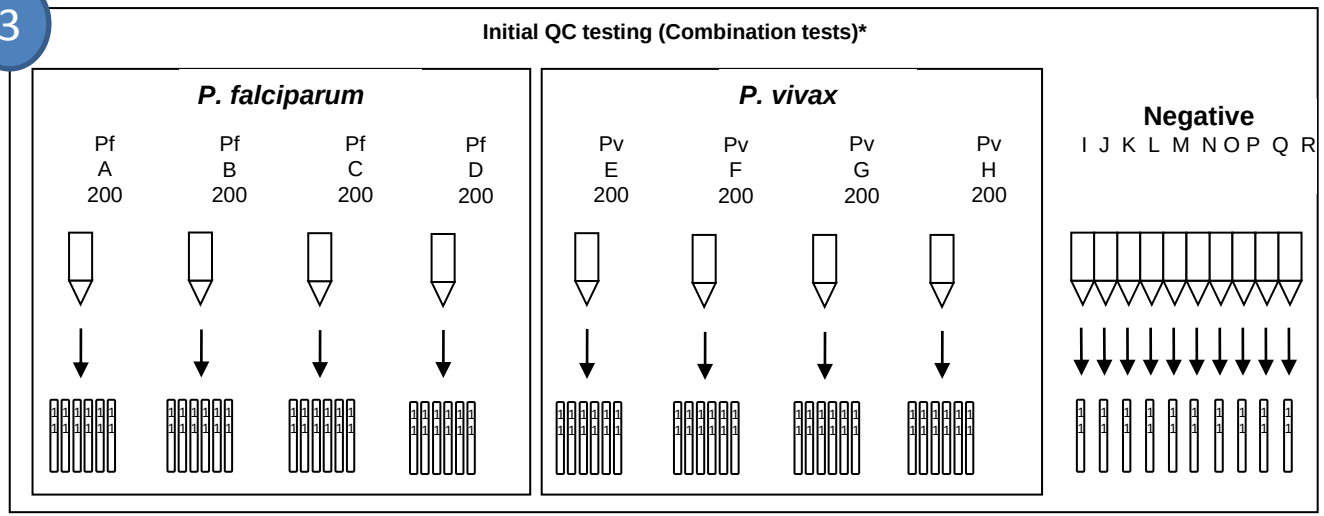


1 **Lot testing request form sent to LT coordinator**

2 **Shipment of RDTs**

Initial Testing

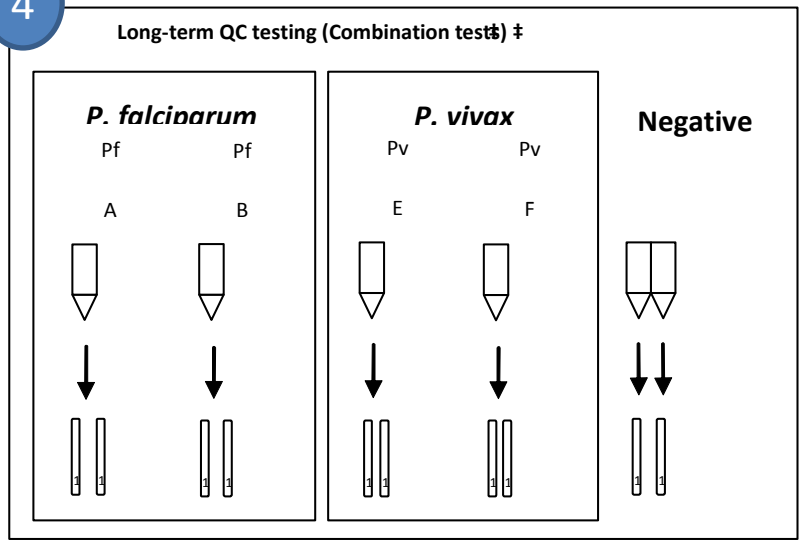
3



*** Initial QC testing :** Use 48 RDTs, and use QC samples from 4 different Pf cases (A, B, C, D) , 4 different Pv cases (E, F, G, H) and 10 different malaria parasite negative cases (I-R).

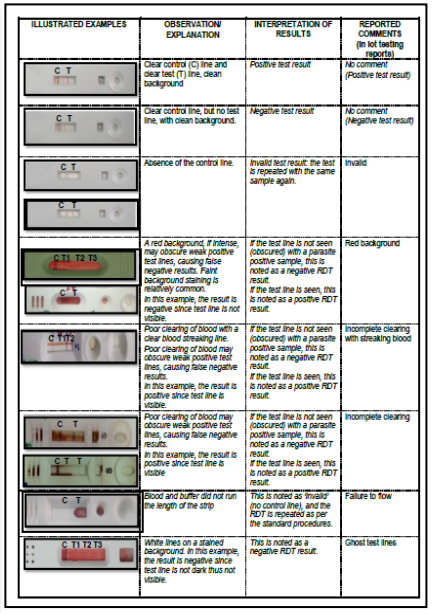
Long term testing (37°C): 6 months prior to expiry

4



‡ Long term QC testing : Use only 8 RDTs, and use QC samples from 2 different Pf cases (A, B), 2 different Pv cases (E, F) and 2 malaria parasite negative cases (I,J) used in the initial QC testing (if possible).

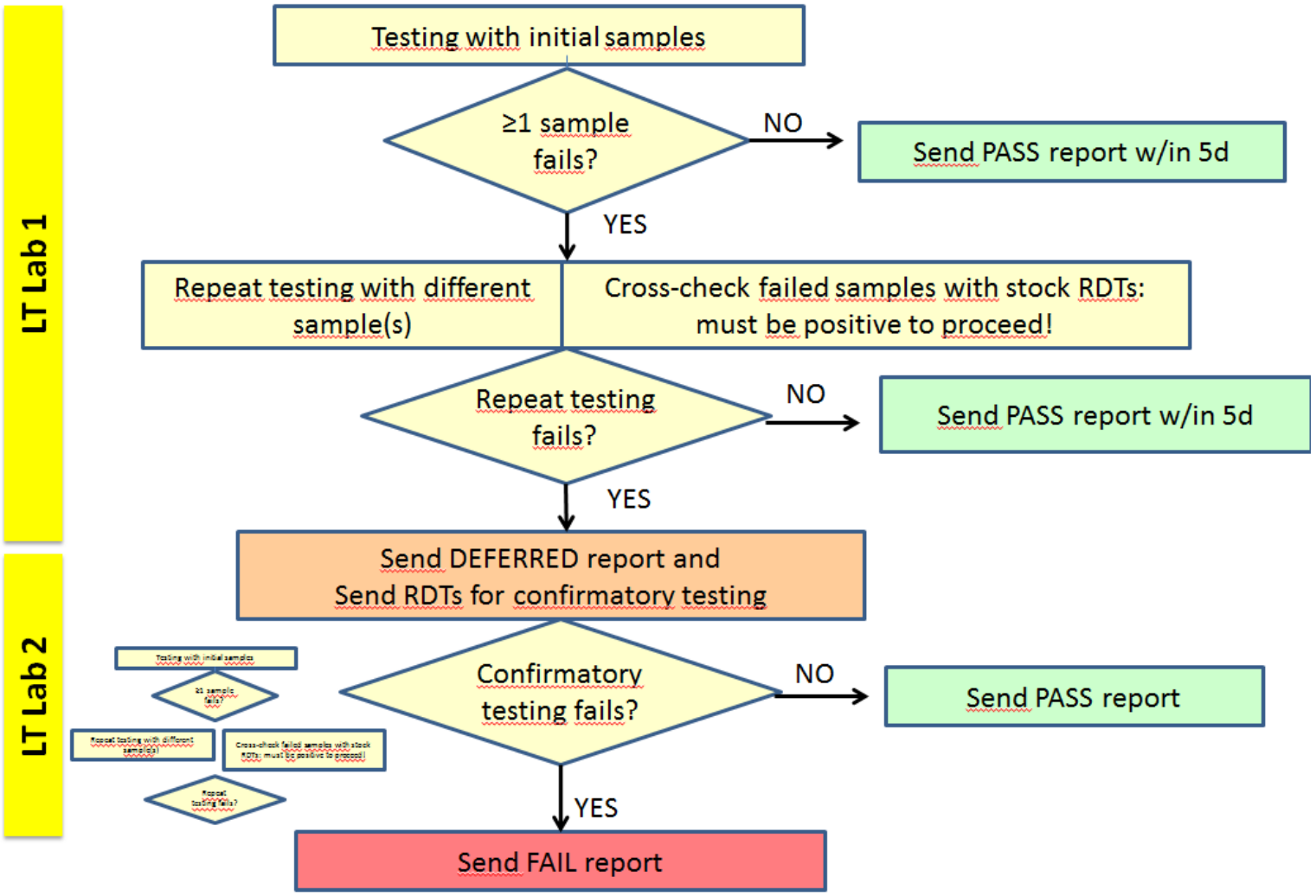
Observations



ILLUSTRATED EXAMPLES	OBSERVATION/ EXPLANATION	INTERPRETATION OF RESULTS	REPORTED COMMENTS (in lot testing report(s))
C T	Clear control (C) line and clear test (T) line, clean background	*Positive test result*	*No comment (Positive test result)*
C T	Clear control line, but no test line, with clean background.	*Negative test result*	*No comment (Negative test result)*
C T	Absence of the control line.	*Invalid test result: the test is repeated with the same sample again.*	Invalid
C T1 T2 T3	*A red background, if intense, may obscure weak positive test lines, causing false negative results. Faint background staining is relatively common.* In this example, the result is negative since test line is not visible.	*If the test line is not seen (obscured) with a parasite positive sample, this is noted as a negative RDT result.* *If the test line is seen, this is noted as a positive RDT result.*	Red background
C T1 T2	*Poor clearing of blood with a clear blood streaking line.* *Poor clearing of blood may obscure weak positive test lines, causing false negative results.* In this example, the result is positive since test line is visible.	*If the test line is not seen (obscured) with a parasite positive sample, this is noted as a negative RDT result.* *If the test line is seen, this is noted as a positive RDT result.*	Incomplete clearing with streaking blood
C T	*Poor clearing of blood may obscure weak positive test lines, causing false negative results.* In this example, the result is positive since test line is visible	*If the test line is not seen (obscured) with a parasite positive sample, this is noted as a negative RDT result.* *If the test line is seen, this is noted as a positive RDT result.*	Incomplete clearing
C T	*Blood and buffer did not run the length of the strip*	*This is noted as 'invalid' (no control line), and the RDT is repeated as per the standard procedures.*	Failure to flow
C T1 T2 T3	*White lines on a stained background. In this example, the result is negative since test line is not dark thus not visible.*	*This is noted as a negative RDT result.*	Ghost test lines

5 **Reporting**

Validation procedure for lot testing



Results summary (2007- 2015 (June)

Year	N° new Products	N° new Manu-facturers	N° RDT lots tested	N° Long Term Testing Carried out	N° Initial Failures**	N° Long term Failures**
2007	8	7	59	23	1	1
2008	6	4	139	181	3	1
2009	2	-	243	741	-	2
2010	7	3	236	702		
2011	4	2	365	405		**9**
2012	4	-	567	241	4	
2013	6	1	1083	359	-	
2014	2	1	927	528	-	-
Jan- End of June 2015	4	2	476	660	2	-
Total	**43**	**20**	**4095**	**3840**	**12**	**19**

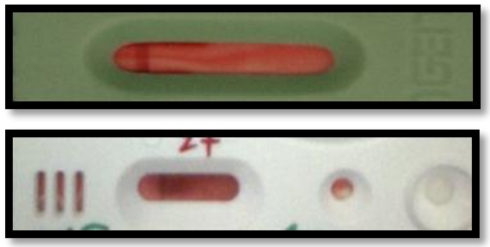
Failures on Pan or Pv test lines against low density *P. vivax* samples

- ** *Long term failures noted the year when an RDT lot was received (routine testing only)*

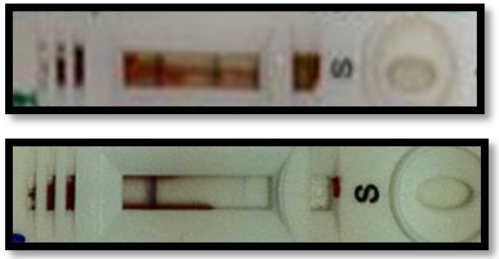
Source: WHO, FIND

RDT anomalies in production lots

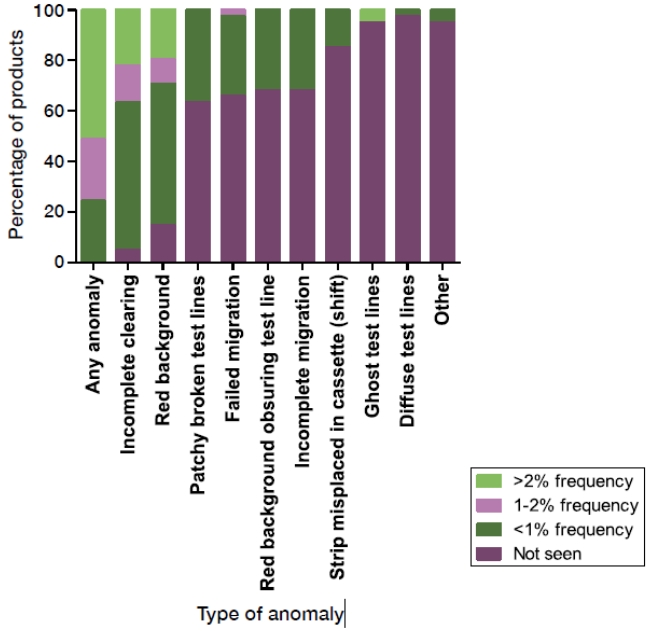
Red background



Incomplete clearing/streaking



Failure to flow



Faint lines

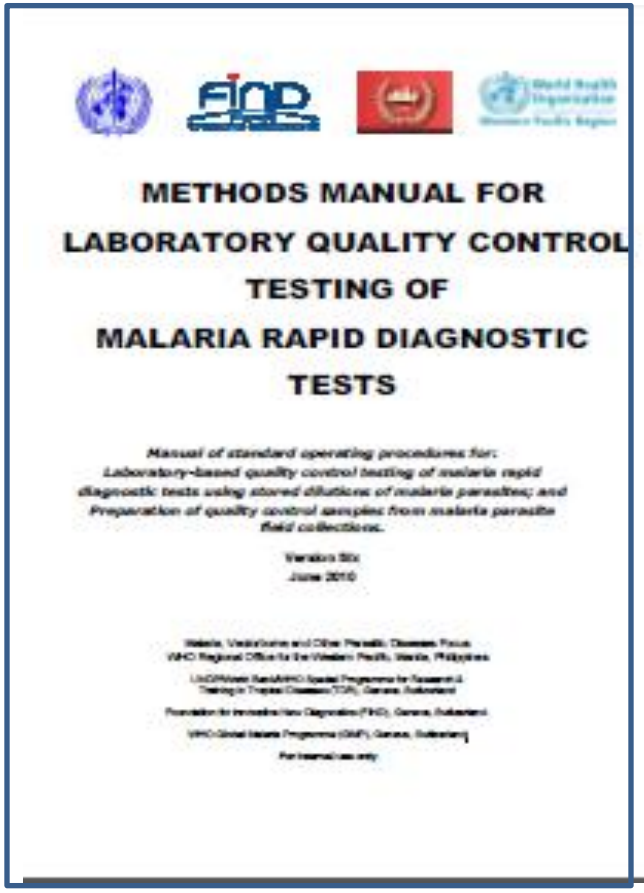
Patchy broken lines

Ghost lines

Diffuse lines

Lot test documents (excerpt)

Lot-testing MM



METHODS MANUAL FOR

LABORATORY QUALITY CONTROL

TESTING OF

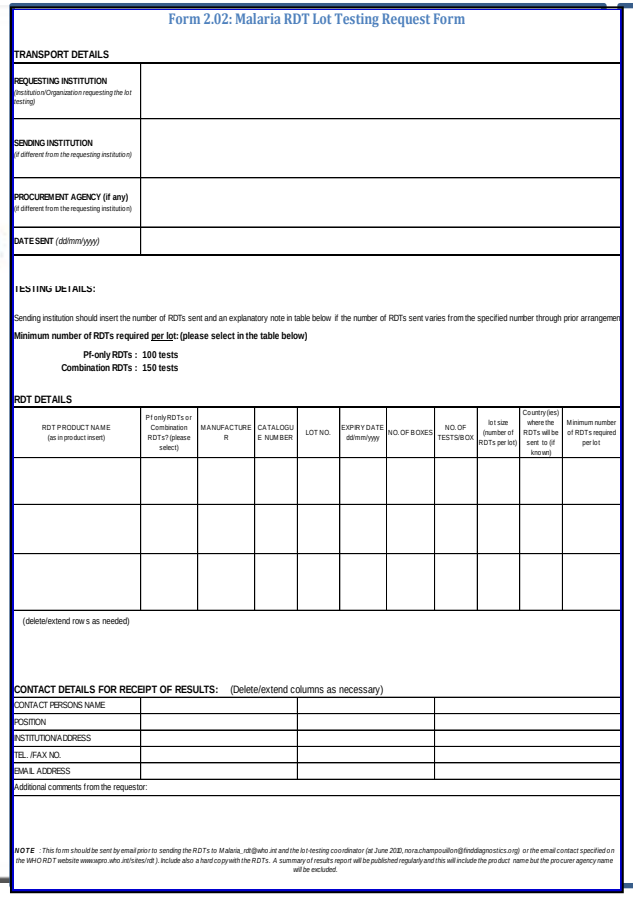
MALARIA RAPID DIAGNOSTIC

TESTS

Manual of standard operating procedures for:
Laboratory-based quality control testing of malaria rapid diagnostic tests using stored dilutions of malaria parasites; and
Preparation of quality control samples from malaria parasite field collections.

Version Six
June 2010

Lot-test Request Form



Form 2.02: Malaria RDT Lot Testing Request Form

TRANSPORT DETAILS

REQUESTING INSTITUTION *(Institution/Organization requesting the lot testing)*	
SENDING INSTITUTION *(if different from the requesting institution)*	
PROCUREMENT AGENCY (if any) *(if different from the requesting institution)*	
DATE SENT *(dd/mm/yyyy)*	

TESTING DETAILS:

Sending institution should insert the number of RDTs sent and an explanatory note in table below if the number of RDTs sent varies from the specified number through prior arrangement

Minimum number of RDTs required per lot: (please select in the table below)

Pf-only RDTs : 100 tests
Combination RDTs : 150 tests

RDT DETAILS

RDT PRODUCT NAME (as in product insert)	Pf only/RDTs or Combination RDTs? (please select)	MANUFACTURER	CATALOGUE NUMBER	LOT NO.	EXPIRY DATE dd/mm/yyy	NO. OF BOXES	NO. OF TESTS/BOX	lot size (number of RDTs per lot)	Country(ies) where the RDTs will be sent to (if known)	Minimum number of RDTs required per lot

(delete/extend row s as needed)

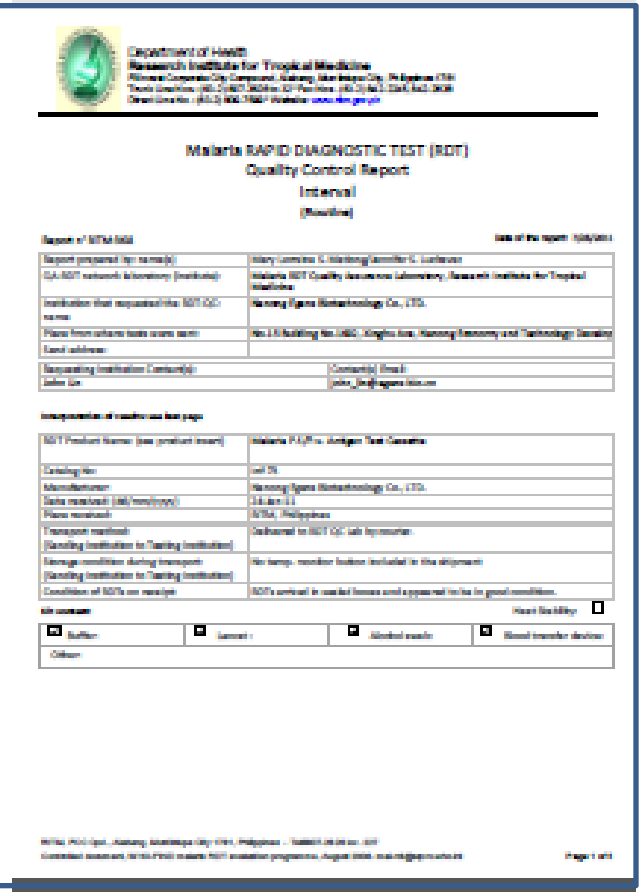
CONTACT DETAILS FOR RECEIPT OF RESULTS: (Delete/extend columns as necessary)

CONTACT PERSONS NAME			
POSITION			
INSTITUTION/ADDRESS			
TEL. /FAX NO.			
EMAIL ADDRESS			

Additional comments from the requestor:

NOTE : This form should be sent by email prior to sending the RDTs to Malaria_rdt@who.int and the lot-testing coordinator (at June 2010, nora.champouillon@finddiagnostics.org) or the email contact specified on the WHO RDT website www.wpro.who.int/sites/rdt/). Include also a hard copy with the RDTs. A summary of results report will be published regularly and this will include the product name but the procurer agency name will be excluded.

Lot-test Report



Malaria RAPID DIAGNOSTIC TEST (RDT)
Quality Control Report
Interval
[Baseline]

WHO Product Testing and PQP of mRDTs

WHO Product Testing of malaria RDTs

IVDs PREQUALIFICATION PROCESS

Overview of prequalification of in vitro diagnostics * pdf, 1.02Mb

Pre-submission Form
The pre-submission form is submitted by the manufacturer to apply for prequalification.

Dossier review
The product dossier is reviewed with the purpose of gaining an understanding of the product, its safety and performance, design and manufacture; and determining if the manufacturer's QMS is of an adequate standard to warrant an inspection.

Site inspection
The manufacturing site inspection is carried out to assess compliance with the quality management standard ISO 13485:2003, with focus on the suitability of the implemented processes and procedures for the reliable supply of products.

Lab evaluation
Laboratory evaluation of the product occurs following a successful review of the product dossier. The laboratory evaluation to assess the operational and performance characteristics of the product is carried out by an evaluation site.

PQ
If a product meets the prequalification requirements then it can become eligible for inclusion in UN procurement tenders.

Prequalification process of in-vitro diagnostic Tests (IVDs)

* http://www.who.int/diagnostics_laboratory/evaluations/140530_pqdx_overview_doc_007.pdf?ua=1

WHO Product Testing and PQP of mRDTs

- The Product Testing programme is the independent performance evaluation component of WHO prequalification of malaria RDTs
- WHO prequalification, in addition to Product Testing, requires a review of a product dossier and inspection of manufacturing site(s).
- WHO is now considering a shift from product testing to prequalification as a requirement for procurement.
- The goal of universal access to diagnosis requires quality-assured products as well as a healthy market and to this end, before adopting new criteria for procurement based on WHO prequalification, WHO/GMP commissioned an independent assessment of the potential impact of this change on RDT quality, supply security and affordability.
- The great majority of public sector procurement is prequalified products, and this is the result of: 1) GMP procurement guidance, based on results of the product testing programme; 2) country preference to purchase the 'best performing' products and 3) the leading companies' capacity to compete and provide low prices.

Prequalified RDTs as of February 2016

Test name	Manfacturer	2014 MS (w/in category)	2014 MS (overall)	Prequalified date
Pf Only				
1 CareStart™ Malaria HRP2 (Pf)	Access Bio	34%	21%	28-May-15
2 First Response® Malaria Ag P.f falciparum (HRP2) Card Test	PMC	15%	9%	25-Feb-15
3 ParaHIT f Ver. 1.0 Rapid Test for P.falciparum Malaria Dipstick	Span/Arkray	0%		7-Oct-14
4 ParaHIT f Ver. 1.0 Rapid Test for P.falciparum Malaria Device	Span/Arkray	3%	2%	7-Oct-14
5 SD BIOLINE Malaria Ag P.f	Alere/SD	41%	26%	6-Dec-10
		93%	58%	
Pf/pan				
1 Carestart pf/pan Combo	Access Bio	12%	4%	28-May-15
2 SD BIOLINE Malaria Ag P.f/Pan	Alere/SD	72%	21%	8-Jul-13
		84%	24%	
Pf/pv				
1 CareStart™ Malaria HRP2/pLDH (Pf/Pv) COMBO	Access Bio	6%	0%	28-May-15
2 SD BIOLINE Malaria Ag P.f/P.v	Alere/SD	94%	5%	16-Oct-15
		100%	6%	
Other				
1 CareStart™ Malaria HRP2/pLDH (Pf)	Access Bio		2%	28-May-15
2 CareStart™ Malaria pLDH (PAN)	Access Bio		0%	28-May-15
3 SD BIOLINE Malaria Ag P.f (HRP2/pLDH)	Alere/SD		1%	16-Oct-15
12			3%	

- The WHO prequalification of *in vitro* diagnostics programme has prequalified eight products in 2015, out of total twelve malaria RDTs prequalified across four main test type categories

Phased transition to WHO PQ

- Results of analyses of the market and the WHO prequalification pipeline suggest that a phased transition to WHO prequalification for malaria RDTs by end 2017 will be beneficial, as it provides an incentive for manufacturers to invest in quality and allows consumers to distinguish between products produced by manufacturers that have invested in strong QMS. To mitigate some of the risks identified, the transition to WHO PQ as procurement requirement for malaria RDTs should be phased in as follows:
  - For *P. falciparum*-only (HRP2-detecting) RDTs where there are already five prequalified products (including 1 dipstick) from four manufacturers and high likelihood of additional RDTs becoming prequalified in the next two years, the shift to WHO prequalification as a prerequisite for WHO procurement new policy could be implemented as per the proposed timeline.

Phased transition to WHO PQ (cont'd)

- For the both the Pf-pan or Pf/pv combination RDTs, where today there are only two prequalified products per test type, and slightly fewer tests are likely to become prequalified, an extended timeline and/or additional incentives should be considered. Extending the timeline until 4-6 products (from different manufacturers) per test type are prequalified would mitigate the risks associated with reliance on a limited number of suppliers.

- For pan-only RDTs, where there is a small but potentially growing need/market, but only one prequalified product and only one other evaluated in Product Testing, that meets the current procurement criteria, an extended timeline is also required.

PQ pipeline for HIV and malaria RDTs

HIV Rapid Tests: progress of the active applications in the prequalification of IVDs assessment pipeline

Product name	Product code(s)	Manufacturer name	Dossier review	On-site inspection	Laboratory evaluation
Anti-human immunodeficiency virus (HIV) antibody diagnostic kit (colloidal gold)	WJ-1810, WJ-1850	Beijing Wantai Biological Pharmacy Enterprise Co., Ltd	F	◆	◆
Aware™ HIV-1/2 OMT	REF-98164, REF-98166 and REF-98169	Calypte Biomedical Corporation	F	◆	🗁
First Response® HIV 1-2-0 Card test	I05FRC30, I05FRC60, I05FRC05, I05FRC01	Premier Medical Corporation Ltd	F	◆	◆
BioTracer™ HIV 1/2 Rapid Card	11112	Bio Focus Co., Ltd.	R		◆
Genie™ Fast HIV 1/2	72330, 72327	Bio-Rad	R	◆	◆
OraQuick HIV 1/2 Rapid Antibody Test	5x4-0010, 5x4-0012	OraSure Technologies, Inc.	◆	◆	◆ 🗁
Coretests® One Step HIV1+2 Test Device	C1021	Core Technology Co.Ltd.	F		◆
DPP® HIV 1/2 Assay	65-9500-1	Chembio Diagnostic Systems, Inc.	F	◆	◆ 🗁
RightSign HIV 1.2.O rapid test cassette (Whole blood/Serum/Plasma)	IHIV-C42W	Hangzhou Biotest Biotech Co,Ltd	abbreviated assessment	F	🗁
Alere HIV Combo	7D2842, 7D2843 and 7D2343SET	Alere Medical Co. Ltd.	F	◆	◆
MP Diagnostics MULTISURE HIV Rapid Test	43031-020	MP Biomedicals Asia Pacific Pte. Ltd.	abbreviated assessment		

R	🗁	◆	F	S
information requested from	in process	stage complete	follow-up amendments	scheduled;

Please note: these tables are updated regularly; while every attempt is made to provide current data, the most recent information might not be reflected. This table is intended only as an update on progress and does not reflect a final decision on prequalification. This table should not be used to inform procurement.mation may not yet be reflected here.
Last update: 11 January 2016
http://www.who.int/diagnostics_laboratory/pq_status/en/index.html

Accessed on 15 March 2016

Malaria: progress of the active applications in the prequalification of IVDs assessment pipeline

Product name	Product code(s)	Manufacturer name	Dossier review	On-site inspection	Laboratory evaluation
N/A					

R	🗁	◆	F	S
information	in process	stage complete	follow-up	scheduled;

Please note: these tables are updated regularly; while every attempt is made to provide current data, the most recent information might not be reflected. This table is intended only as an update on progress and does not reflect a final decision on prequalification. This table should not be used to inform procurement.mation may not yet be reflected here.
Last update: 21 December 2015
http://www.who.int/diagnostics_laboratory/pq_status/en/index.html

Additional risk mitigating strategies

- First, because the buy-side of the malaria RDT market is highly concentrated, it is possible for WHO and major procurers to discuss how current procurement practices contribute to market concentration and what measures could be taken to reduce the risk of supply disruption and ensure competition.
- Secondly, there are several areas of work, led by WHO, that could contribute to a larger number of prequalified malaria RDTs in 2017, for example: i) requiring that products submitted to Product Testing also apply to WHO prequalification; ii) ensuring that malaria RDT manufacturers are knowledgeable about the WHO prequalification process and expectations; and iii) closely monitoring the progress of malaria RDTs through the WHO prequalification process, and responding to major delays if warranted.
- Lastly, clear communications are needed in order to inform both the buy-side and supply-side of the changes, especially because a phased implementation introduces an element of complexity.

Malaria Policy Advisory Committee Meeting

16–17 March 2016, Geneva, Switzerland
Background document for Session 6

Proposal for an Evidence Review Group on field-based quality control of malaria RDT and suspected product failure investigations

March 2016, Geneva, Switzerland

Background

WHO has recommended parasitological confirmation of malaria for all suspects prior to initiating anti-malarial treatment in all transmission settings. Over the past several years, implementation of this recommendation has been accelerated due to the availability of affordable, accurate and user-friendly rapid diagnostic tests (RDTs). Furthermore, an international quality control scheme comprised of independent pre- and post-purchase RDT performance assessments (product testing and lot testing, respectively) has been operational since 2008. WHO has provided guidance on procurement, transport and storage, operational manuals, and multiple training resources to support large-scale implementation. Nevertheless, tools and guidance for RDT quality control (QC) at the point of care and at field level have generally been either lacking or not broadly implemented. As a result, programmes and research institutions have adopted multiple approaches, including the use of RDT cross-checking with microscopy or PCR, dry blood spots, dried tube specimens methods and, in some cases, retrieval and repeat RDT assessment through the lot testing programme, with variable results. In addition, some manufacturers have already commercialized product-specific positive controls, and FIND and their commercial partner, MicroCoat Biotechnologie GmbH, are in the process of developing generic positive control wells (PCWs).

Rationale

Given the significant risk of RDT exposure to high temperatures during transport and storage, which can compromise performance, and factors such as the emergence of *pfhrp2*/*pfhrp3* deletions in Africa, QC options that are currently available and those in the development pipeline need to be carefully considered and, in turn, used to inform WHO guidance for endemic countries. In addition, QC tools and approaches need to be complemented by protocols for reporting and investigating failing RDTs. Countries should have a complaint-reporting mechanism and the basic capacity to efficiently start investigations into the root cause of suspected RDT failure, for example, operator error, suboptimal microscopy, product deterioration due to physical damage and/or exposure to excessive heat, or parasite factors causing detection failures such as *pfhrp2*/*pfhrp3* deletions. Discussions should build on other WHO guidance documents including *Universal access to malaria diagnostic testing*[1] and *Post market surveillance of in vitro diagnostics*.[2]

WHO/HTM/GMP/MPAC/2016.4

Objectives of the Evidence Review Group

1. Review various options for the point-of-care and field-based quality control of malaria RDTs, including cross-checking with microscopy and/or PCR, dried blood spots, dried tube specimens, commercialized controls, and validated positive control wells that have been recently developed.
2. Discuss the human and material resources required for QC implementation, as well as the advantages, disadvantages, and overall appropriateness of different options for point-of-care and/or field-based quality control of malaria RDTs in the various health services delivery settings (community → health facility → referral hospital).
3. Review and revise the proposed 'preferred product characteristics' for a point-of-care RDT QC tool, and assess alignment with the specifications of currently available methods, commercial controls and controls in development.
4. Review the data supporting commercial control tool specifications/claims.
5. Currently, commercial controls are primarily sold separately from the RDT kit; however, in the future they may also be sold with the kit. The group will consider the stringent regulatory authority and WHO PQ requirements for controls sold separately or included in the kit.
6. Review and finalize draft generic protocols for reporting and investigating suspected false positive or false negative malaria RDT results, including suspected *pfhrp2*/*pfhrp3* gene deletions or variants.
7. Discuss and finalize draft generic protocols for the surveillance of suspected *pfhrp2*/*pfhrp3* gene deletions or variants.
8. Discuss the components and feasibility of an external quality assessment scheme for malaria RDTs.

Suggested timetable

Activity	**Timeline**
Preparation of background documents on point-of-care/field-based RDT QC options	April- May 2016
Develop generic protocols for investigating suspected false positive or false negative malaria RDT results, including suspected pfhrp2/pfhrp3 gene deletions or variants	June 2016
Pre-meeting consultation with WHO prequalification +/ – stringent regulatory authority representatives to discuss regulatory requirements for commercial controls	June 2016
Develop draft preferred product characteristics and compile specifications of commercialized controls and products in development	July 2016
Develop draft generic protocols for surveillance of suspected *pfhrp2/pfhrp3* gene deletions or variants	August 2016
Evidence Review Group	September 2016

Notes

1. http://www.who.int/malaria/publications/atoz/9789241502092/en/
2. http://www.who.int/diagnostics_laboratory/postmarket/150819_pms_guidance_final_version.pdf

Malaria Policy Advisory Committee Meeting
16–17 March 2016, Geneva, Switzerland
Background document for Session 7

Ivermectin for malaria transmission control

March 2016, Geneva, Switzerland

Justification

Ivermectin is a broad-spectrum antiparasitic drug that has been used extensively for the control/elimination of onchocerciasis, or in combination with albendazole for the elimination of lymphatic filariasis (LF). It is a core component used in mass drug administration (MDA) in the current efforts to eliminate and stop the transmission of LF and onchocerciasis around the world.

In recent years, modelling, clinical and laboratory studies have indicated that ivermectin has the potential to reduce malaria transmission by killing mosquitoes, thereby reducing their vectorial capacity. These preliminary conclusions have been drawn from studies that either administered ivermectin in combination with artemether plus lumefantrine or albendazole, or assessed single-dose ivermectin in MDA projects. Despite ivermectin's entomological impact, well-designed observational studies and randomized clinical trials are still needed in order to produce detailed evidence on malaria transmission.

Nevertheless, the growing body of work supporting the potential application of ivermectin for malaria has generated increased interest among researchers and other malaria stakeholders, including funding organizations. If an effect on malaria transmission were to be established, ivermectin could indeed play an important role in integrated control measures to target malaria and neglected tropical diseases, particularly in areas where malaria endemicity overlaps with the distribution of onchocerciasis, LF and/or soil-transmitted helminth infections.

In light of ivermectin's potential as a malaria control tool, the WHO Global Malaria Programme (GMP) and the Department for Control of Neglected Tropical Diseases are working to coordinate the efforts of multiple research initiatives with the hope of developing the evidence base needed to evaluate the potential impact of this intervention and to establish a target product profile that would meet the public health needs defined by WHO. Such efforts will also drive research and product development toward stringent regulatory approval and, ultimately, a WHO policy position on the role of ivermectin in malaria control and elimination.

As a first step, in 2015, GMP commissioned a review of the current landscape of available data on the mosquito killing effect of ivermectin. A technical consultation discussing the output of the review and the future of ivermectin as a tool for malaria control is being organized for 30 March – 1 April 2016. The objectives and expected outcomes of the consultation are as follows:

General objective: To define a target product profile (TPP) for ivermectin as a tool for reducing or blocking malaria transmission

Specific objectives:

1. To determine and define the expected levels of ivermectin's efficacy in reducing malaria transmission in order to guide its potential deployment as a public health tool for malaria control and elimination.

WHO/HTM/GMP/MPAC/2016.2

2. To define a target product profile (TPP) for ivermectin as a tool for reducing or blocking malaria transmission.
3. To identify any gaps in the knowledge and evidence needed for policy formulation.
4. To define a clinical and regulatory pathway for ivermectin as a tool for blocking malaria transmission.

Meeting participants: There will be 38–40 participants in the consultation, broken down as follows:

- 14 technical experts
- 11 stakeholders partners/observers
- 13 WHO Secretariat staff from
    - Global Malaria Programme
    - Neglected Tropical Diseases
    - TDR
    - Pre-qualification
    - PAHO

Focal point person: Peter Olumese (WHO/GMP)

Ivermectin for malaria transmission control

Malaria Policy Advisory Committee, Geneva, Switzerland, 16 March 2016

Global **Malaria** Programme

World Health Organization

Presentation outline

- Background
- Justification for involvement of WHO/GMP
- GMP planned action
- Current status of activities

Background

- Ivermectin is a broad-spectrum antiparasitic drug currently used extensively for the
  - control/elimination of onchocerciasis,
  - in combination with albendazole for the elimination of lymphatic filariasis (LF).
- In recent years, modelling, clinical and laboratory studies have indicated that ivermectin has the potential to reduce malaria transmission by killing mosquitoes (reducing their vectorial capacity).
- Despite its entomological impact, well-designed observational studies and randomized clinical trials are needed in order to produce detailed evidence on malaria transmission

Justification

- Renewed interest, and support among researchers and other stakeholders (including funding bodies)
  - Non-coordinated research activities
    - Research questions and objectives
    - Multiplicities of end-points and evaluation criteria
  - Negative impact for policy formulation
    - Non-effective deployment in isolated pilots or projects (not in line with public health principles)
- If an effect on malaria transmission were to be established, ivermectin could play a role
  - in integrated control measures to target malaria and NTDs, particularly in areas where malaria endemicity overlaps with the distribution of onchocerciasis, LF and/or soil-transmitted helminth infections.
  - in tackling residual malaria transmission in the context of elimination

GMP planned action

- GMP in collaboration with the Department for Control of Neglected Tropical Diseases are working to coordinate the efforts of multiple research initiatives with the hope to
  - develop the evidence -base needed to evaluate the potential impact of this intervention and to establish a target product profile that would meet the public health needs defined by WHO.
  - also drive research and product development toward stringent regulatory approval and,
  - ultimately, a WHO policy position on the role of ivermectin in malaria control and elimination.

Current status of activities

- GMP commissioned a review of the present landscape of the mosquito killing / transmission blocking effect of ivermectin (2015).
- A technical consultation of experts and stakeholders is being organised for 30 March – 1 April 2016

Technical consultation on ivermectin for malaria control

- General objective
  - To define a target product profile (TPP) for ivermectin as a tool for reducing or blocking malaria transmission, which will guide a product and policy development pathway
- Specific objectives
  - To determine and define the expected levels of ivermectin's efficacy in reducing malaria transmission in order to guide its potential deployment as a public health tool for malaria control and elimination.
  - To define a TPP for ivermectin as a tool for reducing or blocking malaria transmission.
  - To identify any gaps in the knowledge and evidence needed for policy formulation.
  - To define a clinical and regulatory pathway for ivermectin as a tool for blocking malaria transmission.

Meeting logistics and next steps

- Meeting participants
  - 14 technical experts
  - 11 stakeholders partners/observers
  - 13 WHO Secretariat staff from
    - Global Malaria Programme
    - Neglected Tropical Diseases
    - TDR
    - Pre-qualification
- Expected outcome
  - TTP published
- Financial support
  - MMV
  - MESA

Progress of elimination efforts in the Greater Mekong Subregion

Malaria Policy Advisory Committee

Geneva, Switzerland

Dr EM Christophel/SEARO, Dr R Abeyasinghe/WPRO
Dr M Aregawi/ERAR, Dr W Kazadi

17 March 2016

EMERGENCY RESPONSE TO ARTEMISININ RESISTANCE IN THE GREATER MEKONG SUBREGION

World Health Organization

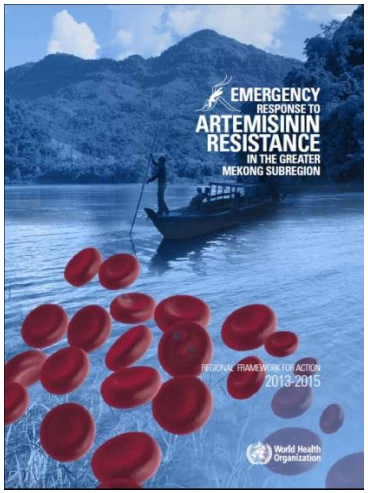
Outline

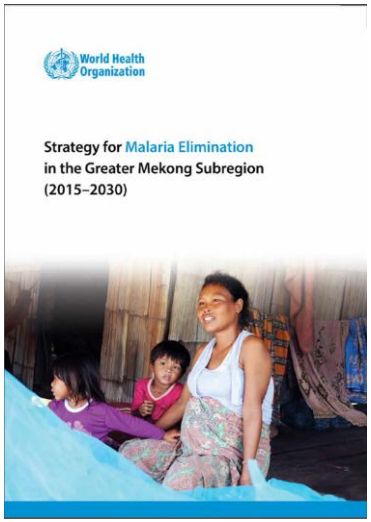
- Strategy
- Country Progress
- Regional Coordination
- Challenges
- Next steps

Mekong River, China/Myanmar border

World Health Organization

ERAR Framework transition to Elimination Strategy





- In April 2013, WHO launched the Emergency response to artemisinin resistance (ERAR) in the GMS;
- A regional hub was established in Phnom Penh, Cambodia, to support the coordination of activities relying on regional staff based in country offices;
- MPAC recommended in September 2014 the adoption of the goal of elimination of *P. falciparum* in the GMS by 2030;
- Subsequently, at the World Health Assembly in May 2015, WHO launched the Strategy for malaria elimination in the GMS (2015–2030), which was endorsed by all GMS countries;
- As a transitional year, in 2016 the ERAR hub will fulfil the objectives agreed in ERAR project and help the countries to update their national strategic plans with the the goal to accelerate towards elimination;
- ERAR hub will evolve into GMS Malaria Elimination hub in 2017 with less staff at the regional level but stronger country offices.

World Health Organization

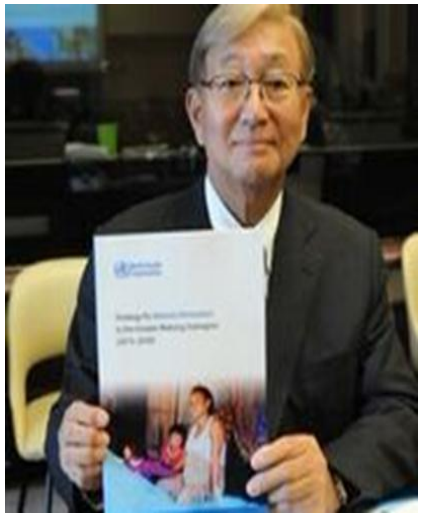
GMS Strategy overview

Goals

- To eliminate malaria by **2030 i**n all Greater Mekong Subregion countries and, considering the urgent action required against multidrug resistance in the GMS, to eliminate *Plasmodium falciparum* malaria by **2025.**
- In areas where malaria transmission has been interrupted, to maintain malaria-free status and prevent reintroduction.

Objectives

1. Interrupt transmission of *P. falciparum* in areas of multidrug resistance, including artemisinin-based combination therapy (ACT) resistance, by no later than **2020**, and in all areas of the GMS by **2025**.
2. Reduce malaria in all high-transmission areas to less than 1 case per 1000 population at risk and initiate elimination activities by **2020.**
3. Prevent the reintroduction of malaria in areas where it has been interrupted.



WHO Regional Directors SEARO and WPRO launch the Strategy, May 2015

World Health Organization

GMS Strategy overview - Prioritization

Regional level priorities

- Urgently and aggressively interrupt transmission in areas with multidrug resistance in the border areas between Cambodia and Thailand;
- Reduce transmission in the high transmission areas in Myanmar;
- Control malaria in areas of resurgence.

Country level priorities

- Eliminate malaria in areas of multidrug resistance;
- Flatten the epidemiological landscape by reducing transmission in areas of high transmission;
- Local analysis may identify additional priorities such as measures targeting certain mobile populations.

Prioritization does not mean that efforts to eliminate malaria in low transmission areas should be put on hold

World Health Organization

GMS Strategy overview - Milestones and targets

2015
- In all GMS countries: Malaria elimination policies/ NSPs updated

2016
- Malaria transmission interrupted in 60% of districts in Thailand

2017
- In all areas of low transmission: surveillance for elimination in place;
- systems strengthened for case & ento. surv. in high transmission areas
- Universal LLIN coverage in areas of malaria transmission

2020
- P.f. transmission interrupted in all areas of MDR
- P.f malaria eliminated in Cambodia;
- Malaria eliminated in Yunnan;
- All 1st level subnational areas in GMS in elimination mode

2025
- Elimination of P.f. malaria in all GMS countries;
- Malaria eliminated in Cambodia and Thailand

2030
- Malaria eliminated in all GMS

World Health Organization

GMS Strategy overview - Key interventions

Case detection and management

- Universal access to quality diagnostics and treatment in public, private sector and in the community
- Detection of asymptomatic carriers
- Treatment with ACTs, primaquine for both *P. falciparum* (single dose) and *P. vivax* (anti-relapse therapy)
- Management of severe cases and imported cases to prevent deaths

Disease prevention in transmission areas

- Vector control
- Drug based approaches

Malaria case and entomological surveillance

- Mandatory notification
- Case based malaria surveillance
- Case, foci investigation and response
- Entomological surveillance
- Outbreak detection and response
- Vigilance

Supporting elements

- Innovation and research
- Enabling environment, including multi sector engagement and governance

World Health Organization

National malaria elimination strategies development

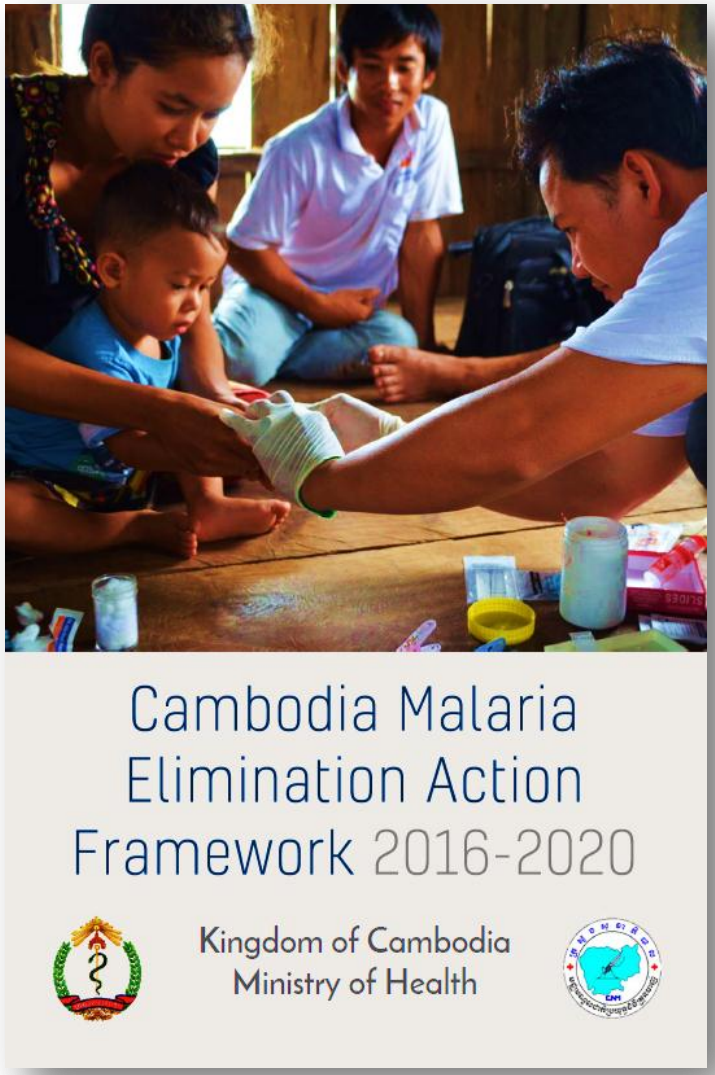
Consensus building during national consultation workshops, and inputs to NSPs & Action Plans

WHO Training on malaria elimination for GMS countries

Peer learning & experience sharing, horizontal technical assistance through WHO Collaborating Centers

World Health Organization

National malaria elimination strategies



Cambodia Malaria Elimination Action Framework 2016-2020

(MEAF)

World Health Organization

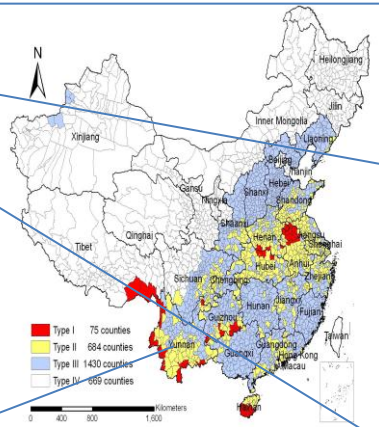
Status of national malaria elimination planning, 2/2016

Country	Status	Period	Cost (USD)	Gap (USD)	Comm.
Cambodia	Completed	2016-2020	**141 351 385**	**36 700 000**	Launched in 1/2016
Yunnan Province/ China	Completed	2015-2020	**7 936 507**	**0**	Yunnan plan only
Lao PDR	Completed	2016-2020	**97 591 611**	**62 814 002**	Submitted to MOH; Launch planned
Myanmar	Draft NSP available	2016-2020	**TBD**	**TBD**	To be finalized after MPR
Thailand	Completed	2017-2026	**97 030 000**	**61 270 000**	Endorsed by NSC
Viet Nam	Completed	2016-2020	**147 434 138**	**82 114 620**	2015-2017 approved by MOH

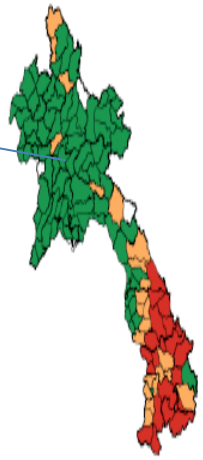
Source: GMS national malaria programs

Malaria risk mapping in the GMS, 2015

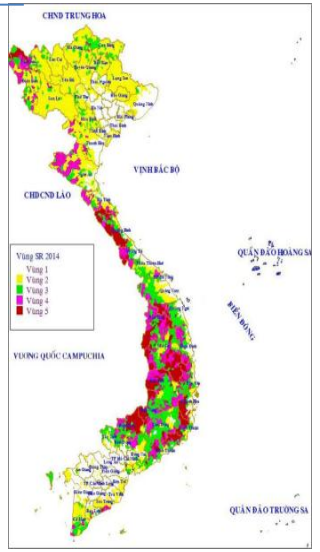
Yunnan Province/China



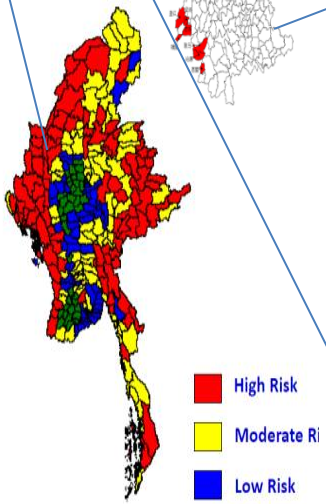
Lao PDR



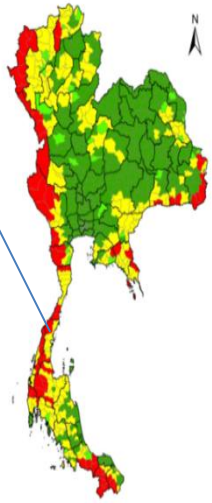
Viet Nam

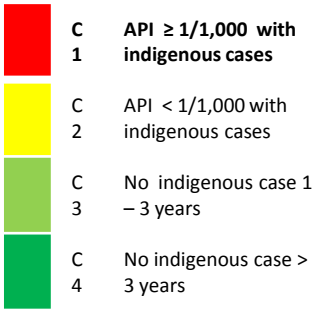


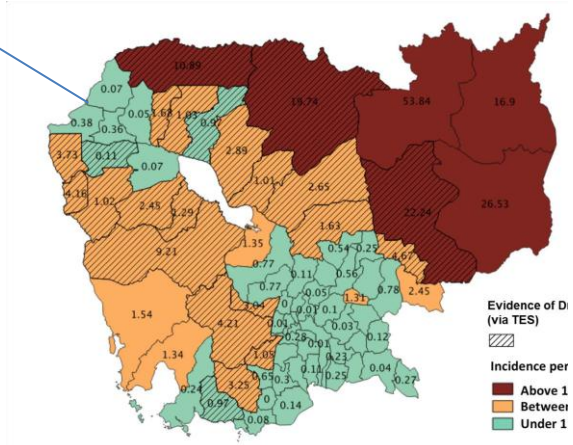
Myanmar



Thailand

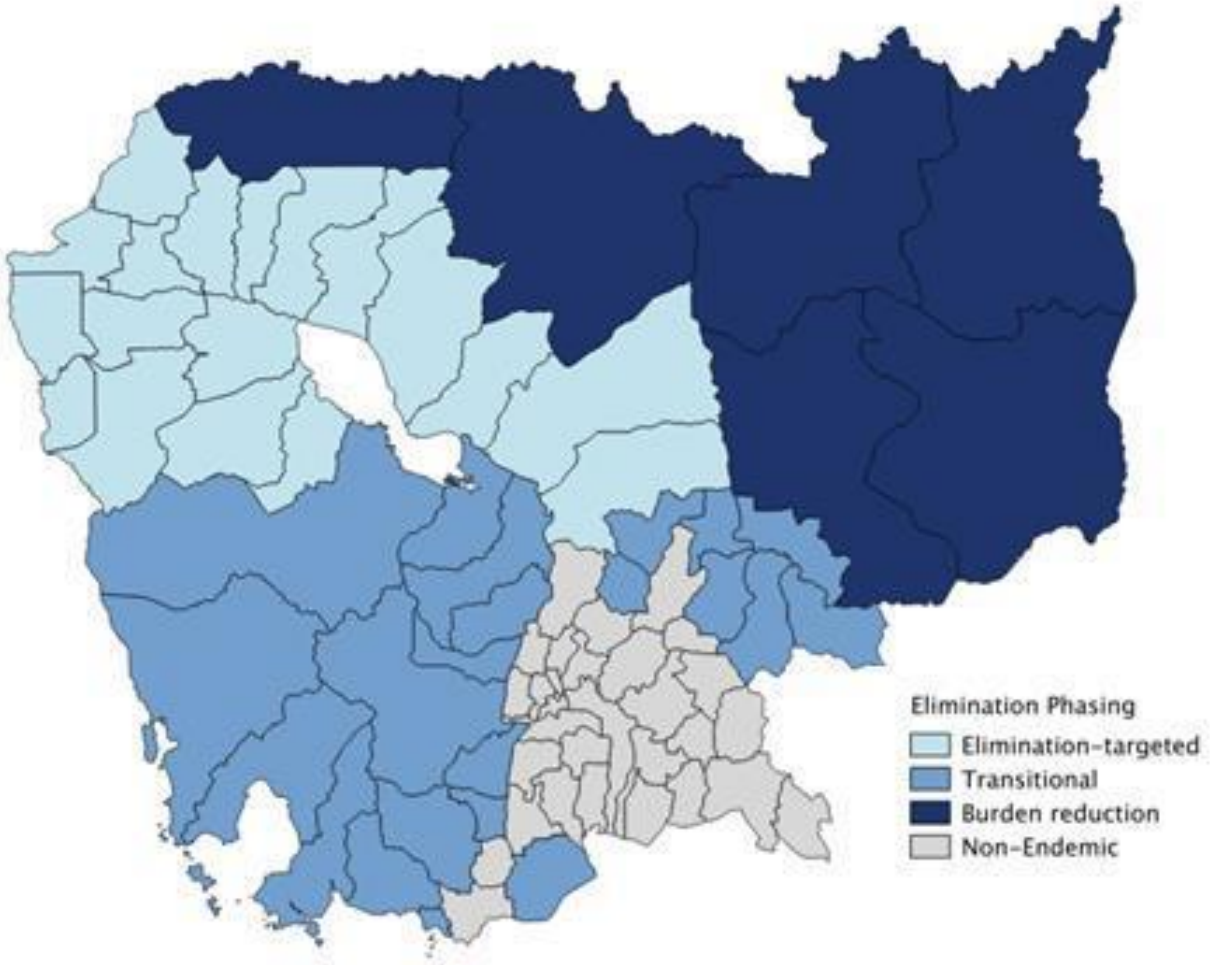






World Health Organization

Operational stratification, by OD, Cambodia, 2016



Source: MEAF 2016-2020

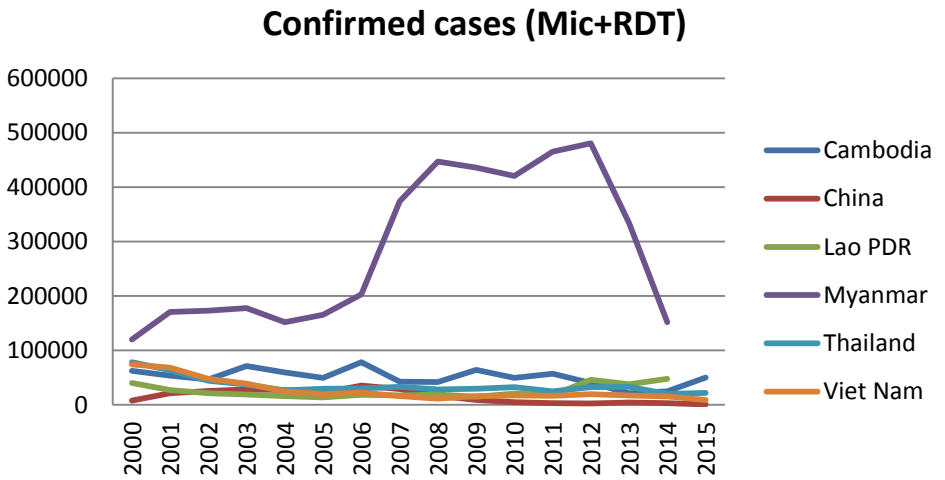
World Health Organization

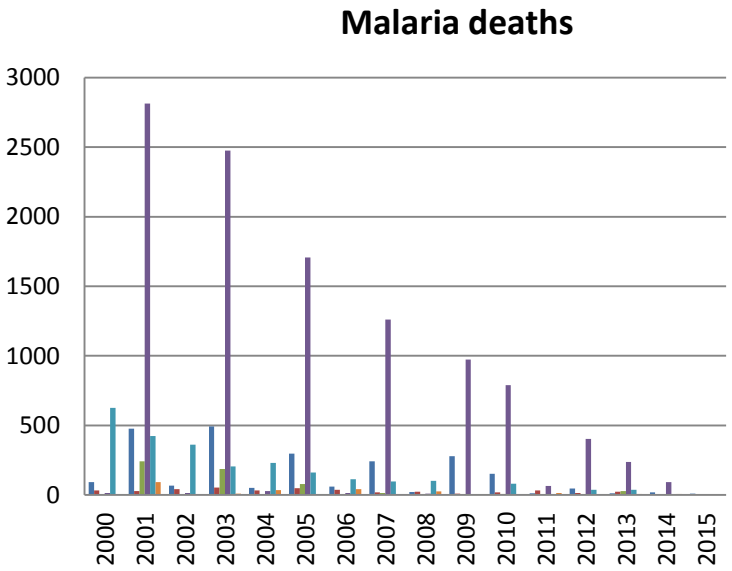
National level coordination & governance

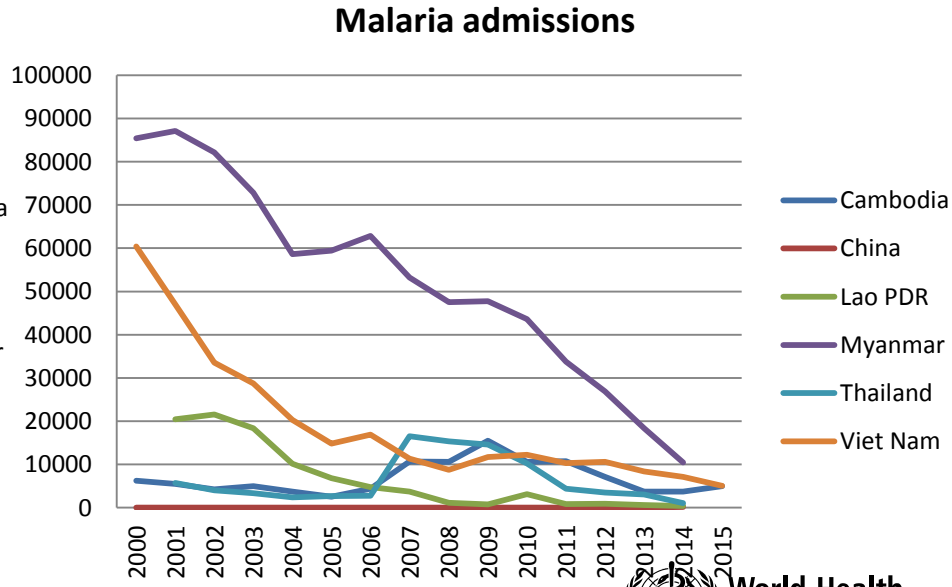
Country	Status
Cambodia	• National Malaria Elimination Task Force meets every 2 months; provincial committees for elimination exist
China	• Multi sectoral high level National Malaria Elimination Committee since 2010
Lao PDR	• Discussions ongoing through Dept. for Control of Com. Diseases (DCCD) to establish National Malaria Elimination Committee
Myanmar	• National Malaria Elimination Committee established but has not yet met
Thailand	• National Steering Committee (chaired by Deputy PM) set up in March 2015; met in Feb 2016 and endorsed NSP
Viet Nam	• National Artemisinin Resistance Containment committee in 2014, chaired by Deputy Minister for Health and convened by PM; expanded into National Steering Committee on Malaria Elimination

World Health Organization

Country updates: Malaria trends in the GMS, 2000-2015



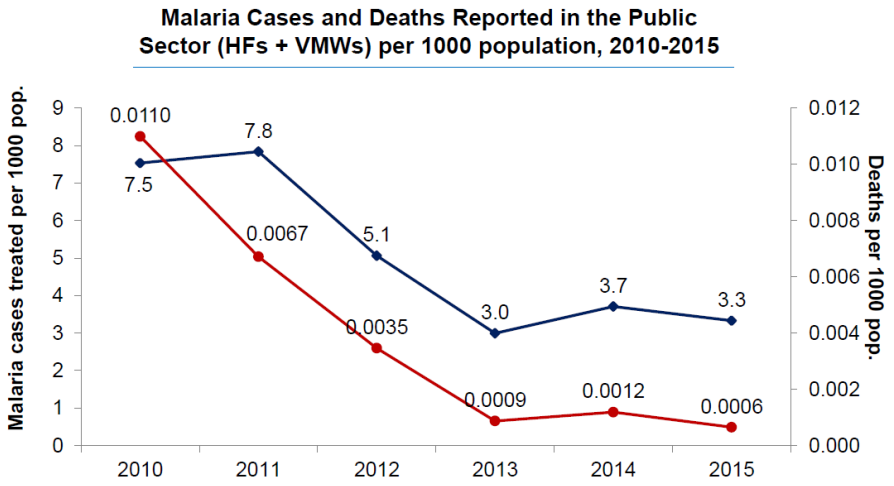




World Health Organization

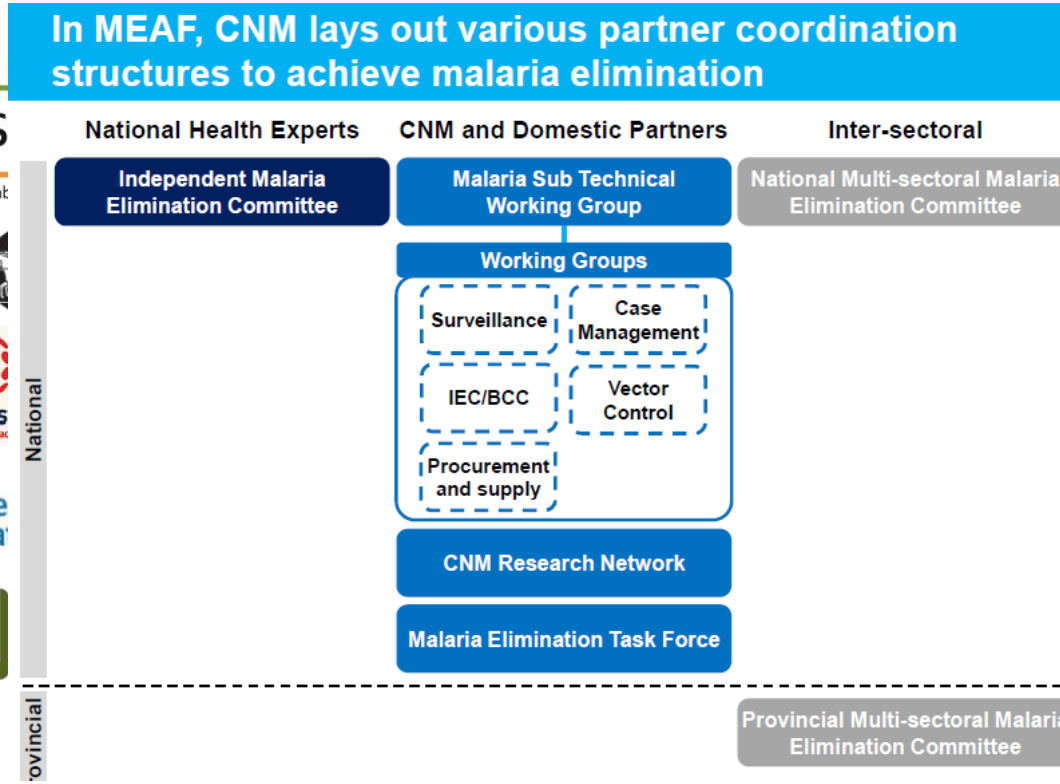
Country updates: **Cambodia**

- Malaria Elimination Action Framework 2016 – 2020 launched and Donor Consultation done.
- Total cost estimate for MEAF is USD 143.2 Mil (34% for VC, 28% for Surveillance, 24% case management); estimate for 2016 & 2017 is USD 49Mi
- Study on safety of low dose primaquir.. ongoing
- Technical support for forecasting , registration, procurement and management of antimalarials
- Failure rates of DHA-PPQ have crossed 60% in Siem Reap and have reached 30-40% in provinces including Oddar Meanchey, Stung Treng and Battambang.



Health Organization

Country updates: **Cambodia** – Partners



World Health Organization

Country updates: **China**

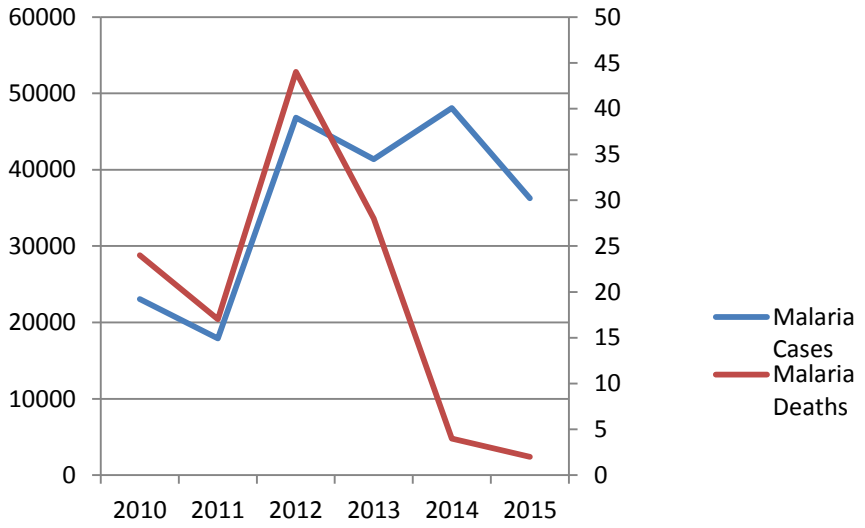
- 21 indigenous cases in 2015, preparing for certification of elimination.
- Completed updating of national elimination strategy & Yunnan elimination strategy (2015)
- Yunnan surveillance training
- Conducts international trainings
- Cross border collaboration meeting between Myanmar and China, 3/2016
- Evaluation of border malaria ports planned.

Yunnan surveillance training

World Health Organization

Country updates: **Lao People's Democratic Republic**

- National Malaria Strategic Plan 2016 – 2020 completed and submitted for endorsement to Minister; launch & donor meeting scheduled for April/May 2016
- Interventions for MMPs started
- Work with private sector expanded
- Integration of malaria surveillance in DHIS2 completed and training rolled out in 5 Southern Provinces
- National slide bank established
- TES completed in Sekong (ACPR 86%) and Champasak (ACPR 90%) provinces

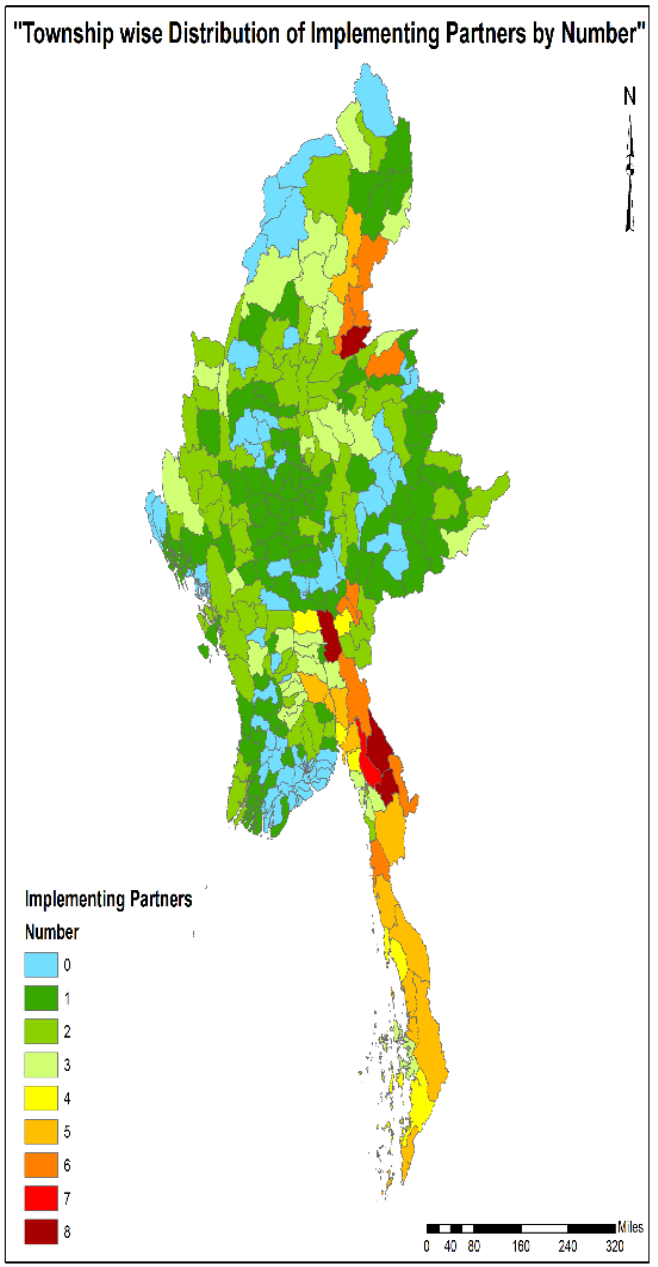


China/Lao border crossing

World Health Organization

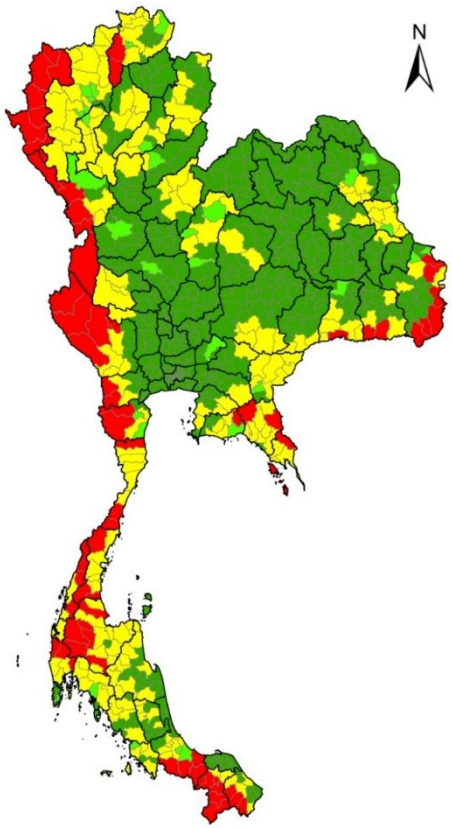
Country updates: **Myanmar**

- 38% reduction in the morbidity and 68% reduction in mortality in 2014 (vs 2013); 41% reduction in morbidity in 2015 (vs 2014) with less than 200 000 cases
- Shift from containment to elimination, draft NSP available
- Malaria Programme Review ongoing, results to be used to finalize NSP & costing (mid April)
- Work on Global Fund Concept Note started (NFM + RAI), submission in June for 4 years
- Cross border meetings with China and with South Asian countries conducted
- Complex partner situation (>25 implementing partners), mapping of partners and related intervention coverage completed
- Strengthened surveillance (> 70 additional M&E staff), MIS ongoing, database establishe
- Strengthened coordination (6 TSG meetings in 2015)



Country updates: **Thailand**

- NSP for malaria elimination (2017-2026) endorsed by the NSC, chaired by DPM on 15 Feb 2016; plan for Cabinet approval in March
- Drug policy was changed in Q2/2015 to DHA-PIP, to be rolled out in 2016
- Microscopy QA being strengthened
- Business Intelligence (BI) Malaria Surveillance Web-based established with GF supported will stop in 2016-requires strategy to sustain
- Future shortfall of malaria competent staff, requires strategy to integrate with other disease control programs
- Evaluation of usefulness of DOT planned

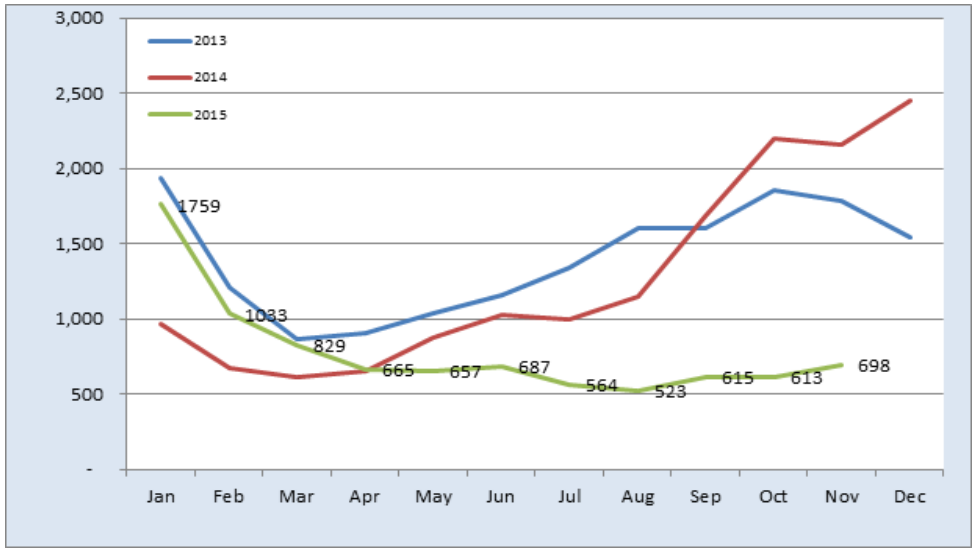


	Control	C 1	API ≥ 1/1,000 with indigenous case
		C 2	API < 1/1,000 with indigenous case
	Elimination	E1	no indigenous case 1-3 year
		E2	no indigenous cases > 3years

World Health Organization

Country updates: **Viet Nam**

- Significant reduction of malaria cases (2013: 17 123; 2015: 9 331).
- Costed work plan based on the national strategic plan and on GMS elimination strategy developed.
- Survey conducted in 5 provinces (2014) revealed 21% (94/445 pharmacies) of pharmacies still selling oAMT.
- Mapping of MMPs completed in 1 province
- Expansion of malaria posts under the reprogramming of RAI conducted to improve access for MMPs – 31 posts already established.



World Health Organization

Regional coordination

Domain	Status
1 Capacity building & technical collaboration	• GMS elimination and surveillance training (Thailand, China) • Elimination operation manual (draft) • Expert consultation (New Delhi)
2 Cross border collaboration	• Ongoing cross-border initiatives: Lao-Thailand, Cambodia-Thailand, China-Myanmar, Myanmar-India/Bangladesh • Draft MMP strategy and toolkit developed • Involvement in country MMP pilot projects
3 Product quality	• WHO Collaborative registration procedure and workshop on WHO Prequalification Programme conducted • Medicines quality issues have been discussed at the ASEAN • Improved collaboration between national stakeholders • Country workplans developed, incl oAMT elimination and surveys
4 High priority research	• Priority GMS research agenda defined (December 2013 through ERAR) , currently updated • Support of several ongoing research projects • Regional Research Coordination group established (11/2014)
5 Surveillance, M& E	• SME country capacity assessments done (in print) • Monthly data collection & analysis • Regional data sharing platform (DHIS2) • Intense TES monitoring through networks (GMS and beyond)
6 Coordination and governance	• Leading and supporting GMS strategy and NSP developments • Facilitate regional collaboration • Partner coordination (incl through annual partners forum) • Tracking/engaging in resource mobilization • Advocacy & communication (website, newsletter)

World Health Organization

Regional coordination: Tracking progress, surveillance

Routine surveillance data submission by country, 9/2015

Country	Jan_15	Feb_15	Mar_15	Apr_15	May_15	Jun_15	Jul_15	Aug_15	Sep_15	Oct_15	Nov_15	Dec_15
Cambodia	■	■	■	■	■	■						
China (Yunnan)	■	■	■	■	■	■	■	■				
Lao PDR												
Myanmar	■	■	■	■								
*Thailand	■	■	■	■	■	■	■	■				
Vietnam	■	■	■	■	■	■	■					

Routine surveillance data submission by country, 3/2016

Country	Jan_15	Feb_15	Mar_15	Apr_15	May_15	Jun_15	Jul_15	Aug_15	Sep_15	Oct_15	Nov_15	Dec_15	Jan_16	Feb_16	Mar_16
Cambodia	■	■	■	■	■	■									
China (Yunnan)	■	■	■	■	■	■	■	■	■	■					
Lao PDR	■	■	■	■	■	■	■	■	■						
**Myanmar	■	■	■	■	■	■	■	■	■	■					
Thailand	■	■	■	■	■	■	■	■	■	■	■	■	■		
Vietnam	■	■	■	■	■	■	■	■	■	■	■	■	■		

- Data elements and indicators defined and agreed (for burden reduction and elimination)
  - New additions: elimination, cross-border, migrant and mobile populations, private sector, gender and community
- Regional Hub Database- Draft version (DHIS2)
  - Compatible for burden reduction-elimination
  - Customizable to country context
  - Monthly data sharing between countries started
  - Bulletin and scorecard report
- Data managers being recruited in each country programme
- Collaboration with Global Fund – RAI

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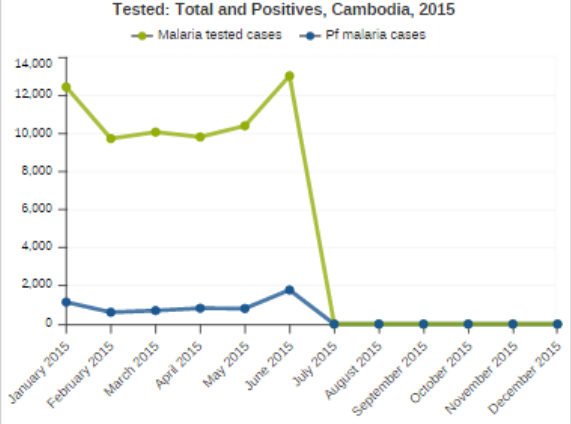

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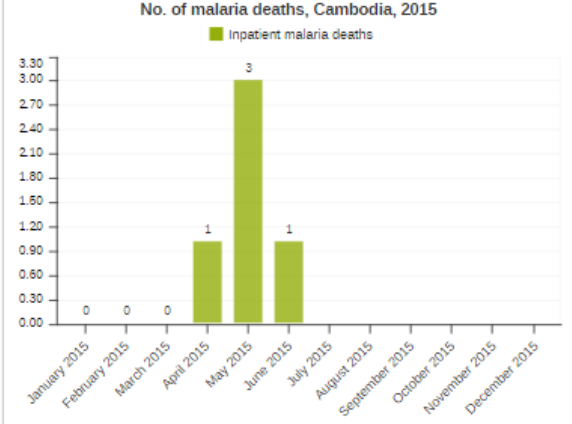

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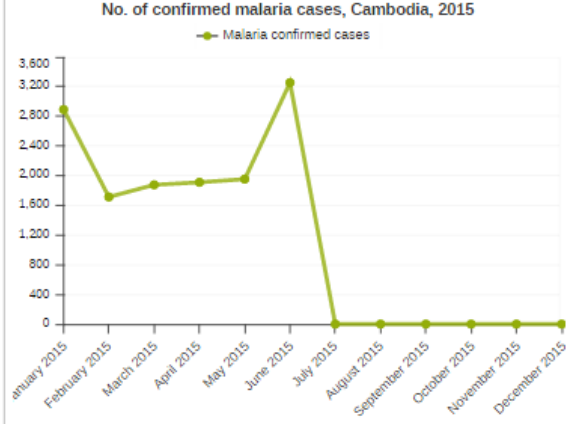

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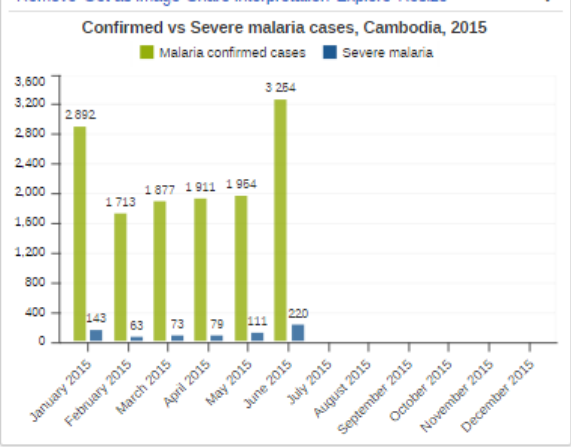

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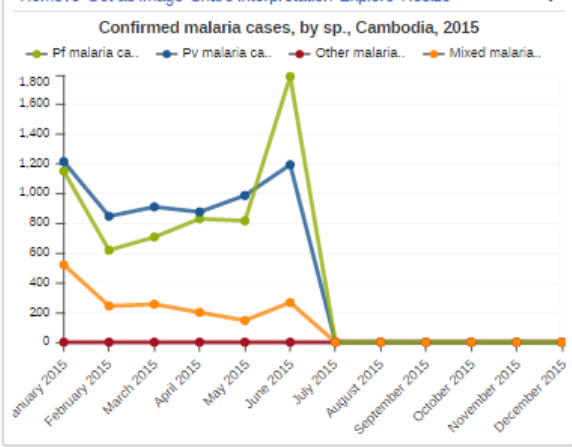

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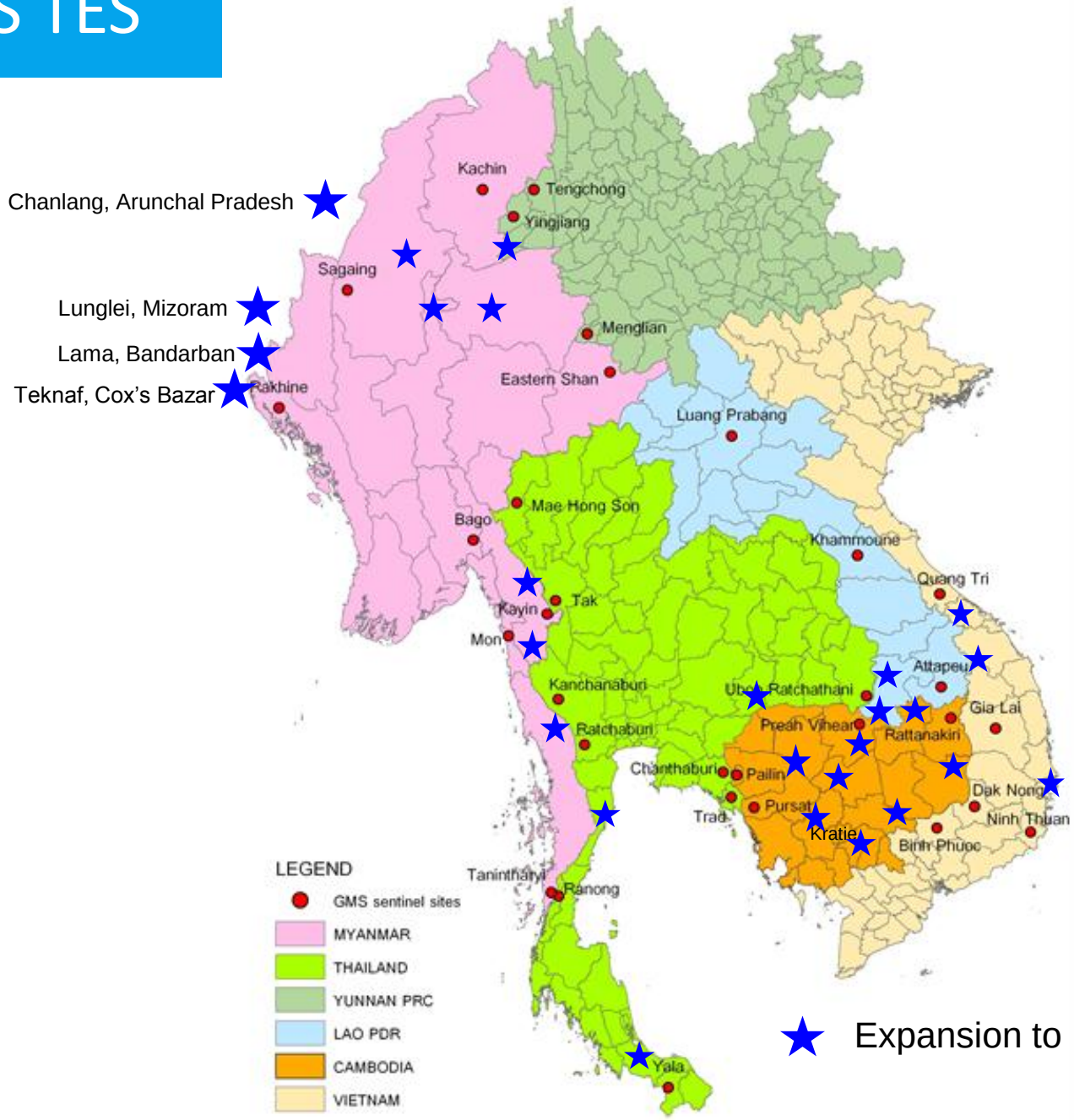
KH TPR 2014

Data					
Organisation units / Periods	January 2014	February 2014	March 2014	April 2014	Ma 201
Banteay Meanchey	25	5.5	12.8	14.3	1
Battambang	25.7	27.3	16.2	26.8	2
Kampong Cham	20.5	14.9	15.8	8	1
Kampong Chhnang	5.4	18.8	10	12.1	1
Kampong Speu	14.9	6.9	11	11.1	
Kampong Thom	12.7	8.3	8.1	7.4	
Kampot	3	3.4	4.6	7	
Kandal	18.6	18	8.2	12.1	1
Kep	11.1	27.3	12.5	9.1	

GMS TES



★ Expansion to new sites (2014-2016)

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Access for migrant and mobile populations to services

> 10 workshops/meetings organized in 2014-15

Guidance documents produced:

- Toolkit http://who.int/malaria/areas/greater_mekong/toolkits/en/

- Approaches for Mobile and Migrant Populations
- Policies/legal framework

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Policy and Implementation Challenges

- Delays in uptake/roll out of WHO Global Policies and Guidance
  - Drug policy change (ACT rotation, primaquine etc.)
  - Choice and targeting of vector control interventions
- The elimination concept is largely new and not yet sufficiently understood
- Weaknesses of health systems (leadership & governance, HR, HIS, health financing, PSM, health technologies incl microsocpy)
- Malaria foci located in hard to reach population groups
- Expanding drug resistance a challenge
- Cross border collaboration and coordination
  - Definition of the focus
  - joint work plans
  - Tracking and documentation
- Fragmentation and stakeholder coordination (multiple and uncoordinated reprogramming).

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Way forward

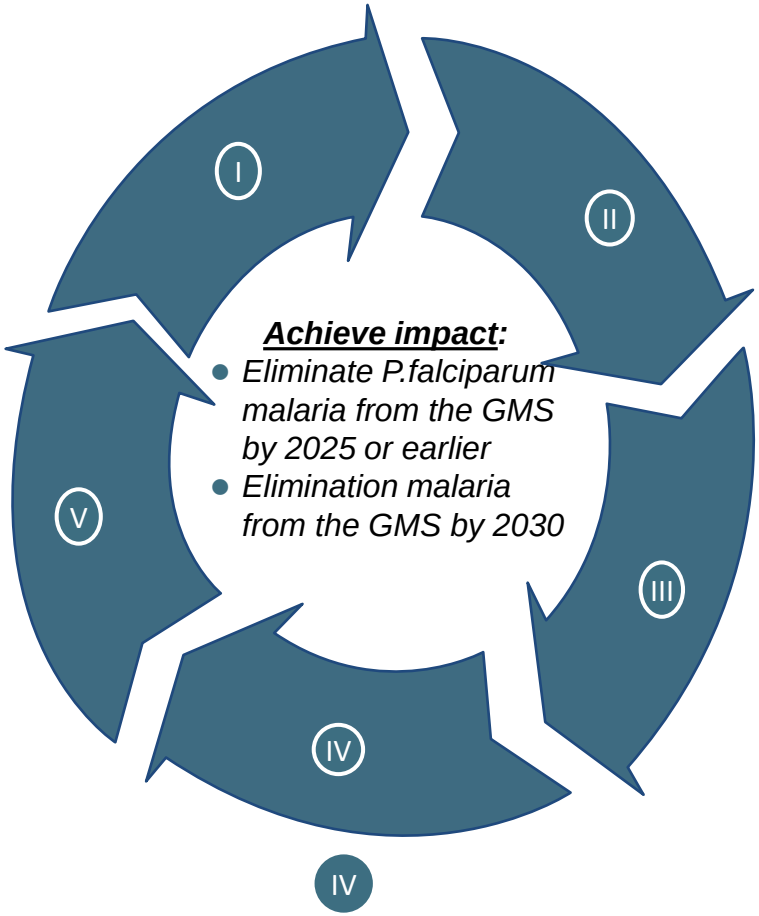
Reorient the Regional Hub from containment to elimination

I

Promote high level and **multi stakeholder engagement** to keep malaria elimination high on the agenda and ensure mutual accountability

II

Strengthen existing malaria **surveillance** systems in their transition towards malaria case-based and entomological surveillance as core intervention



V

Keep an **independent score** of sub regional progress in malaria elimination, including **drug & insecticide resistance and cross border collaboration**

III

Coordinate and synergize **case detection and management, disease prevention and vector control interventions** in-country and across programs and sectors

IV

Plan and implement **capacity strengthening** activities (training, mentoring and supervision)

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THANK YOU

Migrant worker family along the road to Kayah State, Myanmar

World Health Organization

Expert Review Group (ERG) on malaria elimination

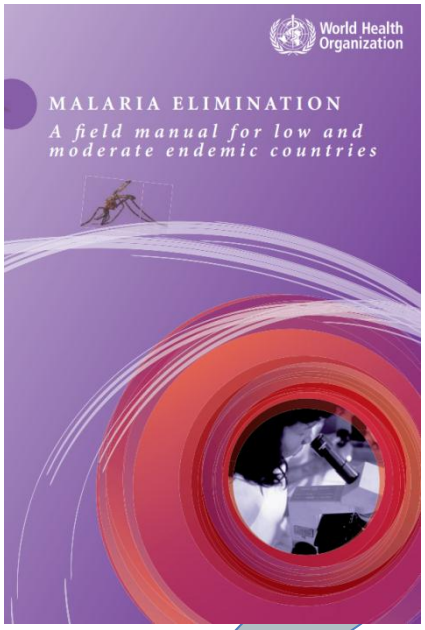
Drs. Hoda Atta and Keith Carter, EMRO and AMRO regional malaria advisors

Malaria Policy Advisory Committee, Geneva, Switzerland, 16 March 2016

Global **Malaria** Programme

World Health Organization

Rationale for an Elimination ERG



- **The malaria landscape has changed dramatically since 2007**
  - Increased funding for malaria programme activities
  - Large-scale implementation of malaria interventions
  - Impressive reductions in malaria burden
  - Increasing number of countries eliminating or considering elimination of malaria
  - Changes in policy recommendations and available tools
  - Development of new Global Technical Strategy for Malaria 2016-2030 (3 pillars incl. elimination, 2 supporting elements)

2015–2016

Need to update the manual to reflect these changes

Objective of the Elimination ERG - membership

- Revise/develop a new *Malaria Elimination Field Manual* to cover all epidemiological settings, provide comprehensive, relevant guidance in the new malaria landscape, in line with mandate of the *Global Technical Strategy for Malaria 2016-2030*.

- 13 members with expertise and experience across relevant disciplines:
  - Dr Majed Al-Zadjali, Department of malaria, MoH, Oman
  - Pr Graham Brown, Nossal Institute for Global Health
  - Pr Tom Burkot, James Cook University
  - Dr Justin Cohen, CHAI
  - Dr Mikhail Ejov, independent consultant
  - Dr Rossitza Mintcheva-Kurdova, independent consultant
  - Dr Bruno Moonen, Bill & Melinda Gates Foundation
  - Dr Gao Qi, Jiangsu Institute of Parasitic Diseases
  - Dr Frank Richards, The Carter Center
  - Pr Christophe Rogier, Pasteur Institute of Madagascar
  - Dr Allan Schapira, independent consultant
  - Pr Robert Snow, KEMRI Wellcome Trust Research Programme
  - Dr Rick Steketee, PATH-MACEPA

Phase 1

June 2015 -> Delhi meeting, 31 July-2 August 2015

- Establishment of a repository/drop box of all guidelines, meeting reports, scientific papers and progress reports relevant to elimination (June-July)
- Deep dive into the current manual (2007) at the 1st ERG meeting in July-August 2015 (9/13 experts attending) with identification of gaps/new content and needed changes for the new guidance (July-August)
- Decision points of the Delhi meeting
  - New title: “Malaria elimination: An operational manual”
  - Audience: all, but primarily National Malaria Control Programme managers
  - Scope of guidance: all epidemiological settings as opposed to countries nearing elimination only
  - Focus: progression of all malaria-endemic countries towards elimination in accord with the GTS, moving away from the previous multi-staged / compartmented process from control to elimination
  - Steps A to E to progress towards elimination (accelerate scale-up, build information systems, clearance of parasites, detect and investigate, and Eliminate and maintain) including interventions and linking with GTS pillars and SEs

Phase 1

June 2015 -> Delhi meeting, 31 July-2 August 2015

- New content identified
  - Chapter "Innovation and Research for elimination"
  - Section on subnational elimination of malaria, referred to as "Subnational verification of malaria elimination" (country process) on the way to the WHO-led process of national certification
  - Special situations, lessons learnt from malaria elimination: examples and or boxes will be inserted where appropriate
  - Glossary to be aligned with the malaria elimination/eradication terminology work underway (led by A. Bosman at WHO and R. Steketee at MACEPA).
- First outline drafted
  - Principles and practice of malaria elimination
  - Planning for elimination
  - Management and mindset for elimination
  - M&E of progress towards elimination
  - Prevention of re-establishment of transmission
  - Subnational verification and national certification
  - Innovation and research
  - Glossary

Writing/peer-reviewing responsibilities assigned to experts and advisors *(WHO staff in support)*

Phase 2

August 2015 -> Montreux meeting, 14-15 December 2015

- Development and peer-review by experts of all sections of the new draft guidance (September-early November)
- Consolidation into one 134-page document (early December)
- Comprehensive analysis and review of the draft during the December Montreux meeting (larger participation, 11/13 attending)
- Decision points of the Montreux meeting:
  - Rewriting work/synthesis to be done jointly by WHO-MACEPA staff based on a final and detailed outline (next slide)
  - Specific components to be developed by experts/GMP coordinators, e.g.:
    - Annex on diagnostic tools (A. Bosman)
    - Short section on surveillance (A. Schapira)
    - Annex: Details on the biology of malaria incl. illustration with a diagram as well (A. Schapira)
    - Definitions: re-introduction vs re-establishment; 1st/2nd/3rd generations; case and focus classification (A. Schapira)

Phase 2

August 2015 -> Montreux meeting, 14-15 December 2015

- Introduction
- Chapter 1 – Principles of malaria elimination: verification/certification, continuum, case and foci classification…
- Chapter 2 – The "what": Interventions
  - Optimizing vector control and case management: receptive/vulnerable areas, stratification…
  - Surveillance: including entomological surveillance and data quality..
  - Clearance of parasites: dealing with foci, asymptomatic carriers…
  - Cross-cutting issues: health systems strengthening, inter-sectoral collaboration, cross-border collaboration
- Chapter 3: The "how": Management and planning
  - General elimination vision (reference to chapter 1)
  - Planning process (stratification)
  - Data for decision-making (M&E): indicators from strata to foci, indicators, independent elimination committee
  - Programme structure and management: malaria programme structure and functioning; enabling environment
- Chapter 4: Verification and certification
- Chapter 5: Prevention of re-establishment
- Chapter 6: Role of R&D: program innovation, programmatic unknowns, new research and tools
- Annexes

Guidance development, step 3 – work ahead

- Review of the draft guidance
- Clear and detailed outline set

- Deep dive into the manual
- Consensus on the gaps and suggested changes
- Outline of new guidance and each chapter
- Focal point to coordinate the process of collecting revised sections and compilation of inputs

Experts to develop working papers, conduct in-depth search or review papers/collect historical experience

Prep. work

1st ERG meeting
New Delhi

2nd ERG meeting
Montreux

July-Aug 2015

Dec 2015

Consultative process

- Discussion at regional meetings
- ITWs with programme managers

Feedback consolidation work

Final review

Write, synthesize and rearticulate

(WHO-PATH/MACEPA)

3rd ERG meeting
China

MPAC presentation

Production & publishing

March 2016

May 2016

2-3 June 2016

14-16 Sept 2016

Oct-Nov 2016
Launch in Cairo (TBC)

Regular teleconferences as needed
Ongoing interactions with GMP coordinators

Global **Malaria** Programme

World Health Organization